Chapter 8
TSH-Secreting Pituitary Adenomas

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Introduction

Central hyperthyroidism (i.e., elevated serum circulating free thyroid hormone levels in the presence of measurable serum TSH concentrations) is a rare condition related to the presence of two different clinical entities: TSH-secreting pituitary adenomas (TSHomas) and resistance to thyroid hormone action (Refetoff Syndrome, RTH) [1, 2]. While patients with TSHoma develop signs and symptoms of hyperthyroidism, subjects with RTH are in general clinically euthyroid (generalized RTH, GRTH), except for those with the so-called pituitary RTH who may present features related to the involvement of some organs such as the heart (tachycardia) and brain (attention deficit, nervousness, insomnia) [2].

Negative feedback mechanism is affected in both RTH and TSHomas. While in THSomas TSH is secreted autonomously, T3 receptor mutations reduce thyrotropes sensitivity to T3 in RTH [1, 2]. Moreover, in TSHomas TSH circadian rhythm is disrupted, and its secretion is characterized by increased pulse frequency and basal secretion [3].

The introduction of both ultrasensitive TSH immunometric assays and circulating free thyroid hormones direct immunoassays greatly improved the recognition of patients with central hyperthyroidism previously misdiagnosed as having a Graves' disease [1, 2].

Once central hyperthyroidism has been diagnosed, it is mandatory to correctly differentiate TSHoma and RTH to avoid improper thyroid ablation or pituitary surgery in patients with RTH. It is worth noting that early diagnosis and correct

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treatment of pituitary tumors prevent the occurrence of neurological complications (i.e., visual defects, headache, hypopituitarism) and should improve cure rate.

Epidemiology

In 1970, the first case of TSHoma was documented. Since then, about 500 patients have been reported. TSHoma is a rare condition accounting for 0.5 to 2% of all pituitary adenomas [2], the prevalence being 1–2 cases per million. Interestingly, the number of reported cases of TSHomas has significantly increased in the last 25 years. This increase in TSHoma diagnosis was related to the introduction of ultrasensitive immunometric assays for TSH as a first-line test for the evaluation of thyroid function that allowed to correctly identify the presence of central hyperthyroidism in patients previously thought to have Graves' disease [2]. The increase in TSHomas incidence has been confirmed by Swedish Pituitary Registry [5]. In fact, an increased incidence of TSHomas overtime was observed (from 0.05 per 1 million per year in 1990–1994 to 0.26 per 1 million per year in 2005–2009), the Swedish prevalence in 2010 being 2.8 per 1 million inhabitants [4].

Although most patients are diagnosed in the third to sixth decade of life, TSHomas may occur at any age (11 to 84 years) with equal frequency in males and females [2].

Macroadenomas (diameter > 1 cm) were recorded in more than 85% of the cases before 1996 [2, 5–8]. Interestingly, the prevalence of microadenomas is progressively increasing as confirmed by data collected by Malchiodi et al. showing that the percentage of microadenomas ranges between 30 and 35% of all TSHomas [9]. However, most TSHomas are diagnosed at the stage of invasive macroadenomas [2, 5–9], extra- and parasellar extension being present in most of cases.

Pathology and Etiopathogenesis

TSHomas are benign tumors that arise from adenomatous transformation of thyrotropes. Up to now TSH-secreting carcinomas with multiple metastases have been described in three patients [10–12], loss of pituitary glycoprotein hormone alpha-subunit (α-GSU) secretion being considered as a marker of malignant transformation [10]. Though the majority of TSHomas secretes TSH alone, about one fourth of them are mixed adenomas that cosecrete TSH and other anterior pituitary hormones. Hypersecretion of TSH and GH is the most frequent association (15–20%), followed by cosecretion of TSH and PRL (8–10%), while no TSHomas cosecreting ACTH have been so far identified. Occasionally pituitary adenomas cosecreting TSH and gonadotropins have been described [2, 13, 14] leading to precocious puberty during childhood or to ovarian hyperstimulation in adult female. The notion that GH and PRL share with TSH common transcription factors (e.g., PROP-1,

Pit-1, and HESX-1) justifies why GH and PRL are frequently cosecreted in TSHomas [15]. However, it is important to remember that a positive immunohistochemistry for pituitary hormones other than TSH does not necessarily correlate with their hypersecretion in vivo [16, 17].

As mentioned before, most TSHomas are macroadenomas that are characterized by high local invasiveness at morphologic and histopathologic analysis. Interestingly, previous thyroid ablation negatively affects clinical behavior. In fact, invasive macroadenomas are found in 49% of patients who had undergone thyroid ablation (i.e., radioiodine or thyroidectomy) versus 27% in those who were untreated thus suggesting that a reduction in T3 and T4 circulating levels might stimulate neoplastic thyrotrope cells growth through an altered feedback mechanism, a situation like that observed in some patients after bilateral adrenalectomy for Cushing's disease (Nelson's syndrome) [2]. TSHomas are frequently very fibrous and sometimes are so hard that they are defined "pituitary stones" [18]. It this respect, overexpression of basic fibroblast growth factor by some TSHomas suggests that it may play a role in the development of fibrosis of this pituitary neoplasm [19].

In patients with confirmed biochemical findings of TSHoma and neuroradiological imaging negative for the presence of a pituitary adenoma, an ectopic TSH secretion should be taken into consideration [20]. TSHoma ectopically occurring in the nasopharyngeal pituitary residue has been reported [21–23].

