Chapter 2

A long-term follow-up study of eighteen patients with thyrotrophin-secreting pituitary adenomas

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Abstract

Objective
Thyrotrophin (TSH)-secreting pituitary adenomas (TSH-omas) are a rare cause of thyrotoxicosis. First-line therapy for these tumors is neurosurgery, although medical therapy with somatostatin analogues (SSAs) is increasingly used for this indication.

Design and patients
We retrospectively reviewed the data of patients with a TSH-oma (n = 18, 67% males) followed between 1989 and 2011 (median follow-up 7 years, range 1 - 21) in three academic medical centers in the Netherlands, focusing on the role of SSA treatment.

Measurements
Patient records were reviewed for clinical, biochemical, imaging, pathological and treatment characteristics.

Results
At initial evaluation, biochemical hyperthyroidism with nonsuppressed TSH concentrations was detected in 94% of the patients. The majority of patients (72%) had a macroadenoma with extrasellar extension. Fourteen patients underwent surgery, resulting in postoperative euthyroidism in six patients (43%). Recurrence of hyperthyroidism developed in three of them after 5, 24, and 32 months, respectively. Adjuvant radiotherapy (n = 2) did not induce remission. Three patients received SSA therapy exclusively, resulting in apparent cure in one of them. During long-term follow-up, 72% of all patients required medical therapy (mostly SSA treatment). Euthyroidism was achieved in all but one patient, who refused all treatments.

Conclusions
Our results demonstrate that patients with TSH-omas, who often present with large macroadenomas with extrasellar extension, have an excellent response to SSA therapy. Because the results of surgery and radiotherapy are disappointing, primary medical therapy may be considered in virtually all patients, except in case of optic chiasm compression, especially in those harboring large adenomas with parasellar extension.
**Introduction**

Thyrotrophin (TSH)-secreting pituitary adenomas (TSH-omas) are uncommon tumors that account for less < 2% of all pituitary adenomas (PAs) \(^1^4\). The secretion of TSH by these tumors causes central hyperthyroidism. This is a rare cause of thyrotoxicosis, which is often initially misdiagnosed.

The biochemical profile of TSH-omas is classically characterized by elevated concentrations of circulating thyroid hormones in the presence of nonsuppressed TSH concentrations \(^5^6\). This profile is shared with patients with the syndrome of resistance to thyroid hormone. Therefore, specific investigations to differentiate between the two disorders are often needed \(^5\). Since the introduction of ultrasensitive TSH assays and improved imaging techniques, TSH-omas are probably recognized with increasing frequency and in earlier stages \(^2^3^7^8\).

The primary therapeutic approach for TSH-omas is neurosurgery. Approximately one-third of all patients are apparently cured after surgery alone \(^2^6\). Radiotherapy might be considered as adjuvant therapy after surgery or as first-line therapy if surgery is contraindicated or declined \(^2\).

Medical treatment, frequently used as pre- or postoperative therapy, has greatly improved since the introduction of somatostatin analogues (SSAs). Beforehand, medical treatment with dopamine agonists (DAs) resulted in variable and often poor responses \(^2^7^9\). SSAs have been shown to reduce TSH secretion in 90% of the patients with TSH-omas, with normalization of TSH and circulating thyroid hormone concentrations in the majority of them. Decrease in tumor mass was reported in approximately 40% of the cases \(^2^5^7^10\). Nevertheless, due to the low prevalence, there are relatively few studies that describe a series of patients with thyrotrophinomas \(^3^4^6^7^11^14\), and the place of SSA treatment in the management of TSH-omas still remains to be fully established.

The aim of this retrospective study was to review the clinical characteristics, management, and follow-up features of patients with TSH-omas, evaluated in three university hospitals in the Netherlands from 1989 until 2011, with a special focus on the long-term outcome of SSA treatment.

