TSH-oma

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8.1 Introduction

Thyrotropin (TSH)-secreting pituitary tumor (TSH-oma) is a rare disease. The excess of TSH secretion from tumoral cells, which are unresponsive to the negative feedback of thyroid hormones, leads to hyperstimulation of the thyroid with consequent hypersecretion of T4 and T3 [1–3]. Thus, TSH-omas can be classified as a form of "central hyperthyroidism."

In 1960, the first case of TSH-oma was documented by measuring serum TSH levels with a bioassay [4], and 10 years later, another case was proved by a RIA assay of TSH [5].

TSH-omas were typically diagnosed at the stage of invasive macroadenoma and were considered difficult to cure, but nowadays they are more often diagnosed at an earlier stage. Indeed, in the last years the routine use of ultrasensitive immunometric assays for TSH as first-line test of thyroid function has allowed to detect

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hyperthyroid patients with unsuppressed TSH secretion in the presence of high free thyroid hormone, improving the diagnostic workup. The recent introduction of the so-called TSH with reflex free T4 strategy (i.e., FT4 measurement only in the presence of abnormal TSH) fails to recognize both central hypo- and hyperthyroidism, thus leading to TSH-omas misdiagnosis.

Thyroid function tests that value characteristic of TSH-oma patients are also recorded in patients with resistance to thyroid hormones (RTHs), and signs and symptoms of hyperthyroidism are frequently found in the so-called pituitary RTH (PRTH), characterized by a more severe resistance to thyroid hormone action at the pituitary level than at the peripheral tissue level [6–8].

These rare entities represent a diagnostic and therapeutic challenge, because failure in distinguishing between the two disorders may result in improper treatment, while the correct identification of a TSH-oma may prevent the occurrence of both neurological and endocrinological complications, thus leading to a better cure rate.

8.2 Epidemiology

TSH-oma is a very rare disorder; it accounts for about 0.5–2% of all pituitary tumors. The prevalence in the general population is 1–2 cases per million [1, 3]. However, an increase in the number of reported cases was registered in the last decade, confirmed by data obtained from the Swedish Pituitary Registry [9]. This recent study demonstrated an increasing incidence of TSH-omas over time, with a national prevalence of 2.8 per one million inhabitants in 2010. The increased incidence of TSH-omas is principally due to a reasonable catch up effect resulting from improved diagnostic tools. The introduction of the ultrasensitive TSH assays in the late 1980s, which detects low TSH, allowed a distinction between primary hyperthyroidism (Graves' disease) and syndrome of inappropriate TSH secretion [1, 3, 6, 8].

TSH-omas has been reported at ages ranging from 8 to 84 years [3, 10, 11], with a peak of onset in the fifth/sixth decade of life. In contrast with other more common thyroid disorders, TSH-omas occur with equal frequency in men and women and occur mainly as sporadic forms; nevertheless, familial cases can be part of multiple endocrine neoplasia type 1 (MEN1) syndrome [12] and familial isolated pituitary adenoma (FIPA) with AIP mutation [13].

8.3 Pathogenesis

TSH-omas can be classified in functional and silent tumors. Classically, TSH-omas present with elevated thyroid hormones and elevated or inappropriately normal TSH levels. Patients with TSH-secreting adenomas present signs and symptoms of hyperthyroidism, whereas silent thyrotropinomas are positive for β-TSH by immunohistochemistry without clinical or biochemical evidence of central hyperthyroidism [14, 15].

The presence of TSH beta subunit, either free or combined, has been confirmed in all tumor cells from every type of thyrotropinoma by immunostaining studies, with few exceptions [1, 3, 16–18].

In 70% of the cases, thyrotropinomas secrete TSH only, often accompanied by unbalanced hypersecretion of alpha-subunit of glycoprotein hormones (alpha-GSU) (Table 8.1). Interestingly, by double gold particle immunostaining, the existence of thyrotropinoma composed of two different cell types, one secreting alpha-GSU alone and another cosecreting alpha-GSU and the entire TSH molecules (mixed TSH/alpha-GSU tumors), has been documented [17]. In particular, the presence of a mixed TSH/alpha-GSU adenoma is suggested by the finding of an extremely high alpha-GSU/TSH molar ratio and/or by the observation of dissociated alpha-GSU and TSH responses to TRH [1, 19].