The molecular pathogenetic mechanisms leading to TSHomas formation are presently unknown. As demonstrated in other secreting and nonsecreting pituitary adenomas, TSHomas originate from the clonal expansion of a single transformed cell [24]. Therefore, a transforming event leading to an increased cell proliferation and secondary mutations or alterations favoring tumor progression is needed to induce TSHoma formation. However, no mutations in oncogenes commonly activated in human neoplasia have been so far reported in TSHomas. Moreover, none of the screened TSHomas has been shown to express activating mutations of genes encoding for stimulatory or inhibitory G protein subunits (i.e., αs, αq, α11, or αi2) or TRH receptor [25]. Since Pit-1 is a transcription factor involved in TSH gene expression, it has been studied and shown to be overexpressed but not mutated in a series of TSHomas [26]. As for oncogenes, no mutations affecting common antioncogenes (i.e., *p53, Rb, Menin*) have been so far identified. Though the presence of a TSHoma has been reported in five cases within a familial setting of MEN1, a screening study carried out on sporadic TSHomas found LOH on 11q13, where menin is located, but none of these tumors had a menin mutation [27]. Finally, a mutation of aryl hydrocarbon receptor-interacting protein (AIP) was found in a single patient with TSHoma [28]. A recently published whole-exome sequencing study of 12 TSHomas identified several candidate somatic mutations (e.g., SMOX and SYTL3) and changes in copy numbers [29]. However, the low number of mutations, as well as the absence of recurrence of mutations in the tumors studied, seems to further confirm the benign nature of these tumors.

TSHomas are characterized by an extreme refractoriness to the negative feedback mechanism exerted by thyroid hormones, this observation leading to search for alterations in thyroid hormone receptor (TR) expression and function [30, 31].

While the absence of TRα1, TRα2, and TRβ1 expression was reported in one TSHoma, aberrant alternative splicing of TRβ2 mRNA encoding TRβ variant lacking T3-binding activity was recently shown as a mechanism responsible for impaired T3-dependent negative regulation of both TSHβ and α-GSU in tumoral tissue [32]. Recently it has been suggested that somatic mutations of TRβ may be responsible for the defective negative feedback mechanism at least in some TSHomas [33]. Finally, knock-in mutant mice harboring a mutation in the TRβ gene spontaneously develop TSHomas via phosphatidylinositol 3-kinase signaling activation [34].

Tumorous thyrotropes express somatostatin receptor type 2 and 5 (SST2 and SST5), this expression explaining the antisecretory and antiproliferative effects exerted by somatostatin analogs in patients with TSHoma [35]. Though no mutations affecting somatostatin receptor genes have been identified, LOH and polymorphisms at the somatostatin receptor type 5 gene locus seem to be associated with an aggressive phenotype and resistance to medical treatment [36].

Clinical Features

Patients with TSHomas present signs and symptoms of hyperthyroidism frequently associated with the consequences of tumor compression on the surrounding anatomical structures (i.e., visual field defects, loss of vision, headache, and partial or complete hypopituitarism) (Table 8.1). In this respect, while the occurrence of bilateral exophthalmos may be the consequence of a coexistent autoimmune thyroiditis, unilateral exophthalmos may represent the consequence of orbital invasion by pituitary tumor [2, 37, 38]. In many cases, patients are diagnosed after a long history of thyroid dysfunction (diagnosed as Graves' disease or toxic multinodular goiter), and about 30% of them underwent inappropriate surgical or radiometabolic thyroid ablation [2, 39, 40] that may negatively affect tumor behavior, invasive macroadenomas being found in half of patients who had undergone thyroid ablation [2]. Interestingly, Macchia et al. observed a mean estimated latency of 39 months

Table 8.1 Clinical features in patients with TSHoma

Clinical features	
Female/male ratio	1.4
Previous thyroidectomy	30%
Severe thyrotoxicosis	15%
Goiter	90%
Thyroid nodule(s)	58%
Macroadenomas	70%
Visual field defects	30%
Headache	18%
Menstrual disorders	35%
Galactorrhea	25%
Acromegaly	17%

between first symptom appearance and diagnosis of TSHoma, this latency being significantly shorter in the case of macroadenomas (mean, 24 vs 50 months) [41].

In general, clinical features of hyperthyroidism are milder than expected on the basis of circulating thyroid hormone levels [42, 43]. Though severe thyrotoxic features (e.g., atrial fibrillation, cardiac failure) are observed in 25% of cases, some patients with untreated TSHoma may be clinically asymptomatic, thus suggesting that tumorous thyrotropes may secrete TSH molecules with a reduced biological activity [44]. The presence of these clinically "silent" TSHomas makes mandatory the systematic measurement of both TSH and FT4 in all patients with pituitary tumor, this approach being useful also to rule out the presence of a central hypothyroidism in non-TSH-secreting pituitary tumors.

It is worth noting that in patients bearing pituitary tumors cosecreting TSH and other pituitary hormones, hyperthyroidism may be missed. This is the case of GH cosecretion that leads to the appearance of acromegaly symptoms that overshadow those related to TSH hypersecretion [2, 40]. Disorders of the gonadal axis are frequently seen not only in patients with mixed TSH/PRL or mixed TSH/FSH adenomas but also in 30% of patients with pure TSHoma [2].

Goiter is observed in more than 90% of patients, and the presence of multinodular goiter has been reported in several patients. Progression toward functional autonomy seems to be infrequent [45], and circulating antithyroid autoantibodies are found in 8% of patients, this figure being similar to that found in the general population. However, Graves' hyperthyroidism may coexist with TSHoma in some patients [46].