**Subjects and Methods**

**Patients**

Between 1989 and 2011, 18 patients with a TSH-oma were assessed and followed in three university hospitals in the Netherlands (VU University Medical Center (VUmc)
n = 6, Academic Medical Center of the University of Amsterdam (AMC) n = 7, and Leiden University Medical Center (LUMC) n = 5). These patients were identified by means of searches in the hospital diagnoses code registries from the participating university hospitals. In addition, endocrinologists at the university hospitals were asked if they were aware of any further relevant cases for the study. Partial data of six patients have previously been reported. The Medical Ethics Committee of each of the three hospitals declared that no formal ethical approval and written informed consent was needed for this anonymous retrospective chart review.

The medical records of the patients were retrospectively reviewed. Collected data included demographics, medical history, relevant findings on physical examination, visual field tests, laboratory investigations, radiological imaging, treatment modalities, and pituitary immunohistochemistry.

The diagnosis of TSH-oma was based on the biochemical findings of elevated thyroid hormone concentrations in the presence of inappropriately normal or elevated TSH concentrations, clinical signs of hyperthyroidism or tumor compression, and evidence of a pituitary tumor on computed tomography (CT) scan and/or magnetic resonance imaging (MRI). In some cases, the diagnostic workup included dynamic tests with thyrotrophin-releasing hormone (TRH), triiodothyronine (T3) or octreotide, measurements of serum alpha-subunit or sex hormone binding globulin (SHBG), or mutation analysis of the thyroid hormone receptor. Furthermore, when possible, histological and immunohistochemical studies to confirm the diagnosis were performed.

The evaluation of additional pituitary hormone secretion was performed using baseline hormone sampling and dynamic test results, as well as data obtained from medical records including prescribed substitution therapy.

Follow-up started on the date of initial assessment in the participating university hospitals. Patients were evaluated at various intervals according to the protocol of the attended medical center.

Patients were considered apparently cured if biochemical signs of hormone hypersecretion had normalized in the absence of medical treatment and if pituitary imaging showed no evidence of residual tumor during follow-up. Adequate control of hormone hypersecretion with medical therapy was not defined as apparent cure.

Remission was defined as a remission of clinical and biochemical signs of hyperthyroidism after therapy in the absence of medical treatment.

A recurrence was defined as an initial remission followed by either recurrent biochemical or clinical hyperthyroidism, or tumor growth, or newly introduced therapy.
Biochemical evaluation

Endocrine investigations were performed in the laboratories of the participating university hospitals before start of treatment and during follow-up. In one patient, who underwent surgery and radiotherapy elsewhere in 1977 and received medical therapy afterwards, only postoperative laboratory results were available. At initial assessment, the evaluation was performed after withdrawal of octreotide for 4 weeks.

TSH, free thyroxine (FT4), free T3 (FT3), thyroxine (T4), T3 and alpha-subunit concentrations were measured by commercial immunometric assays. At the AMC, in-house assays were used for measurement of T4 and T3 concentrations. The reference ranges for the different assays used are shown in table 1.

A TRH test was performed in 13 patients by intravenous injection of 200 µg TRH. The TSH response to TRH administration was considered normal if TSH concentrations were either increased by > 200% of the baseline value or by > 5.0 mU/l.

An octreotide suppression test was performed in five patients. In three patients (tested at the LUMC) TSH was measured following intravenous administration of 50 µg octreotide. Two other patients were subcutaneously injected with a single dose of 100 µg octreotide.

The response of TSH to T3 administration was investigated in one patient, who was orally treated with 100 µg T3 on day 5 and 200 µg T3 on day 10 of the T3 suppression test. A decrease in TSH concentration to < 10% of the baseline was considered as normal.

Pituitary imaging

Anatomic evaluation of the pituitary gland by either MRI (n = 17), in the majority of patients before and after intravenous gadolinium injection, or contrast-enhanced CT (n = 1) was performed in all patients at the time of initial assessment in the participating university hospitals. Radiological follow-up with MRI was available in all patients.

According to tumor size, pituitary tumors were divided into microadenomas (maximal diameter < 10 mm) and macroadenomas (maximal diameter ≥ 10 mm).