The remaining 30% of cases are classically considered mixed tumors since they cosecrete TSH and other anterior pituitary hormones (GH, PRL, and LH/FSH) (Table 8.1). In this regard, hypersecretion of GH and/or PRL is the most frequently found, possibly leading to acromegaly and/or amenorrhea/galactorrhea syndrome. The occurrence of these mixed tumors may rely on the expression of common transcription factors, such as Prop-1 and Pit-1, by thyrotroph, somatotroph, and lactotroph cells. On the contrary, no association with ACTH hypersecretion has been documented so far, probably due to the distant origin of corticotroph and thyrotroph lineages. Rare is the occurrence of mixed TSH/FSH/LH tumors [20].

It has to be taken into account that silent TSH-secreting tumors may give positive immunohistochemical results for one or more pituitary hormones without a

Table 8.1 Recorded cases of different types of TSH-secreting tumors

	Number of cases	% of total
Total TSH-secreting tumors	470	---
Pure TSH--secreting tumors	332	70.6
TSH-secreting tumors associated with other pituitary hormones hypersecretion (mixed tumors)	138	29.4
Mixed TSH/GH-secreting tumors	83	17.7
Mixed TSH/PRL-secreting tumors	47	10.0
Mixed TSH/FSH/LH-secreting tumors	8	1.7

correlation with its or their hypersecretion in vivo [17, 21, 22]. In addition, the coexistence of TSH-secreting tumors with Hashimoto's thyroiditis and hypothyroidism has been reported [2, 23].

When diagnosed, most thyrotropinomas have a diameter size >1 cm presenting invasive features in the surrounding structures (i.e., the dura mater and bone) with extrasellar extension in the supra- and/or parasellar direction found in the majority of cases [1, 16, 17, 18, 24, 25]. Interestingly, patients with intact thyroid display a significantly lower occurrence of invasive tumors with respect to those who underwent previous thyroid ablation by surgery or radioiodine [1, 3]. In these cases, the reduction in circulating thyroid hormone levels due to thyroid ablation may be the cause of feedback mechanism alterations, thus supporting tumor growth. Thyrotropinomas with a diameter <1 cm were usually found in less than 15% of the cases [25], but their prevalence is progressively increasing thanks to improved testing of thyroid function and awareness among endocrinologists. Indeed, 30% of thyrotropinomas have been found with a diameter <1 cm in the series recently published [7, 26].

As for majority of pituitary lesions, the molecular mechanisms leading to the formation of thyrotropinoma are not fully understood. TSH-secreting tumors are usually characterized by a very fibrous consistency [27]. This observation has been linked to enhanced basic fibroblast growth factor (bFGF) blood levels and specific transcript in the tissues removed from two patients with invasive mixed PRL/TSH-secreting tumors and displaying by marked fibrosis [28]. This finding suggests a possible autocrine role for bFGF in tumor development. According to X-chromosomal inactivation analysis, thyrotropinomas derive from the clonal expansion of a single cell initially transformed cell as most pituitary tumors [29]. The hypothesis of a transforming event favoring gain of cell proliferation followed by secondary mutations or alterations leading to tumor progression is supposed to be applicable to TSH-omas. Mutations of proto-oncogenes (Rb, MEN1), either oncogenes (Ras, protein kinase C, G-protein subunits, TRH receptor) or pituitary-specific genes, able to confer growth advantage to pituitary cells, have been screened extensively. However, to date, no mutations in these candidate genes have been found. In particular, none of the thyrotropinomas screened presented activating mutations of genes encoding for G-protein subunits, such as αs, αq, α11, or αi2 [30]. On the contrary, GH-secreting tumors frequently present mutations in the oncogene *gsp*. Similarly, no mutations in the gene encoding for TRH receptor have been found in 9 and 3 thyrotropinomas, respectively [30, 31]. Since the transcription factor Pit-1 is a key regulator of cell differentiation and in PRL, GH, and thyrotropin gene expression, Pit-1 gene has been screened for mutations in 14 thyrotropinomas but found to be wild type [1]. However, Pit-1 resulted to be overexpressed in thyrotropinomas, similarly to what observed in GH-omas, although the biological meaning of this finding remains to be clarified [18, 20, 32].