The presence of differentiated thyroid carcinoma (DTC) has been reported [2, 47, 48]. In a recently published series of 62 TSHomas, DTC incidence of 4.8% has been reported as possibly related to the chronic TSH hypersecretion [48]. However, it has been demonstrated that the outcome of patients with the coexistence of TSHoma and DTC is in general favorable despite the presence of non-suppressible TSH [47]. Finally, though all these data suggest the opportunity to perform a high-resolution ultrasound of the thyroid in all patients with TSHoma [48], no consensus regarding the management of patients with DTC and TSHoma has been so far agreed. It remains to be demonstrated that an aggressive management of these patients might result in a more favorable outcome (i.e., the complete removal of the tumor followed by radioablation and attempts to reduce serum TSH to the lowest tolerable level).

The diagnosis of TSHoma may be delayed in patients in whom hypothyroidism is coexistent with the pituitary tumor [2, 48–50]. In these patients, an autonomous TSH hypersecretion should be suspected when TSH does not adequately normalize/suppress during LT4 replacement therapy.

Diagnostic Work-Up

Elevated levels of circulating thyroid hormones in the presence of detectable TSH concentrations are the biochemical characteristics of central hyperthyroidism. Diagnosis of central hyperthyroidism should be suspected in patients who have

undergone thyroid ablation in whom high/normal TSH levels are found in the presence of high FT4 and FT3 levels during L-T4 treatment [2].

It is necessary to exclude all those factors (i.e., abnormalities in the pituitary-thyroid axis, laboratory artifacts, or drugs) that may lead to wrongly diagnose a condition of central hyperthyroidism. In this respect, inhibition of T4 to T3 conversion induced by iodine-containing drugs (e.g., povidone, amiodarone, iodinated contrast media) or nonthyroidal illness may induce the presence of high FT4 levels with detectable TSH that are, however, associated with normal or low-normal T3. Some laboratory artifacts can give spuriously high hormone levels and possibly simulate the biochemical characteristics of central hyperthyroidism. This is the case of heterophilic antibodies directed against mouse gamma globulins or anti-TSH antibodies. The presence of anti-T4 or anti-T3 autoantibodies or both as well as the familial *dysalbuminemic hyperthyroxinemia* (a condition characterized by abnormal circulating albumin with increased T4 affinity) may cause FT4 and/or FT3 overestimation, particularly when "one-step" analog methods are used [2, 51].

In TSHomas, extremely variable levels of serum TSH and thyroid hormones have been reported, and no difference in basal values of TSH and free thyroid hormone levels was seen between patients with TSHoma and those with RTH [1, 2]. Interestingly, any significant correlation between immunoreactive TSH and free thyroid hormone levels has been observed in patients with TSHoma, as demonstrated by the observation that in 30% of them, high levels of free thyroid hormones are associated with immunoreactive TSH levels within the normal range. In this respect, it has hypothesized that adenomatous thyrotropes secrete TSH molecules with peculiar glycosylation and biologic properties [44, 52, 53].

An unbalanced excess of circulating free α-GSU levels and elevated α-GSU/TSH molar ratio are detected in patients with TSHoma [2, 54], a ratio greater than 1.0 being possibly indicative of the presence of TSHoma provided that appropriate control groups matched for TSH and gonadotropin levels are considered. Interestingly, normal α-GSU levels and α-GSU/TSH molar ratio are observed in the majority of microadenomas [6], this finding demonstrating a possible relationship between the size of the tumor and its secretory activity. Furthermore, it has been suggested that a spontaneous and marked decrease in both TSH and α subunit might indicate that the tumor is becoming less differentiated and might correlate with invasive and metastatic behavior [10].

The degree of tissue hyperthyroidism may be evaluated by measuring several parameters of peripheral thyroid hormone action [2]. Sex hormone-binding globulin (SHBG) , cholesterol, angiotensin-converting enzyme, osteocalcin, red blood cell sodium content, and carboxyterminal cross-linked telopeptide of type I collagen (ICTP) have been proposed, SHBG and ICTP being those more frequently used in differentiating patients with TSHoma from those with RTH [55, 56]. In fact, as it occurs in all forms of hyperthyroidism, patients with TSHoma have high ICTP and SHBG levels, while they are into the normal range in patients with central hyperthyroidism due to RTH [1, 2].

Though several stimulatory and inhibitory tests have been proposed to confirm the diagnosis of TSHoma, none of them has a clear-cut diagnostic value. Recently,

the guideline for the diagnosis of TSHoma endorsed by the European Thyroid Association suggests that both stimulatory and inhibitory tests (i.e., TSH stimulation test and T3 suppression test) should be used in the differential diagnosis of central hyperthyroidism [54]. Patients with TSHoma are characterized by a blunted/absent TSH increase after TRH stimulation test (200 μg bolus intravenously, sampling at 0, 20, 60, 90, and 120 min) and fail to completely suppress TSH following T3 suppression test (80–100 μg/day divided in three administrations for 10 days, sampling at 0, 5 and, 10 days). T3 suppression is considered as the most specific and sensitive test to be used when a TSHoma is suspected in previously thyroidectomized patients [2, 6].

High-resolution computed tomography (CT) and nuclear magnetic resonance imaging (MRI) are used to visualize a TSHoma. Though microadenomas are now reported with increasing frequency (up to 30%), 70% of TSHomas are diagnosed with frequent suprasellar extension or sphenoidal sinus invasion [2]. However, ectopic tumors in the pharyngeal region have been reported [21, 23]. In these cases, pituitary scintigraphy with radiolabeled octreotide (octreoscan) has been shown to successfully localize TSHomas [2, 58].