Immunohistochemistry

Data on histopathological studies of resected tumor specimens were obtained in 13 of the 14 operated patients. Immunohistochemical characterization of pituitary tumor cells in paraffin sections was performed on 12 specimens, using the indirect immunoperoxidase method with specific antisera to TSH beta-subunit (BTSH).
Statistical analysis
Categorical data are expressed as number (percentage), while continuous data are either expressed as median (range) or mean ± SD. Categorical variables were compared by the Fisher’s exact test, while continuous variables were compared by the Student’s t-test or nonparametric tests when appropriate. The level of significance was set at p < 0.05.

Data were analyzed using the statistical software package SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL).

Results
Clinical features
Eighteen patients, with a median follow-up time of 7 years (range 1 - 21 years), were diagnosed with a TSH-oma. Their demographic and clinical data at initial assessment are shown in table 2.

Biochemical evaluation
At presentation, biochemical hyperthyroidism with a nonsuppressed TSH concentration was found in 17 patients. In one clinically hyperthyroid patient, thyroid hormone concentrations were just within the normal range at initial assessment. Repeated biochemical evaluation did reveal biochemical hyperthyroidism, while pituitary MRI showed a macroadenoma. Further studies, including dynamic tests, mutation analysis of the thyroid hormone receptor and immunohistochemical studies, confirmed the diagnosis in this patient.

The biochemical characteristics of the patients are summarized in table 1. In 10 of the 18 (56%) patients, the TSH concentration was inappropriately normal.

Three patients had concomitant biochemical growth hormone (GH) excess (with clinical symptoms of acromegaly in two of the three patients). None of the patients with a microadenoma had biochemical evidence of cosecretion of other anterior pituitary hormones.

The response of TSH to TRH stimulation (n = 13) was considered abnormal in 10 (77%) patients. The response of TSH to 50 µg iv octreotide (n = 3) resulted in a decrease in TSH concentration to 48%, 49% and 42% of the baseline value, respectively. In two other patients, who were injected with 100 µg octreotide, TSH concentrations decreased to 71% and 46% of baseline, respectively. The T3 suppression test (n= 1) showed a decrease in TSH concentration to 44% of baseline.
Table 1 | Biochemical characteristics

<table>
<thead>
<tr>
<th>Biochemical characteristic</th>
<th>Median (range) or percentage</th>
<th>Median (range) percentage deviation from the upper limit of the reference range</th>
<th>Above the reference range in % of tested patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH, mU/l (n=18)</td>
<td>4.3 (0.9 - 51.5)</td>
<td>89% (18 - 1144)</td>
<td>44%</td>
</tr>
<tr>
<td>fT4, pmol/l (n=15)</td>
<td>37.6 (24.5 - 70.0)</td>
<td>172% (122 - 350)</td>
<td>100%</td>
</tr>
<tr>
<td>T4, nmol/l (n=8)</td>
<td>155.0 (108.0 - 210.0)</td>
<td>103% (72 - 140)</td>
<td>75%</td>
</tr>
<tr>
<td>fT3, pmol/l (n=2)</td>
<td>15.8 (12.6 - 19.0)</td>
<td>243% (194 - 292)</td>
<td>100%</td>
</tr>
<tr>
<td>T3, nmol/l (n=12)</td>
<td>3.3 (1.7 - 4.9)</td>
<td>123% (61 - 181)</td>
<td>83%</td>
</tr>
<tr>
<td>Alpha-subunit, µg/l (n=11)</td>
<td>1.6 (0.1 - 15.0)</td>
<td>172% (12 - 1875)</td>
<td>64%</td>
</tr>
<tr>
<td>Alpha-subunit/TSH molar ratio (n=11)</td>
<td>3.5 (0.5 - 32.6)</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>SHBG, nmol/l (n=12)</td>
<td>86.0 (34.0 - 128.0)</td>
<td>96% (41 - 180)</td>
<td>42%</td>
</tr>
<tr>
<td>Hormonal cosecretion (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRL (%)</td>
<td>11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH (%)</td>
<td>11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH and PRL (%)</td>
<td>6%</td>
<td></td>
<td></td>
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<tr>
<td>TRH test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ TSH, mU/l (n=12)</td>
<td>0.92 (0.15 - 26.9)</td>
<td></td>
<td></td>
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<tr>
<td>% Increase in TSH (n=12)</td>
<td>125.9 (107.7 - 802.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ Alpha-subunit, µg/l (n=7)</td>
<td>0.95 (0 - 3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Increase in alpha-subunit (n=7)</td>
<td>139.7 (96.8 - 205.3)</td>
<td></td>
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</tbody>
</table>