Another candidate gene investigated is located on 11q13 and named MEN1. The MEN1 gene, encoding for menin, is linked to the multiple endocrine neoplasia type 1 (MEN1). About 3–30% sporadic pituitary tumors show loss of heterozygosity (LOH) at 11q13, which has been associated with the transition from the noninvasive

to the invasive phenotype. LOH on 11q13 has been found in 3 out 13 thyrotropinomas tested, but no MEN1 mutations were found [33]. Interestingly, hyperthyroidism due to thyrotropinomas has been reported in five cases within a familial setting of MEN1 syndrome [12].

As far as the loss of tumor suppressor genes is concerned, no loss of p53 was found in one thyrotropinoma studied, and analysis on retinoblastoma gene (Rb) is still lacking in thyrotropinomas. Mutations in the aryl hydrocarbon receptor-interacting protein (AIP) are involved in sporadic pituitary tumors, to note that AIP mutations were found in two patients with TSH-omas [13, 34].

Interestingly, recent whole-exome sequencing analysis is allowed to identify several candidate somatic mutations and variation in copy numbers in 12 sporadic TSH-secreting tumors [35]. Further studies in combination with epigenetic and transcriptomic approaches are needed to reveal the potential of such genetic lesions.

Thyroid hormone receptors (TRs) have been proposed as a potential candidate oncogenes and alterations in the feedback control mechanisms, as factors involved in the thyrotropinomas pathogenesis have been evaluated. Somatic mutations of thyroid hormone receptor beta (TRb) and aberrant alternative splicing of TRb2 mRNA encoding a TRb variant lacking T3-binding activity have been associated with impaired negative feedback on TSH secretion in some thyrotropinomas [36]. An aberrant expression of a thyroid hormone receptor β isoform (TRβ4) may partly cause the inappropriate secretion of TSH in thyrotropinomas [37].

In vitro studies on primary cultures from TSH-secreting tumors showed that these tumors express a large number of functioning receptors [3], although TSH response to TRH is usually lacking in vivo. Similarly, almost all TSH-omas express somatostatin receptors (SSTR) at variable ratio. Higher SSTR expression levels have been found in mixed GH/TSH-secreting tumor [38–40]. The inhibitory response to somatostatin analogs appears to be correctly mediated by SSTR in these tumors with resulted decrease in TSH secretion by neoplastic thyrotrophs [41–44]. Specific polymorphisms and LOH at the somatostatin receptor type 5 (SSTR5) gene locus seem to be associated with an aggressive phenotype and pharmacological resistance to somatostatin analogs, possibly because of absent somatostatin-induced inhibition of thyrotropin secretion [45]. In addition, the presence of dopamine receptors on the tumor thyrotrophs was the rationale for therapeutic trials with dopaminergic agonists, such as bromocriptine [38, 46, 47], with several studies showing a wide heterogeneity of TSH responses to dopaminergic agents, either in primary cultures or in vivo [48–50]. To date, no mutations in dopamine type 2 receptor (DRD2) have been found in TSH-omas [30, 31] and the effects of these inhibitory agents should be re-evaluated in light of the demonstration of the possible occurrence of SSTR5 and DRD2 heterodimerization [51].

Finally, the transformation of a TSH-oma into a carcinoma is an extremely rare event [52–54]. However, very high circulating levels of free alpha-subunit may be predictable of a progression toward a malignant behavior. Moreover, spontaneous and strong decrease in both TSH and alpha-GSU serum concentrations might indicate that the tumor is becoming less differentiated and correlates with invasive and metastatic features. In this regard, it has to be mentioned that, in a mouse model of

TSH-secreting tumor, the activation of phosphatidylinositol 3-kinase pathway favored pituitary growth that may induce transformation of the benign tumor into a carcinoma [55].

8.4 Clinical Presentation

Patients with TSH-omas usually present signs and symptoms of hyperthyroidism (Fig. 8.1). Many patients had been mistakenly diagnosed as having primary hyperthyroidism (Graves' disease), and about one third had inappropriate thyroidectomy and/or radioiodine treatment prior to the correct diagnosis. However, a true coexistence of Graves' disease and TSH-oma has been reported in a few cases [56, 57] and several untreated patients with TSH-oma were described as clinically euthyroid [11, 58]. The prevalence of circulating antithyroid autoantibodies (antithyroglobulin: Tg-Ab, and antithyroid peroxidase: TPO-Ab) is similar to that found in the general population, but some patients develop Graves' disease after pituitary surgery and few others present bilateral exophthalmos due to autoimmune thyroiditis [3, 59, 60] or unilateral exophthalmos due to orbital invasion by the pituitary tumor. It is worth