The coexistence of high thyroid hormones levels and measurable circulating TSH is sufficient to rule out the diagnosis of Graves' disease, uni- or multinodular toxic goiter or activating mutations of TSH receptor. Once the presence of methodological interferences is excluded [2, 51, 57], it is mandatory to exclude a possible RTH (Table 8.2). The presence of neurological signs and symptoms (e.g., visual defects and headache) or clinical features of concomitant hyper- or hyposecretion of other pituitary hormones are characteristically seen in patients with TSHoma. Furthermore, an alteration of the pituitary gland at MRI or CT scan strongly sup-

Table 8.2 Parameters useful in differentiating patients with TSH-secreting pituitary adenomas (TSHomas) from those with resistance to thyroid hormones (RTH) [3]

Parameter	Significant differences	
Serum TSH mU/L	No	
High α-GSU levels	Yes	(in TSHomas)
High α-GSU/TSH m.r.	Yes	(in TSHomas)
Serum FT4 pmol/L	No	
Serum FT3 pmol/L	No	
Serum SHBG nmol/L	Yes	(in TSHomas)
Serum ICTP μg/L	Yes	(in TSHomas)
Abnormal TSH response to T3 suppression[a,b]	No	
Blunted TSH response to TRH test	Yes	(in TSHomas)

α-GSU, pituitary glycoprotein hormone alpha-subunit; SHBG, sex hormone-binding globulin; ICTP, carboxyterminal cross-linked telopeptide of type I collagen

[a]T3 suppression test, i.e., Werner's test (80–100 μg T3 for 8–10 days). Complete inhibition of both basal and TRH-stimulated TSH levels has never been recorded in either group of patients

[b]Although abnormal in quantitative terms, TSH response to T3 suppression test was qualitatively normal in the majority of RTH patients

ports the diagnosis of TSHoma. In this respect, it is worth noting that a nonfunctioning pituitary incidentaloma may be found in a patient with RTH, thus suggesting that pituitary imaging should be performed only when all clinical and biochemical finding point to the presence of TSHomas [57]. Elevated α-GSU concentrations or high α-GSU/TSH molar ratio, high circulating levels of parameters of peripheral thyroid hormone action (SHBG, ICTP), and TSH unresponsiveness to TRH stimulation or to T_3 suppression tests are characteristically associated with the presence of a TSHoma [1, 2, 57]. Since familial cases of TSHomas have not been documented, the finding of a similar biochemical profile in relatives points to the presence of RTH. Finally, an apparent association between TSHoma and RTH has been recently reported, and somatic mutations in the thyroid hormone receptor have been found in some tumors [32, 33], thus the occurrence of TSHoma in patients with RTH should be carefully considered [59–61].

Treatment and Follow-Up

As recently stated by the European Thyroid Association guideline for the diagnosis and treatment of TSHomas, surgical removal of the adenoma remains the first-line therapy [57]. Though methimazole (or propylthiouracil) or somatostatin analogs (i.e., octreotide and lanreotide) along with propranolol could be administered to restore euthyroidism before surgery, it has been demonstrated that presurgical medical treatment seems not to significantly improve surgical outcome (63% vs 57%) [9]. Complete removal of the tumor is achieved in up to 80% of patients with microadenoma, whereas no more than 50–60% of patients with macroadenoma may be considered as cured after the surgical procedure [9, 40]. The reasons of surgical failure are the marked fibrosis frequently seen in TSHomas and the frequent extra- and parasellar extension of the tumor [5–9, 40, 62]. If surgery is contraindicated or declined, pituitary fractionated stereotaxic radiotherapy or radiosurgery might be considered. The therapeutic dose is suggested to be between 45 and 55 Gy administered by conventional fractionated radiotherapy or 10–25 Gy if radiosurgery is used. Available studies do not show any significant difference between conventional fractionated radiotherapy and radiosurgery [9]. Recently, Malchiodi et al. demonstrated that radiotherapy was effective in controlling hormone hypersecretion in 37% of patients within 2 years, 32% of patients developing new pituitary deficiencies from 18 to 96 months from treatment [9]. In summary, while thyroid hormone level normalization and apparent complete removal of tumor mass are achieved by surgery alone or combined with radiotherapy in one third of patients, thyroid hormone normalization without complete removal of the adenoma is demonstrated in a third of patients, thus indicating that about 60–70% of TSHomas are controlled with surgery, irradiation, or both.

Tumorous thyrotropes express somatostatin receptor subtypes 1, 2A, 3, and 5, and it has been demonstrated that long-acting somatostatin analogs (i.e., octreotide

LAR® or lanreotide SR® or lanreotide Autogel®) are highly effective in reducing TSH secretion in patients with TSHomas [57]. Interestingly, FT4 and FT3 circulating level normalization is observed in up to 90% of cases, goiter size being significantly reduced in 30% of them [5–9, 54]. As demonstrated in patients with acromegaly, somatostatin analog treatment induces a significant tumor mass shrinkage in about 40% of patients [57]. Resistance to somatostatin analog treatment, tachyphylaxis (i.e., escape of TSH secretion from the inhibitory effects of the drug), or discontinuation of treatment due to side effects (e.g., nausea, abdominal discomfort, bloating, diarrhea, glucose intolerance, and cholelithiasis) was documented in a minority of cases. If somatostatin analogs are not tolerated, dopamine agonists (bromocriptine, cabergoline) can be used even though only partial TSH suppression is seen in most of cases [57].

Thyroidectomy is reserved to patients with goiter in whom pharmacotherapy or surgery of the pituitary lesion has failed; in these patients thyroid hormone replacement should be initiated at a dose which maintains the serum-free T4 concentration in the upper 50 percent of the normal range; in fact serum TSH cannot be used to monitor therapy, since it is not suppressible [57].