TSH, thyrotrophin; fT4, free thyroxine; T4, thyroxine; fT3, free triiodothyronine; T3, triiodothyronine; SHBG, sex hormone binding globulin; PRL, prolactin; GH, growth hormone; TRH, thyrotrophin-releasing hormone
Percentage deviation from the upper limit of the reference range, baseline value divided by the upper value of the reference range x 100; n, number of cases studied; Δ, peak value minus baseline value; % increase, peak value divided by baseline value x 100. Normal ranges for the different assays used are as follows: TSH, 0.3 - 4.5 mU/l at VUMC, 0.5 - 5 mU/l at AMC, 0.4 - 4.8 mU/l at LUMC; fT4, 11 - 23 pmol/l at VUMC, 10 - 20 pmol/l at AMC, 10 - 24 pmol/l at LUMC; fT3, 3.5 - 6.5 pmol/l at VUMC, 3.3 - 8.2 pmol/l at AMC; T4, 70 - 150 nmol/l; T3, 1.3 - 2.7 nmol/l at AMC, 1.2 - 2.6 nmol/l at LUMC; alpha-subunit, < 0.8 µg/l for males, < 0.9 µg/l for premenopausal females and < 1.2 µg/l for postmenopausal females; alpha-subunit/TSH molar ratio (as described by Beck-Peccoz et al. 2), < 5.7 in patients with normal TSH, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations, < 29.1 in patients with normal TSH but elevated LH and FH concentrations, < 0.7 in patients with elevated TSH but normal LH and FSH concentrations, < 1.0 in patients with elevated TSH, LH and FH concentrations; SHBG, 13 - 71 nmol/l for males, 18 - 114 nmol/l for females.

Neuroradiological evaluation
The neuroradiological characteristics of the patients at initial assessment are presented in table 3. Visual field defects were present in three of the five (60%) patients with compression of the optic chiasm.
### Table 2 | Clinical characteristics

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>n (%)</th>
<th>Mean ± SD</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis, years</strong></td>
<td>48 ± 15</td>
<td>0.7 (0.2 - 26.8)</td>
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<tr>
<td><strong>Male</strong></td>
<td>12 (67%)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Duration of symptoms, years</strong></td>
<td>0.7 (0.2 - 26.8)</td>
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<tr>
<td><strong>Symptoms of thyrotoxicosis</strong></td>
<td>16 (89%)</td>
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<tr>
<td>Palpitations</td>
<td>10 (59%)</td>
<td></td>
<td></td>
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<tr>
<td>Atrial fibrillation</td>
<td>4 (24%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>1 (6%)</td>
<td></td>
<td></td>
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<tr>
<td>Increased perspiration</td>
<td>10 (59%)</td>
<td></td>
<td></td>
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<tr>
<td>Restlessness</td>
<td>8 (47%)</td>
<td></td>
<td></td>
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<tr>
<td>Weight loss</td>
<td>5 (29%)</td>
<td></td>
<td></td>
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<tr>
<td>Nervousness</td>
<td>5 (29%)</td>
<td></td>
<td></td>
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<tr>
<td>Tremor</td>
<td>4 (24%)</td>
<td></td>
<td></td>
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<tr>
<td>Agitation</td>
<td>3 (18%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired concentration</td>
<td>3 (18%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>3 (18%)</td>
<td></td>
<td></td>
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<tr>
<td>Dyspnea</td>
<td>2 (12.5%)</td>
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<td></td>
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<tr>
<td>Headache</td>
<td>6 (33%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual field defect</td>
<td>4 (22%)</td>
<td></td>
<td></td>
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<tr>
<td>Thyroid nodule</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goiter</td>
<td>4 (22%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acromegalic features</td>
<td>2 (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amenorrhoeab</td>
<td>2 (33%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galactorrhoea</td>
<td>1 (6%)</td>
<td></td>
<td></td>
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<tr>
<td>Hypogonadotrophic hypogonadism</td>
<td>1 (6%)</td>
<td></td>
<td></td>
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<tr>
<td><strong>n=17 (missing data in one patient)</strong></td>
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<td></td>
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<tr>
<td><strong>Only female patients were considered</strong></td>
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</tbody>
</table>