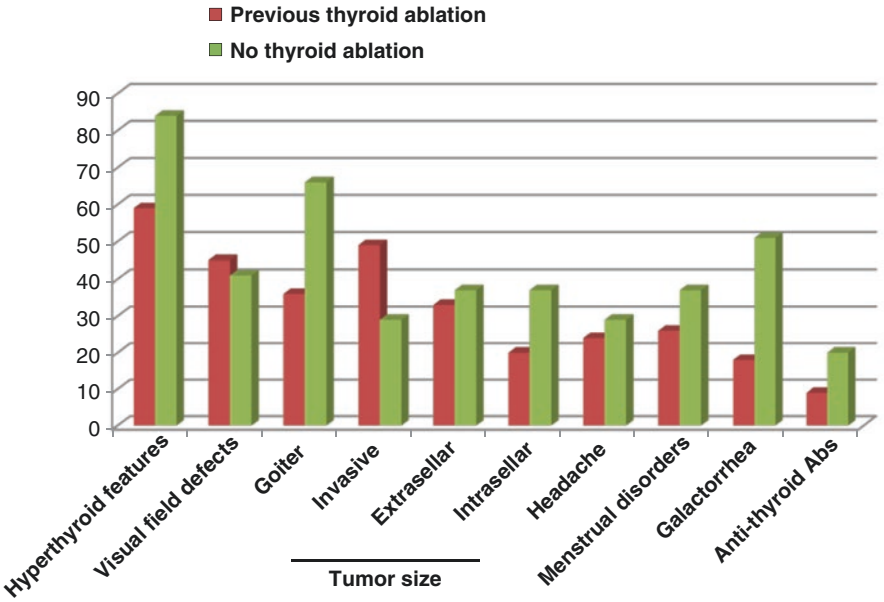

Fig. 8.1 Clinical manifestations in patients with TSH-omas. Based on previous thyroid ablation, patients have been divided into two groups. Patients usually present signs and symptoms of hyperthyroidism. As other pituitary adenomas, TSH-omas present clinical features caused by mass pressure effects. Invasive tumors are seen in about half of the patients with previous thyroidectomy and in 1/4 of untreated patients. TSH strong stimulation causes uni- or multi-nodular goiter. The prevalence of circulating antithyroid autoantibodies (Abs) is similar to that found in the general population (modified from Beck-Peccoz et al., Endotext, 2019)

noting that patients with mixed TSH/GH adenomas may have hyperthyroid features overshadowed by those of acromegaly [61–64]. This underlines the importance of TSH and FT4 systematic measurement in patients with pituitary tumors.

In about 72% of cases, the TSH strong stimulation causes uni- or multi-nodular goiter; however, the progression toward functional autonomy seems to be rare [3, 65].

Moreover, in sporadic cases cardiotoxicosis with atrial fibrillation and cardiac failure have been reported [66–70]. Two patients with typical episodes of periodic paralysis [71, 72] or a high prevalence of radiological vertebral fracture [73] have also been described.

Other symptoms can be tachycardia, tremors, heat intolerance, asthenia, and irritability.

As other pituitary adenomas, TSH-omas may present clinical features caused by mass pressure effects. The tendency to the invasiveness and the frequent over-sellar extension found in these adenomas increase the probability that the clinical symptomatology linked to the mass effect is manifest. Typical features that may occur are as follows:

1. Alterations in the visual field in about 50% of patients, due to the compression of the optic chiasm and the possible subsequent involvement of the optic nerve [74].
2. Ophthalmoplegia or diplopia due to compression of the cranial nerves at the level of cavernous sinus.
3. Hydrocephalus due to compression of the third ventricle and occlusion of foramen of Monroe.
4. Clear rhinorrhea due to erosion of the sellar floor with infiltration in the sphenoid sinus.

Furthermore, in 20–25% of patients frontal headache, continuous and resistant to analgesics can appear, caused by the distension of the sellar diaphragm that can be more rarely associated with other symptoms and signs of intracranial hypertension such as vomiting and edema of the papilla caused by the expanding intracranial mass.