There are no well-established criteria to define as cured a TSHoma after transsphenoidal surgery [57]. However, some parameters can help to assess the efficacy of the treatment. Clinical remission of hyperthyroidism, disappearance of neurological symptoms, resolution of neuroradiological alterations, and normalization of thyroid hormones, TSH, or α-GSU/TSH molar ratio may reflect the cure of a TSHoma [57]. Interestingly, the presence of undetectable TSH levels 1 week after surgery seems to be a sign of a complete adenomectomy, provided that presurgical treatment with antithyroid drugs or daily somatostatin analog injections were stopped at least 10 days before surgery [63]. Since only patients in whom T3 administration completely inhibits basal and TRH-stimulated TSH secretion may be considered as cured, T3 suppression test remains the most sensitive and specific test to document the complete removal of the adenoma [57, 63].

The recurrence of the TSHomas does not appear to be a frequent event, at least in the first years after successful surgery [2, 9]. In general, the evaluation of the patient should include the measurement of TSH and circulating free thyroid hormones two or three times the first year and then every year. Pituitary imaging should be performed 4 months postoperatively and then every 2 or 3 years. In patients with persistent macroadenoma, a close follow-up of visual fields is required.

TSHoma patients should be evaluated clinically and biochemically two or three times the first year postoperatively and then every year. TSH and circulating free thyroid hormones should be measured. Pituitary imaging (MRI) should be performed 3–4 months after surgery, and then every 2 or 3 years, but should be promptly done in the presence of a sudden rise in THS and FT4/FT3 levels. In the case of persistent macroadenoma, a close follow-up of visual fields is required to ensure that visual function is not threatened [57].

Data on the recurrence rate of TSHoma in patients who are judged to be cured after surgery or radiotherapy are area scarce. In this respect, Malchiodi et al. recently observed a tumor or hormonal recurrence within the first 2 years after surgery [9].

TSHomas in Children and Adolescents

Only eight cases (four boys and four girls) of TSHomas in patients aged 15 and under (range 8–15 years) have been so far reported [61, 64–70]; presenting symptoms were mainly related to T4 and T3 excess (Table 8.3). Tumors were reported to be microadenomas in two cases and macroadenomas in five cases. All patients underwent surgical treatment and in one case patient was pre-treated with octreotide without any significant effect on TSH secretion. Interestingly, in one of these cases, the coexistence of TSHoma and RTH was demonstrated [61]. Finally, TSHoma was considered as cured in three patients only.

Summary

Patients with TSHoma present with high levels of circulating free thyroid hormones in the presence of normal/high concentrations of TSH. It is mandatory to check the results using different methods of measurement and to establish a close collaboration with the Institution laboratory to exclude any methodological interference in the measurement technique of both TSH and free thyroid hormones that may mimic the biochemical picture of TSHomas.

The clinical appearance of hyperthyroidism may be mild, sometimes overshadowed by signs and symptoms of concomitant acromegaly or by neurological symptoms (headache, visual field defect). It is mandatory to differentiate between a TSHoma and syndromes of thyroid hormone resistance by performing both TRH stimulation test and T3 suppression test to avoid unnecessary treatments.

Since the restoration of euthyroidism and the prevention of neurological symptoms due to the mass effect exerted by the tumor on surrounding structures are the

Table 8.3 Clinical presentation and outcome of pediatric patients with TSHoma

Sex	Age	Tumor size	Presenting symptoms	Medical treatment	Surgery	Cure	Refs.
M	11	Macro	Hyperthyroidism; intrachranial hypertension	No	Yes	No	[63]
M	15	Macro	NA	NA	NA	NA	[64]
M	13	Macro	School performance deterioration, behavioral changes and secondary enuresis	Yes	Yes	No	[65]
F	11	Macro	Hyperthyroidism; goiter	No	Yes	No	[66]
F	13	Micro	Poor weight gain and pubertal delay	No	Yes	Yes	[67]
F	15	NA	NA	NA	NA	NA	[68]
M	8	Macro	Emaciation and muscle weakness of the legs	No	Yes	Yes	[69]
F	12	Micro	Goiter, sinus tachycardia, and tremors	No	Yes	Yes	[70]

main objective of the treatment, the first-line approach to TSHomas remains the surgical removal of the adenoma. If surgery is contraindicated or declined, as well as in the case of surgical failure, long-acting somatostatin analog administration is indicated, octreotide or lanreotide being successful in most patients with TSHoma.