### Table 3 | Neuroradiological characteristics

<table>
<thead>
<tr>
<th>Neuroradiological characteristic</th>
<th>n (%)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microadenoma</td>
<td>5 (27.8%)</td>
<td></td>
</tr>
<tr>
<td>Macroadenoma</td>
<td>13 (72.2%)</td>
<td></td>
</tr>
<tr>
<td>Tumor size, mm^a (n=12)</td>
<td>25 (6 - 80)</td>
<td></td>
</tr>
<tr>
<td>Extrasellar extension</td>
<td>13 (72.2%)</td>
<td></td>
</tr>
<tr>
<td>Suprasellar extension</td>
<td>9 (50%)</td>
<td></td>
</tr>
<tr>
<td>Involvement of optic chiasm</td>
<td>5 (27.8%)</td>
<td></td>
</tr>
<tr>
<td>Parasellar extension</td>
<td>10 (55.6%)</td>
<td></td>
</tr>
<tr>
<td>Infrasellar extension</td>
<td>10 (55.6%)</td>
<td></td>
</tr>
</tbody>
</table>

^a Maximal diameter

^n, number of cases
Previous thyroid treatment
Two patients had received thyroid block and replacement therapy before referral to a university hospital, while three other patients had a history of (partial) thyroidectomy performed elsewhere (in 1959, 1976 and 1982, respectively). There were no significant differences between these patients and the other patients in duration of symptoms, the occurrence of hyperthyroid symptoms or visual field defects, tumor size, TSH and thyroid hormone concentrations and surgical outcome.

Management
Figure 1 summarizes the management of the patients in our series, which was based on a multidisciplinary approach, individual patient characteristics, and available treatment modalities at the time of diagnosis. Three patients received SSA therapy exclusively, fourteen patients underwent surgery in order to try to achieve apparent cure or to debulk tumor mass, and one patient refused all forms of treatment, but remained closely monitored. In the three patients treated with SSA therapy exclusively, the decision to continue with primary medical therapy rather than to proceed to surgery was mainly based on the rapid and successful response to SSA treatment and on the patients’ decisions.

Surgical therapy
Transsphenoidal surgery induced initial clinical and biochemical remission of hyperthyroidism in six of the fourteen (43%) operated patients (figure 1): two of these patients were surgically apparently cured (no tumor remnant on MRI), while the other four still had evidence of residual tumor on pituitary imaging. In the latter group, three patients developed recurrent biochemical hyperthyroidism, without tumor regrowth, after 5, 24 and 32 months, respectively. Postoperative initial clinical and biochemical remission was achieved in 4 of the 11 (36%) macroadenomas and in 2 of the 3 (67%) microadenomas.

In 79% of the cases, no surgical complications were reported. In one patient, venous epidural bleeding and bitemporal quadrantanopsia were observed. In another patient, leakage of cerebral spinal fluid and left sided hemianopsia, caused by a hematoma laterally from the right optic nerve, occurred. One patient had transient diabetes insipidus.