Additionally, the compressive effect of adenomatous cells on surrounding adeno-pituitary cells can result in hypopituitarism in 25% of patients. The different sensitivity of adeno-pituitary cells to the compression effect establishes the progressive order according to which the secretory deficit occurs: first the GH-secreting cells, then the gonadotropin-secreting cells, then the TSH-secreting ones, and finally the corticotropic ones. Instead, the compression of the hypothalamic–pituitary peduncle is a cause of both the pseudo-hyperprolactinemia that is the consequence of dopamine-mediated inhibition on prolactin secretion and the diabetes insipidus due to the interruption of the axonic flow that carries the neurohypophysial hormones. Besides, dysfunction of the gonadal axis with menstrual disorders has been described mainly in mixed TSH/PRL adenomas and central hypogonadism, delayed puberty, and decreased libido in a number of male patients with TSH-oma and/or TSH/FSH adenomas [1, 49, 75, 67].

Finally, a recent publication has evidenced an estimated incidence of 4.8% of differentiated thyroid cancer (DTC) in patients who underwent surgery for TSH-oma, suggesting a possible role of TSH hypersecretion in the development of thyroid tumors [76].

8.5 Diagnosis

Patients harboring TSH-oma present with signs and symptoms of hyperthyroidism that usually are milder than expected owing to the levels of circulating FT4 and FT3, probably due to the long duration of the disease. From a biochemical point of view, the confirmed presence of elevated serum FT4/FT3 and measurable TSH levels (Fig. 8.2) is sufficient to exclude Graves' disease or other causes of primary hyperthyroidism. It is worth mentioning that a measurable TSH associated with high FT4/FT3 levels during levothyroxine replacement therapy may be caused by poor compliance or to the administration of levo-T4 (L-T4) before blood sampling.

A correct diagnosis of thyrotropinoma allows to avoid dramatic consequences, such as improper thyroid ablation (thyroidectomy or radioiodine) that may cause the pituitary tumor volume further expand. Since clinical features of hyperthyroidism can be overshadowed by those of acromegaly in case of mixed thyrotropin/GH-secreting tumors, systematic measurement of thyrotropin and FT4 is recommended in patients who have pituitary tumor.

Measurements of different parameters are proposed as quantifying the degree of tissue hyperthyroidism [2]. An unbalanced hypersecretion of circulating free α-GSU levels and elevated α-GSU/thyrotropin molar ratio (Table 8.1) is found in 80% of patients who have thyrotropinomas [3]. Accordingly to recently published data, such α-GSU hypersecretion is a phenomenon correlated with progressive tumor volume increase [16, 17, 20] since serum α-GSU levels are almost always normal in microadenomas.

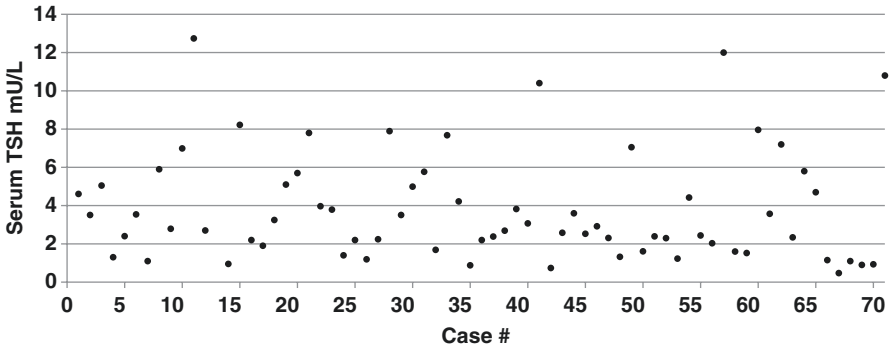

Fig. 8.2 Baseline serum TSH levels in TSH-omas from our case series. The biochemical hallmarks of TSH-omas are high serum free T3 and T4 concentrations while, as shown in the figure, TSH may be inappropriately normal or high

8.5.1 Dynamic Tests

TRH test and T3 suppression are recommended for the diagnosis of thyrotropinoma, although none of them is of clear-cut diagnostic value. Thus, the combination of both stimulatory and inhibitory tests increases the specificity and sensitivity of the diagnostic workup [3, 17, 20].