References

1. Gurnell M, Visser TJ, Beck-Peccoz P, Chatterjee VK. Resistance to thyroid hormone. In: Jameson JL, DeGroot LJ, editors. Endocrinology adult and pediatric. 7th ed. Philadelphia: Elsevier Saundres; 2016. p. 1648–65.
2. Beck-Peccoz P, Lania A, Persani L. TSH-producing adenomas. In: Jameson JL, DeGroot LJ, editors. Endocrinology adult and pediatric. 7th ed. Philadelphia: Elsevier Saundres; 2016. p. 266–74.
3. Roelfsema F, Pereira AM, Keenan DM, Veldhuis JD, Romijn JA. Thyrotropin secretion by thyrotropinomas is characterized by increased pulse frequency, delayed diurnal rhythm, enhanced basal secretion, spikiness, and disorderliness. J Clin Endocrinol Metab. 2008;93:4052–7.
4. Ónnestam L, Berinder K, Burman P, Dahlqvist P, Engström BE, Wahlberg J, Nyström HF. National incidence and prevalence of TSH-secreting pituitary adenomas in Sweden. J Clin Endocrinol Metab. 2013;98:626–35.
5. Socin HV, Chanson P, Delemer B, Tabarin A, Rohmer V, Mockel J, et al. The changing spectrum of TSH-secreting pituitary adenomas: diagnosis and management in 43 patients. Eur J Endocrinol. 2003;148:433–42.
6. Brucker-Davis F, Oldfield EH, Skarulis MC, Doppman JL, Weintraub B. Thyrotropin-secreting pituitary tumors: diagnostic criteria, thyroid hormone sensitivity, and treatment outcome in 25 patients followed at the National Institutes of Health. J Clin Endocrinol Metab. 1999;84:476–86.
7. Foppiani L, Ruelle A, Cavazzani P, Del Monte P. TSH-secreting adenomas: rare pituitary tumors with multifaceted clinical and biological features. J Endocrinol Investig. 2007;30:603–9.
8. Clarke MJ, Erickson D, Castro MR, Atkinson JLD. Thyroid-stimulating pituitary adenomas. J Neurosurg. 2008;109:17–22.
9. Malchiodi E, Profka E, Ferrante E, Sala E, Verrua E, Campi I, et al. Thyrotropin-secreting pituitary adenomas: outcome of pituitary surgery and irradiation. J Clin Endocrinol Metab. 2014;99:2069–76.
10. Mixson AJ, Friedman TC, Katz DA, Feuerstein IM, Taubenberger JK, Colandrea JM, et al. Thyrotropin-secreting pituitary carcinoma. J Clin Endocrinol Metab. 1993;76:529–33.
11. Brown RL, Muzzafar T, Wollman R, Weiss RE. A pituitary carcinoma secreting TSH and prolactin: a non-secreting adenoma gone awry. Eur J Endocrinol. 2006;154:639–43.
12. Lee W, Cheung AS, Freilich R. TSH-secreting pituitary carcinoma with intrathecal drop metastases. Clin Endocrinol. 2012;76(4):604–6.
13. Tritos NA, Eppakayala S, Swearingen B, Hedley-Whyte ET, Miller KK, et al. Pathologic and clinical features of pituitary adenomas showing TSH immunoreactivity. Pituitary. 2013;16:287–93.
14. Vargas G, Balcazar-Hernandez LJ, Melgar V, Magriña-Mercado RM, Gonzalez B, Baquera J, Mercado M. An FSH and TSH pituitary adenoma, presenting with precocious puberty and central hyperthyroidism. Endocrinol Diabetes Metab Case Rep. 2017;7:2017.
15. Pfäffle R, Klammt J. Pituitary transcription factors in the aetiology of combined pituitary hormone deficiency. Best Pract Res Clin Endocrinol Metab. 2011;25(1):43–60.
16. Bertholon-Grégoire M, Trouillas J, Guigard MP, Loras B, Tourniaire J. Mono- and plurihormonal thyrotropic pituitary adenomas: pathological, hormonal and clinical studies in 12 patients. Eur J Endocrinol. 1999;140:519–27.

17. Azzalin A, Appin CL, Schniederjan MJ, Constantin T, Ritchie JC, Veledar E, et al. Comprehensive evaluation of thyrotropinomas: single-center 20-year experience. Pituitary. 2016;19:183–93.
18. Webster J, Peters JR, John R, Smith J, Chan V, Hall R, Scanlon MF. Pituitary stone: two cases of densely calcified thyrotropin-secreting pituitary adenomas. Clin Endocrinol. 1994;40: 137–43.
19. Ezzat S, Horvath E, Kovacs K, Smyth HS, Singer W, Asa SL. Basic fibroblast growth factor expression by two prolactin and thyrotropin-producing pituitary adenomas. Endocr Pathol. 1995;6:125–34.
20. Thompson LD, Seethala RR, Muller S. Ectopic sphenoid sinus pituitary adenoma (ESSPA) with normal anterior pituitary gland: a clinicopathologic and immuno-phenotypic study of 32 cases with a comprehensive review of the english literature. Head Neck Pathol. 2012;6: 75–100.
21. Collie RB, Collie MJ. Extracranial thyroid-stimulating hormone-secreting ectopic pituitary adenoma of the nasopharynx. Otolaryngol Head Neck Surg. 2005;133:453–4.
22. Song M, Wang H, Song L, Tian H, Ge Q, Li J, et al. Ectopic TSH-secreting pituitary tumor: a case report and review of prior cases. BMC Cancer. 2014;14:544–7.
23. Wang Q, Lu XJ, Sun J, Wang J, Huang CY, Wu ZF. Ectopic suprasellar thyrotropin-secreting pituitary adenoma: case report and literature review. World Neurosurg. 2016;95:617.e13–8.
24. Ma W, Ikeda H, Watabe N, Kanno M, Yoshimoto T. A plurihormonal TSH-producing pituitary tumor of monoclonal origin in a patient with hypothyroidism. Horm Res. 2003;59:257–61.
25. Dong Q, Brucker-Davis F, Weintraub BD, Smallridge RC, Carr FE, Battey J, et al. Screening of candidate oncogenes in human thyrotroph tumors: absence of activating mutations of the Gαq, Gα11, Gαs, or thyrotropin-releasing hormone receptor genes. J Clin Endocrinol Metab. 1996;81:1134–40.
26. Pellegrini-Bouiller I, Morange-Ramos I, Barlier A, Gunz G, Enjalbert A, Jaquet P. Pit-1 gene expression in human pituitary adenomas. Horm Res. 1997;47(4–6):251–8.
27. Asteria C, Anagni M, Persani L, Beck-Peccoz P. Loss of heterozigosity of the MEN1 gene in a large series of TSH-secreting pituitary adenomas. J Endocrinol Investig. 2001;24:796–801.
28. Daly AF, Tichomirowa MA, Petrossians P, Heliövaara E, Jaffrain-Rea ML, Barlier A, et al. Clinical characteristics and therapeutic responses in patients with germ-line AIP mutations and pituitary adenomas: an international collaborative study. J Clin Endocrinol Metab. 2010;95:E373–83.
29. Sapkota S, Horiguchi K, Tosaka M, Yamada S, Yamada M. Whole-Exome Sequencing Study of Thyrotropin-Secreting Pituitary Adenomas. J Clin Endocrinol Metab. 2017;102(2): 566–75.
30. Gittoes NJ, McCabe CJ, Verhaeg J, Sheppard MC, Franklyn JA. An abnormality of thyroid hormone receptor expression may explain abnormal thyrotropin production in thyrotropin-secreting pituitary tumors. Thyroid. 1998;8:9–14.
31. Tagami T, Usui T, Shimatsu A, Beniko M, Yamamoto H, Moriyama K, Naruse M. Aberrant expression of thyroid hormone receptor beta isoform may cause inappropriate secretion of TSH in a TSH-secreting pituitary adenoma. J Clin Endocrinol Metab. 2011;96:E948–52.
32. Ando S, Sarlis NJ, Oldfield EH, Yen PM. Somatic mutation of TRbeta can cause a defect in negative regulation of TSH in a TSH-secreting pituitary tumor. J Clin Endocrinol Metab. 2001;86:5572–6.
33. Ando S, Sarlis NJ, Krishnan J, Feng X, Refetoff S, Zhang MQ, et al. Aberrant alternative splicing of thyroid hormone receptor in a TSH-secreting pituitary tumor is a mechanism for hormone resistance. Mol Endocrinol. 2001;15:1529–38.
34. Lu C, Willingham MC, Furuya F, Cheng SY. Activation of phosphatidylinositol 3-kinase signaling promotes aberrant pituitary growth in a mouse model of thyrois-stimulating hormone-secreting pituitary tumors. Endocrinology. 2008;149:3339–45.
35. Horiguchi K, Yamada M, Umezawa R, Satoh T, Hashimoto K, Tosaka M, et al. Somatostatin receptor subtypes mRNA in TSH-secreting pituitary adenomas: a case showing a dramatic reduction in tumor size during short octreotide treatment. Endocr J. 2007;54:371–8.