Histopathological studies confirmed the presence of a PA in 10 out of 13 (77%) cases. In three patients with microadenomas, the surgical specimen was not informative. Immunohistochemical staining of tumor specimens (n = 9, no data on immunostaining available in one patient) resulted in positive immunoreactivity for TSH in all cases.
The role of somatostatin analogue therapy

**Somatostatin analogue therapy exclusively**

Three patients received long-acting SSA therapy (n = 2 octreotide-LAR, n = 1 lanreotide) exclusively (figure 1) for a mean period of 40 ± 6 months.

In two of these patients, both long-term normalization of TSH, fT4 and alpha-subunit concentrations, and shrinkage of the pituitary macroadenoma, 16% (due to central tumor necrosis this percentage is probably an underestimation) and 100% decrease in maximal tumor diameter, respectively, were observed. In the other patient, fT4 concentrations remained elevated despite suppressed TSH concentrations. Further evaluation revealed the coexistence of a toxic multinodular goiter, for which the patient was treated with radioactive iodine and thyrostatics 15. Due to these factors, achievement of euthyroidism was complicated in this patient. Nevertheless, after resuming SSA therapy for the persisting TSH-oma, clinical and biochemical euthyroidism was obtained, while pituitary tumor size remained stable.

One patient developed gallstones after approximately 3 years of therapy, eventually resulting in a cholecystectomy. One of the primarily treated patients, recently reported in more detail 17, was apparently cured by SSA therapy.

**Presurgical somatostatin analogue therapy**

Seven of the fourteen patients who underwent surgery were presurgically treated with SSAs (n = 4 short-acting octreotide, n = 2 octreotide-LAR, n = 1 octreotide-LAR followed by lanreotide), combined with quinagolide treatment in one patient with cosecretion of prolactin (PRL). In five of these patients, presurgical SSA therapy was used to restore euthyroidism before surgery. In two other patients, SSA therapy was followed by surgery because SSA treatment did not induce tumor reduction or led to side effects.

Normalization of TSH and fT4 was observed in all treated patients (n = 6, no biochemical data available in one patient). Tumor shrinkage (33% and 38%, respectively) occurred in two patients, while in one patient tumor progression was reported despite SSA and DA treatment. Cholecystitis occurred in one patient, who initially refused surgery and was therefore treated with long-acting SSAs for 8 years.

In four of the seven (57%) presurgically treated patients, surgery induced initial remission of hyperthyroidism, whereas in the other operated patients who had not

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**Figure 1** | Management and outcome
TSH, thyrotrophin; SSA, somatostatin analogue; DA, dopamine agonist

a n=7 were presurgically treated with SSAs
b One patient used SSAs for elevated IGF-1 concentrations (TSH already normal)
Figure 1

Management and outcome

TSH, thyrotrophin; SSA, somatostatin analogue; DA, dopamine agonist

a n=7 were presurgically treated with SSAs
b One patient used SSAs for elevated IGF-1 concentrations (TSH already normal)

TS H-secreting
pituitary adenoma
n = 18

SSA only
n = 3

- Apparently cured after SSA withdrawal
  n = 1
- Continuation SSA
  n = 2

Pituitary surgery
n = 14

- Refusal of treatment
  n = 1

- Initial clinical and biochemical remission
  n = 6
  - Apparently cured after SSA withdrawal
    n = 2
  - Remission
    n = 4
  - Recurrence
    n = 3

Medication
n = 9

- SSA
  n = 6
- DA
  n = 1
- Thiamazole
  n = 2

Radiotherapy
n = 2

- DA
  n = 1
- SSA
  n = 1
received presurgical medical therapy remission was achieved in two of the seven (29%) cases (p = 0.296).