Classically, the T3 suppression test has been used to evaluate the presence of thyrotropinomas. The failure of a complete inhibition of TSH secretion after T3 suppression test (80–100 mg per day per 8–10 days) is typical of patients with thyrotropinoma (see Table 8.1). T3 suppression test is the most sensitive and specific test, particularly in patients who have had previous thyroid ablation [2, 77], whereas is contraindicated in elderly patients and in those with coronary heart disease.

As far as stimulatory tests are concerned, TRH injection (200 μg i.v.) does not increase either TSH or α-GSU levels in up to 85% of patients with thyrotropinoma [2]. Thus, this test has been used widely in the workup of thyrotropinomas. The finding of a discrepant response to TRH between thyrotropin and α-GSU (or GH in the case of acromegaly), however, is pathognomonic of pituitary tumors cosecreting thyrotropin and other hormones (Fig. 8.2) [16]. Interestingly, the administration of native somatostatin or its analogs (i.e., octreotide or lanreotide) induces a decrease in circulating TSH levels in normal and in the majority of the tumoral thyrotrophs [35, 36, 38, 53, 56, 65, 72], and this inhibitory response may predict the efficacy of long-term treatment with somatostatin analogs [78].

8.5.2 Differential Diagnosis

Primary hyperthyroidism in a hyperthyroid patient is ruled out by the presence of detectable TSH levels. However, in patients on L-T4 replacement for primary hypothyroidism, poor compliance is by far the most common cause of apparent inappropriate secretion of TSH (TSH still too high for the levels of the thyroid hormones). This underscores the importance of studying patients in steady state [79]. Inadequate measurement of TSH and peripheral thyroid hormones should always be taken into consideration. This may occur, for example, in medical therapy with amiodarone [79].

It is crucial to exclude the presence of methodological interferences due to the presence of circulating autoantibodies (e.g., against T3 and T4) or heterophilic antibodies (e.g., for TSH) that may give falsely elevated serum levels of thyrotropin or free thyroid hormones (i.e., rule out the presence of primary hyperthyroidism and the various forms of euthyroid hyperthyroxinemia) [2].

A thyrotropinoma must be suspected in the presence of neurologic signs and symptoms such as visual defects (25% of patients), headache (20%), and hypopituitarism (50%), all these being possible expressions of a tumor expansion [3, 17, 20]. Moreover, alteration of hypothalamic–pituitary–gonadal axis is frequent in case of pituitary tumors, with menstrual disorders present in all patients who have mixed thyrotropin/PRL tumors and in one third of those who have pure thyrotropinomas.

Delayed puberty, central hypogonadism, and decreased libido are also found in men with thyrotropinomas or mixed thyrotropin/FSH tumors.

Once the diagnosis of central hyperthyroidism is confirmed, additional diagnostic steps have to be performed to differentiate thyrotropinoma from RTH, in particular PRTH [2, 3, 7, 16, 17, 78, 80] (Table 8.2). Liver (sex hormone-binding globulin [SHBG]) and bone (carboxyterminal cross-linked telopeptide of type I collagen [ICTP]) parameters are successfully used to differentiate hyperthyroid patients who have thyrotropinoma from those who have PRTH. Higher serum SHBG and ICTP levels are common in patients with thyrotropinoma, whereas they are in the normal range in patients who have RTH. No statistically significant differences in terms of sex, age, TSH levels, or free thyroid hormone concentrations have been observed between patients with thyrotropinoma and those with RTH [2]. As far as dynamic tests are concerned, typically TSH-omas do not respond to TRH stimulation and/or to T3 suppression tests. Moreover, elevated α-GSU concentrations or high α-GSU/thyrotropin molar ratio and thyrotropin unresponsiveness to TRH stimulation or to T3 suppression tests, or both, favor the presence of a thyrotropinoma.