36. Filopanti M, Ballaré E, Lania AG, Bondioni S, Verga U, Locatelli M, et al. Loss of heterozygosity at the SS receptor type 5 locus in human GH- and TSH-secreting pituitary adenomas. J Endocrinol Investig. 2004;27:937–42.
37. Kourides IA, Pekonen F, Weintraub BD. Absence of thyroid-binding immunoglobulins in patients with thyrotropin-mediated hyperthyroidism. J Clin Endocrinol Metab. 1980;51: 272–4.
38. Yovos JG, Falko JM, O'Dorisio TM, Malarkey WB, Cataland S, Capen CC. Thyrotoxicosis and a thyrotropin-secreting pituitary tumor causing unilateral exophthalmos. J Clin Endocrinol Metab. 1981;53:338–43.
39. Varsseveld NC, Bisschop PH, Biermasz NR, Pereira AM, Fliers E, Drent ML. A long-term follow-up study of eighteen patients with thyrotrophin-secreting pituitary adenomas. Clin Endocrinol. 2014;80:395–402.
40. Yamada S, Fukuhara N, Horiguchi K, Yamaguchi-Okada M, Nishioka H, Takeshita A, et al. Clinicopathological characteristics and therapeutic outcomes in thyrotropin-secreting pituitary adenomas: a single-center study of 90 cases. J Neurosurg. 2014;121:1462–73.
41. Macchia E, Gasperi M, Lombardi M, et al. Clinical aspects and therapeutic outcome in thyrotropin-secreting pituitary adenomas: a single center experience. J Endocrinol Investig. 2009;32(9):773–9.
42. Lim EM, Bhagat CI, Walsh J. Asymptomatic thyrotropin-secreting pituitary microadenoma. Intern Med J. 2001;31:428–9.
43. Rabbiosi S, Peroni E, Tronconi GM, Chiumello G, Losa M, Weber G. Asymptomatic thyrotropin-secreting pituitary macroadenoma in a 13-year-old girl: successful first-line treatment with somatostatin analogs. Thyroid. 2012;22:1076–9.
44. Beck-Peccoz P, Persani L. Variable biological activity of thyroid-stimulating hormone. Eur J Endocrinol. 1994;131:331–40.
45. Abs R, Stevenaert A, Beckers A. Autonomously functioning thyroid nodules in a patient with a thyrotropin-secreting pituitary adenoma: possible cause-effect relationship. Eur J Endocrinol. 1994;131:355–8.
46. Kamoun M, d'Herbomez M, Lemaire C, Fayard A, Desailloud R, Huglo D, Wemeau JL. Coexistence of thyroid-stimulating hormone-secreting pituitary adenoma and Graves' hyperthyroidism. Eur Thyroid J. 2014;3:60–4.
47. Ünlütürk U, Sriphrapradang C, Erdoğan MF, Emral R, Güldiken S, Refetoff S, Güllü S. Management of differentiated thyroid cancer in the presence of resistance to thyroid hormone and TSH-secreting adenomas: a report of four cases and review of the literature. J Clin Endocrinol Metab. 2013;98:2210–7.
48. Perticone F, Pigliaru F, Mariotti S, Deiana L, Furlani L, Mortini P, Losa M. Is the incidence of differentiated thyroid cancer increased in patients with thyrotropin-secreting adenomas? Report of three cases from a large consecutive series. Thyroid. 2015;25(4):417–24.
49. Idiculla JM, Beckett G, Statham PF, Ironside JW, Atkin SL, Patrick AW. Autoimmune hypothyroidism coexisting with a pituitary adenoma secreting thyroid-stimulating hormone, prolactin and a-subunit. Ann Clin Biochem. 2001;38:566–71.
50. Losa M, Mortini P, Minelli R, Giovanelli M. Coexistence of TSH-secreting pituitary adenoma and autoimmune hypothyroidism. J Endocrinol Investig. 2006;29:555–9.
51. Koulouri O, Moran C, Halsall D, Chatterjee K, Gurnell M. Pitfalls in the measurement and interpretation of thyroid function tests. Best Pract Res Clin Endocrinol Metab. 2013;27: 745–62.
52. Gesundheit N, Petrick P, Nissim M, et al. Thyrotropin-secreting pituitary adenomas: Clinical and biochemical heterogeneity. Ann Intern Med. 1989;111:827.
53. Magner JA, Kane J. Binding of thyrotropin to lentil lectin is unchanged by thyrotropin-releasing hormone administration in three patients with thyrotropin-producing pituitary adenomas. Endocr Res. 1992;8:163.
54. Terzolo M, Orlandi F, Bassetti M, et al. Hyperthyroidism due to a pituitary adenoma composed of two different cell types, one secreting alpha-subunit alone and another cosecreting alpha-subunit and thyrotropin. J Clin Endocrinol Metab. 1991;72:415–21.