**Adjuvant medical therapy**

In two postoperatively irradiated patients with a follow-up duration of 13 and 20 years, respectively, TSH hypersecretion persisted after radiotherapy (figure 1). Both patients, irradiated in 1977 and 1993, respectively, had large macroadenomas that could not be completely resected. One of these patients, with a TSH- and PRL-secreting adenoma, received adjuvant treatment with octreotide-LAR, later combined with cabergoline. This normalized thyroid function tests and lowered PRL concentrations. However, due to noncompliance the medical treatment was temporarily discontinued and afterwards the patient preferred cabergoline treatment only. The other irradiated patient was initially treated with bromocriptine. Thereafter, he was switched to octreotide-LAR which led to adequate biochemical control.

All other patients with recurrent or persistent disease after surgery were also treated with adjuvant medical therapy (n = 9). Six of these patients received SSAs (n = 4 octreotide-LAR, n = 1 lanreotide, n = 1 short-acting octreotide at his own preference). Mean duration of SSA therapy was 5.5 ± 5.4 years. Restoration of the euthyroid state was obtained in five patients. In the other patient, SSA therapy was indicated for excessive GH secretion and not for central hyperthyroidism, which had been cured after surgery. In this patient, the insulin-like growth factor 1 (IGF-1) concentration was lowered to the normal range. Tumor shrinkage was noted in two patients (44% in one patient, percentage not available in the other patient). Mild abdominal complaints and diarrhea were reported in two patients.

At the last evaluation, euthyroidism was present in all but one patient. This was achieved by either exclusive SSA therapy (n = 3, of which one patient was apparently cured), or surgery alone (n = 3, two patients apparently cured, one in remission), or surgery and SSA therapy (n = 6, in one patient indicated for persistent postoperative GH hypersecretion), or surgery and DA treatment (n = 1, indicated for persistent postoperative PRL and GH hypersecretion), or surgery and thiamazole therapy (n = 2, one patient with a poor general condition had an empty sella and mild hyperthyroidism, the other patient experienced psychological complaints after only one SSA injection), or surgery and radiotherapy and DA therapy (n = 1), or surgery and radiotherapy and SSA therapy (n = 1). One patient refused all treatments. His TSH and thyroid hormone concentrations remained unchanged.
Discussion

Although an increase in incidence was recently observed by Önnestam et al. [4], TSH-omas remain rare tumors [1,2,5,7]. Their diagnosis and management are often difficult and challenging [2-6,11,13]. Our study demonstrates that multimodality treatment of TSH-omas results in long-term clinical remission in virtually all patients. Furthermore, the rates of apparent surgical cure are low, the tumors seem refractory to irradiation, and the majority of the patients are still in need of medical therapy during long-term follow-up. Although first-line surgical debulking of tumor mass is mandatory in patients with optic chiasm compression in order to protect vision, given the high efficacy of SSAs in inducing long-term biochemical control, primary medical therapy may be considered in virtually all other TSH-oma patients, especially in those harboring large adenomas with parasellar extension.

The treatment of choice in patients with TSH-omas has traditionally been transsphenoidal surgery [2,4,13]. In the literature, as well as in our series, achievement of apparent surgical cure has proven to be difficult in TSH-omas [11-13,18,19]. Although an increase in surgically apparently cured patients has been observed in recent years, rates vary from 0 to 72.7% [4,6,7,11-13,18,19]. It must be taken into consideration, however, that comparison and interpretation of results in the literature, as pointed out by Losa et al. [14], are complicated, due to the heterogeneity in the criteria used for cure or remission, and the differences in follow-up time.

The difficulties in achieving apparent cure by surgery alone, might be explained by the often fibrous and hard consistency of TSH-omas, which is possibly due to the expression of fibroblast growth factor [12,20]. Moreover, the high number of large macroadenomas with extrasellar extension at the time of presentation complicates total resection [2,7]. Delay in diagnosis and prior treatment directed at the thyroid may play a role in the development of these large tumors [12]. In our series, the rate of diagnosed macroadenomas (72.2%) was high, possibly influencing our surgical results. In the literature, the majority of the reported rates are comparable or higher [6,11-13,21]. Nevertheless, in a recent study by Önnestam et al. [4], 57% of the patients had a macroadenoma at diagnosis, while Socin et al. [7] observed an increase in the proportion of diagnosed microadenomas during their study period.