Another parameter that can be useful for the differential diagnosis is the evaluation of the sensitivity to long-acting somatostatin analogs [81]. More than 90% of

Table 8.2 Differential diagnosis between TSH-oma and PRTH

Parameter	TSH-omas	PRTH	*P*
F/M	1.3	1.4	NS
Familial cases (%)	0	85	<0.0001
Thyrotropin mU/L	2.7 ± 0.6	2.1 ± 0.3	NS
FT4 pmol/L	40.0 ± 4.2	30.5 ± 2.6	NS
FT3 pmol/L	14.5 ± 1.4	12.7 ± 1.2	NS
SHBG nmol/L[a]	113 ± 17	60 ± 5	<0.0001
Presence of lesion at CT scan or MRI (%)	98	5	<0.0001
High α-GSU levels (%)	65	3	<0.0001
High α-GSU/thyrotropin m.r. (%)	81	2	<0.0001
Abnormal thyrotropin response to T3 suppression test (%)[b]	100	100	NS
Blunted thyrotropin response to TRH test (%)	94	4	<0.0001

TSH-oma are sensitive, and two or more administrations of analog are usually sufficient to induce significant decreases or normalization of circulating free thyroid hormone. These modifications have never been observed in PRTH patients (Table 8.2). Finally, TRβ gene analysis may be useful in the differential diagnosis, as genomic TRβ mutations have been detected in patients with RTH only [7].

8.5.3 Imaging Studies and Localization of the Tumor

Nuclear MRI currently represents the imaging strategy of choice for the visualization of a thyrotropinoma. High-resolution CT is the alternative approach in case MRI is contraindicated (e.g., in the presence of a pacemaker). Although the diagnosis of TSH-oma is strongly supported by the presence of a pituitary lesion at neuroradiological imaging, a pituitary lesion has been identified at MRI in about 20% of RTH, indicating that a pituitary incidentaloma and RTH may coexist [82]. The differential diagnosis with PRTH may be problematic when the pituitary adenoma is small in size or in the case of confusing lesions, such as empty sella, pituitary incidentalomas, or ectopic tumors [81]. Pituitary scintigraphy with radiolabeled octreotide (Octreoscan) has been used to detect thyrotropinomas expressing somatostatin receptors [83]. Although the specificity of this procedure is low, it has been useful in the recognition of nasopharyngeal mass in few patients with clinical and biochemical features of central hyperthyroidism [84, 85].

8.6 Management

As recommended by the guidelines published by the European Thyroid Association [80], the first-line therapy for TSH-omas is surgical resection by transsphenoidal or subfrontal adenomectomy, the choice of the route depending on the tumor volume, and its suprasellar extension and invasiveness. This procedure aims to removing neoplastic tissue and normalizing normal pituitary/thyroid function. The operation may be difficult as the tumor may present a marked fibrosis, possibly related to high expression of basic fibroblast growth factor [28], and local invasion involving the cavernous sinus, internal carotid artery, or optic chiasm. Particular attention has to be paid to presurgical preparation of the patient, particularly in the preanesthetic period [86]: Antithyroid drugs along with propranolol should be used aiming at restoration of euthyroidism. Presurgical treatment with somatostatin analogs (octreotide LAR, lanreotide autogel) might be effective in reducing TSH-oma size and normalizing circulating thyroid hormones levels [87]. It should be noted that this approach may cause TSH secretion from normal thyrotropes to be re-activated, leading to the loss of a useful parameter to evaluate the complete removal of the adenoma, which is undetectable TSH levels few days after successful surgery. Neurosurgical intervention may cause a partial or complete hypopituitarism. However, a case of thyroid storm after pituitary surgery was reported [88]. In case of failure of pituitary surgery and in the presence of life-threatening hyperthyroidism, total thyroidectomy or

thyroid ablation with radioiodine is indicated [89]. According to the largest published series, pituitary surgery is effective in restoring euthyroidism in 75–83% of patients with TSH-omas [61, 90].

When the patients decline surgery or in case of surgical failure, radiotherapy and/or medical treatment with somatostatin analogs should be considered [80].

In case of radiotherapy, the recommended dose is no less than 45 Gy fractionated at 2 Gy per day or 10–25 Gy in a single dose if a stereotactic gamma unit is available [80, 91]. This procedure manages in normalizing thyroid function in 37% of patients within 2–4 years [61].