55. Beck-Peccoz P, Roncoroni R, Mariotti S, et al. Sex hormone-binding globulin measurement in patients with inappropriate secretion of thyrotropin (IST): evidence against selective pituitary thyroid hormone resistance in nonneoplastic IST. J Clin Endocrinol Metab. 1990;71:19–25.
56. Persani L, Preziati D, Matthews CH, Sartorio A, Chatterjee VK, Beck-Peccoz P. Serum levels of carboxyterminal cross-linked telopeptide of type I collagen (ICTP) in the differential diagnosis of the syndromes of inappropriate secretion of TSH. Clin Endocrinol. 1997;47:207–14.
57. Beck-Peccoz P, Lania A, Beckers A, Chatterjee K, Wemeau JL. European thyroid association guidelines for the diagnosis and treatment of thyrotropin-secreting pituitary tumors. Eur Thyroid J. 2013;2:76–82.
58. Losa M, Magnani P, Mortini P, Persani L, Acerno S, Giugni E, et al. Indium-111 pentetreotide single-photon emission tomography in patients with TSH-secreting pituitary adenomas: correlation with the effect of a single administration of octreotide on serum TSH levels. Eur J Nucl Med. 1997;24:728–31.
59. Watanabe K, Kameya T, Yamauchi A, et al. Thyrotropin-producing microadenoma associated with pituitary resistance to thyroid hormone. J Clin Endocrinol Metab. 1993;76:1025–30.
60. Safer JD, Colan SD, Fraser LM, Wondisford FE. A pituitary tumor in a patient with thyroid hormone resistance: a diagnostic dilemma. Thyroid. 2001;11:281–91.
61. Teng X, Jin T, Brent GA, Wu A, Teng W, Shan Z. A patient with a thyrotropin-secreting microadenoma and resistance to thyroid hormone (P453T). J Clin Endocrinol Metab. 2015;100:2511–4.
62. Elston MS, Conaglen JV. Clinical and biochemical characteristics of patients with thyroid-stimulating hormone-secreting pituitary adenomas from one New Zealand centre. Intern Med J. 2010;40(3):214–9.
63. Losa M, Giovanelli M, Persani L, Mortini P, Faglia G, Beck-Peccoz P. Criteria of cure and follow-up of central hyperthyroidism due to thyrotropin-secreting pituitary adenomas. J Clin Endocrinol Metab. 1996;81:3086–90.
64. Suntornlohanakul S, Vasiknanont P, Mo-Suwan L, Phuenpathom N, Chongchitnant N. TSH secreting pituitary adenoma in children: a case report. J Med Assoc Thail. 1990;73(3):175–8.
65. Stanley JM, Najjar SS. Hyperthyroidism secondary to a TSH-secreting pituitary adenoma in a 15-year-old male. Clin Pediatr (Phila). 1991;30(2):109–11.
66. Phillip M, Hershkovitz E, Kornmehl P, Cohen A, Leiberman E. Thyrotropin secreting pituitary adenoma associated with hypopituitarism and diabetes insipidus in an adolescent boy. J Pediatr Endocrinol Metab. 1995;8(1):47–50.
67. Avramides A, Karapiperis A, Triantafyllidou E, Vayas S, Moshidou A, Vyzantiadis A. TSH-secreting pituitary macroadenoma in an 11-year-old girl. Acta Paediatr. 1992;81(12):1058–60.
68. Korn EA, Gaich G, Brines M, Carpenter TO. Thyrotropin-secreting adenoma in an adolescent girl without increased serum thyrotropin-alpha. Horm Res. 1994;42(3):120–3.
69. Gannage MH, Maacaron C, Okais N, Halaby G. Thyroid-stimulating hormone hypophyseal adenoma. A case report. J Med Liban. 1997;45(2):97–101.
70. Nakayama Y, Jinguji S, Kumakura S, et al. Thyroid-stimulating hormone (thyrotropin)-secretion pituitary adenoma in an 8-year-old boy: case report. Pituitary. 2012;15(1):110–5.