Adjuvant radiotherapy has been applied less frequently in recent years, especially since the medical treatment of TSH-omas has improved. In the past, medical therapy mainly depended on DA administration. Although beneficial effects of DAs have been observed in some mixed TSH- and PRL-secreting adenomas [2], results were often heterogeneous and disappointing in TSH-secreting adenomas [5,7,22]. This was also
observed in our study. In contrast, SSAs have shown to be able to suppress TSH secretion in approximately 90% of the cases, with normalization of elevated TSH concentrations in about 75%. Normalization of thyroid hormone concentrations has been reported in 95% of the patients. In addition, reduction of adenoma size has been detected in approximately 40% of the cases.

The actions of somatostatin are mediated through various somatostatin receptors (SSTs) located on the membranes of neoplastic thyrotropic cells. The inhibitory pathway induced by the binding of SSAs to these receptors appears to be intact in TSH-omas. Moreover, the presence of SSA binding sites on tumor cells has been correlated to in vivo and in vitro TSH responsiveness. In recent years, new insights have been gained about a possible functional interaction between the SST subtype 5 (SST5) and the dopamine subtype 2 (D2) receptor on the cell membrane. This has led to a renewed interest in the literature in combined treatment with DAs and SSAs, as well as in treatment with newly developed chimeric compounds that bind to both SST5 and D2 receptor.

In the present study, SSAs were highly effective in restoring the euthyroid state in both pre- and postoperatively treated patients, also in the long-term, even though tumor shrinkage occurred less frequently. These results support the role of SSAs, both as preoperative and adjuvant therapy. The development of gallstones, the potentially most important side effect which may occur in approximately 10% of the cases, was observed in two patients. Nevertheless, SSA therapy was generally well tolerated, a finding which has also been observed in acromegalic patients with long-term SSA therapy.

In addition, our limited data on first-line exclusive SSA treatment suggest that SSAs may also be indicated as primary therapy. Likewise, Maiza et al. have shown in a larger study that long-term primary SSA treatment is effective in patients with acromegaly. They suggest the use of first-line SSA therapy when surgery is contraindicated or declined by the patient, or pituitary MRI shows a normal pituitary gland or an empty sella turcica, or success of surgery is unlikely. A similar approach may also be useful in patients with TSH-omas.

One of our patients, previously described in more detail, was even apparently cured by first-line SSA therapy. Similarly, in a study on medical treatment of prolactinomas, it was suggested that in a subset of patients with prolactinomas, DA treatment can successfully be withdrawn after normalization of PRL concentrations and disappearance of the tumor. A similar treatment strategy might also be feasible in a subset of patients with TSH-omas, although further research on this particular subject is clearly needed.
In summary, TSH-omas are uncommon tumors, classically characterized by central hyperthyroidism and a PA on MRI. Although increased awareness as well as the advent of ultrasensitive TSH assays have facilitated earlier recognition, the diagnostic process can still be complicated. Achievement of apparent cure through surgery may prove difficult, because the majority of patients have large adenomas with extrasellar extension at the time of presentation. Therefore, multimodality treatment is often required. Most patients are adequately controlled by adjuvant medical therapy. Indeed, our results demonstrate the efficacy of long-term SSA treatment, which has even led to apparent cure in on patient. With the exception of patients with optic chiasm compression, primary medical therapy may be considered in virtually all patients, especially in case of macroadenomas with extrasellar extension, when complete surgical removal is unlikely.

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Chapter 2

References

16. Roelfsema F, Pereira AM, Keenan DM et al. Thyrotropin secretion by thyrotropinomas is characterized by increased pulse frequency, delayed diurnal rhythm, enhanced basal secretion, spikiness, and disorderliness. J Clin Endocrinol Metab 2008; 93(10):4052-4057.