Some patients require medical therapy in order to control hyperthyroidism, although earlier diagnosis has improved the surgical cure rate of TSH-omas. The medical treatment of TSH-omas is based on long-acting somatostatin analogs, such as octreotide or lanreotide [27, 41, 42, 80, 92–94]. Treatment with these analogs leads to a reduction in TSH and alpha-GSU secretion in almost all cases, with restoration of the euthyroid state in about 95% of patients. Somatostatin analogs are safe even though side effects, such as cholelithiasis and carbohydrate intolerance, may appear. They are safe even during pregnancy [26]. Octreotide treatment in pregnant women was reported to be effective in restoring euthyroidism in the mother and had no side effects on development and thyroid function of the fetuses [7, 26, 48]. Many papers suggest the use of somatostatin analogs as first-line therapy for patients with TSH-omas, particularly for invasive macroadenomas [95–98]. During somatostatin analog therapy, tumor shrinkage occurs in about 50% of patients and vision improvement is seen in 75% [61, 90, 99]. Very rapid shrinkage of the tumor has been described [100]. Dose should be tailored for each patient, depending on therapeutic response. Tolerance is usually very good, as gastrointestinal side effects are transient with long-acting analogs [38, 41, 42, 99, 101].

Resistance to somatostatin analogs treatment has been documented in a minority of cases. The presence of dopamine receptors in TSH-omas was the rationale for the use of dopaminergic agonists, such as bromocriptine and cabergoline. A heterogeneity of TSH responses to these drugs has been described with the best effects achieved in mixed PRL/TSH tumors [69, 102, 103].

8.7 Follow-Up

Few data on TSH-oma recurrence in patients considered cured after surgery or radiotherapy have been reported so far. However, recurrence of the adenoma seems to be an infrequent event, at least in the first years after successful surgery [64, 104]. In general, postoperatively, the patient should be evaluated clinically and biochemically 2 or 3 times during the first year and then once a year. Pituitary imaging should be performed every 2 or 3 years, but should be promptly done whenever an increase in TSH and thyroid hormone levels, or clinical symptoms occur. In the case of a persistent macroadenoma, close visual field follow-up is required, since visual function could be threatened. Emergency surgical decompression is not always able to reverse even a recent visual deficit.

8.8 Prognosis

The criteria of cure of patients operated or irradiated for TSH-omas have not been clearly defined, due to the rarity of the disease and the great heterogeneity of the methods used. Some of these criteria are inapplicable if patients underwent previous thyroid ablation (Table 8.3).

A positive prognostic event is the absence of neurological signs and symptoms, but lacks both sensitivity and specificity, as even an incomplete debulking of the tumor may cause visual field defects and headache disappearance. It is logical that cured patients have clinical and biochemical reversal of thyroid hyperfunction after withdrawal from antithyroid medications. Nevertheless, the presence of normal free thyroid hormone concentrations or normalization of parameters peripheral thyroid hormone action (SHBG, ICTP, etc.) does not attest the complete removal or destruction of tumoral cells, since transient clinical remission accompanied by normalization of thyroid function is possible [32, 64, 104–106]. The criteria of normalization of circulating TSH are not applicable to previously thyroidectomized patients and to the 26% of patients with normal basal values of TSH. In our practice, undetectable TSH levels 1 week after surgery indicate complete adenomectomy, provided that the patient was hyperthyroid and presurgical treatments were stopped before surgery [64]. Normalization of alpha-GSU and/or the alpha-GSU/TSH molar ratio is in general a good index for the evaluation of therapy efficacy [16, 64]. However, both parameters are characterized by less than optimal sensitivity, as they are normal in about 25% of patients with TSH-oma. The most sensitive and specific test to document the complete removal of the adenoma, in the absence of contraindication, is

Table 8.3 Criteria for the evaluation of treatment outcome

Criteria	Comments
Remission from hyperthyroid manifestations (clinical and biochemical)	Clinical improvement may be transient *No predictive value*
Undetectable TSH 1 week after neurosurgery	Applicable to hyperthyroid patients that stopped treatments at least 10 days before surgery *Good prognostic value*
Normalization of circulating TSH levels	Not applicable to patients with normal TSH *Poor predictive value*
Normalization of free thyroid hormone levels	Biochemical remission may be transient *Poor predictive value*
Positive T3 suppression test with undetectable TSH and no response to TRH (or central hypothyroidism)	Not applicable to elderly patients or in those with cardiac diseases *Optimal sensitivity/specificity and predictive value*
Normalization of alpha-GSU levels and alpha-GSU/TSH molar ratio	Not applicable to patients with normal values before neurosurgery *Lack of sensitivity*
Disappearance of neurological manifestations (adenoma imaging, visual field defects, headache)	May be transient *Poor predictive value*

the T3 suppression test [64]: Only patients in whom T3 administration completely inhibits basal and TRH-stimulated TSH secretion can be defined as cured.

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