THYROTROPIN-SECRETING PITUITARY ADENOMAS

Paolo Beck-Peccoz, MD, Professor Emeritus, University of Milan, Via Pietro Custodi 16-20136 Milan, Italy (paolo.beckpeccoz@unimi.it)

Luca Persani, MD, PhD, Professor of Endocrinology, Department of Medical Biotechnologies and Translational Medicine, University of Milan, and San Luca Hospital, Istituto Auxologico Italiano, Piazzale Brescia 20, 20149-Milan, Italy

Andrea Lania, MD, PhD, Professor of Endocrinology, Department of Biomedical Sciences, Humanitas University, and IRCCS Humanitas Research Hospital, Via Manzoni 56-20089 Rozzano, Milan, Italy

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ABSTRACT

Thyrotropin-secreting pituitary tumors (TSH-omas) are a rare cause of hyperthyroidism and account for less than 1% of all pituitary adenomas. It is, however, noteworthy that the number of reported cases increased over the last few years because of the routine use of ultrasensitive immunometric assays for measuring TSH levels. Contrary to previous RIAs, ultrasensitive TSH assays allow a clear distinction between patients with suppressed and those with non-suppressed circulating TSH concentrations, i.e., between patients with primary hyperthyroidism (Graves' disease or toxic nodular goiter) and those with central hyperthyroidism (TSH-oma or pituitary resistance to thyroid hormone action, PRTH). Failure to recognize the presence of a TSH-oma may result in dramatic consequences, such as improper thyroid ablation that may cause the pituitary tumor volume to further expand. The presence of neurological signs and symptoms (visual defects, headache) or clinical features of concomitant hypersecretion of other pituitary hormones (acromegaly, galactorrhea/amenorrhea) strongly supports the diagnosis of TSH-oma. Nevertheless, the differential diagnosis between TSH-oma and PRTH may be difficult when the pituitary adenoma is very small, or in the case of confusing lesions, such as an empty sella or pituitary incidentalomas. First-line treatment of TSH-omas is pituitary adenomectomy followed by irradiation in the case of surgical failure. However, medical treatment with long-acting somatostatin analogues, such as octreotide and lanreotide, are effective in reducing TSH secretion in more than 90% of cases with consequent normalization of FT4 and FT3 levels and restoration of the euthyroid state.

INTRODUCTION

Thyrotropin (TSH)-secreting pituitary adenomas (TSH-omas) are a rare cause of hyperthyroidism. In this situation, TSH secretion is autonomous and refractory to the negative feedback of thyroid hormones (inappropriate TSH secretion) and TSH itself is responsible for the hyperstimulation of the thyroid gland and the consequent hypersecretion of T4 and T3 (1, 2). Therefore, this entity can be appropriately classified as a form of "central hyperthyroidism". The first case of TSH-oma was described in 1960 by measuring serum TSH levels with a bioassay (3). In 1970, Hamilton et al. (4) reported the first case of TSH-oma proved by measuring TSH by RIA.

Classically, TSH-omas were diagnosed at the stage of invasive macroadenoma and were considered difficult to cure. However, the advent of ultrasensitive

immunometric assays, routinely performed as first line test of thyroid function, has greatly improved the diagnostic workup of hyperthyroid patients, allowing the recognition of the cases with unsuppressed TSH secretion. Therefore, TSH-omas are now more often diagnosed at an earlier stage, before they become a macroadenoma, and an increased number of patients with normal or elevated TSH levels in the presence of high free thyroid hormone concentrations have been recognized. Signs and symptoms of hyperthyroidism along with values of thyroid function tests similar to those found in TSH-oma may be recorded also among patients affected with resistance to thyroid hormones (5-7). This form of resistance to thyroid hormones is called pituitary resistance to thyroid hormones (PRTH), as the resistance to thyroid hormone action appears more severe at the pituitary than at the peripheral tissue level. The clinical importance of these rare entities is based on the diagnostic and therapeutic challenges they present.

Failure to recognize these different diseases may result in dramatic consequences, such as improper thyroid ablation in patients with central hyperthyroidism or unnecessary pituitary surgery in those with PRTH. Conversely, early diagnosis and the correct treatment of TSH-omas may prevent the occurrence of neurological and endocrinological complications, such as visual defects by compression of the optic chiasm, headache, and hypopituitarism, and should improve the rate of cure.

EPIDEMIOLOGY

TSH-producing adenoma is a rare disorder, accounting for about 0.5% to 2% of all pituitary adenomas, the prevalence in the general population being 1 to 2 cases per million (1, 2, 8-69). However, this figure is probably underestimated as confirmed by data obtained from The Swedish Pituitary Registry (70), demonstrating an increased incidence of TSH-

omas over time (0.05 per 1 million per year in 1990-1994 to 0.26 per 1 million per year in 2005-2009), the national prevalence in 2010 being 2.8 per 1 million inhabitants. The increased number of reported cases principally results from the introduction of ultrasensitive TSH immunometric assays and from improved general practitioner and endocrinologist awareness. Based on the finding of measurable serum TSH levels in the presence of elevated FT4 and FT3 concentrations, many patients, previously thought to be affected with primary hyperthyroidism (Graves' disease on multinodular goiter), can nowadays be correctly diagnosed as patients with TSH-oma or, alternatively, with PRTH (1, 2, 5-7).

The presence of a TSH-oma has been reported at ages ranging from 8 to 84 years (2, 58, 58a,59), the mean age at diagnosis being 46 ± 6 years (59a). TSH-omas occur with equal frequency in men and women, in contrast with the female predominance seen in other thyroid disorders, a recent structured review of 535 adult cases of adult cases confirmed a female to male ratio of 1.07 (59a) Familial cases of TSH-oma have been reported as part of multiple endocrine neoplasia type 1 (MEN1) syndrome (10) and in familial isolated pituitary adenoma (FIPA) families with an *AIP* mutation (52).

PATHOLOGICAL ASPECTS

Immunostaining studies showed the presence of TSH beta subunit, either free or combined, in all adenomatous cells from every type of TSH-oma, with only few exceptions (1, 2, 8, 9, 71, 71a). Most TSH-secreting adenomas (72%) are secreting TSH alone, often accompanied by unbalanced hypersecretion of alpha-subunit of glycoprotein hormones (alpha-GSU) (Table 1). Interestingly, the existence of TSH-omas composed of two different cell types, one secreting alpha-GSU alone and another co-secreting alpha-GSU and the entire TSH molecules (mixed

TSH/alpha-GSU adenomas), was documented by using double gold particle immunostaining (72). 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 TSH and alpha-GSU responses to TRH (1, 72). Classic mixed adenomas characterized by concomitant hypersecretion of other anterior pituitary hormones are found in about 30% of patients.

| Table 1. Recorded Cases of TSH-Secreting Adenomas of Different Type		
	Number	% of total
Total TSH-secreting adenomas (TSH-omas)	598	---
Pure TSH-omas	450	75.2
TSH-omas with associated hypersecretion of other pituitary hormones (mixed TSH-omas)	148	24.8
Mixed TSH/GH-omas	90	15.1
Mixed TSH/PRL-omas	50	8.4
Mixed TSH/FSH/LH-omas	8	1.3

(Updated end May 2022 and personal unpublished observations)

Hypersecretion of GH and/or PRL, resulting in acromegaly and/or an amenorrhea/galactorrhea syndrome, are the most frequent associations (59a). This may be due to the fact that somatotroph and lactotroph cells share with thyrotropes common transcription factors, such as Prop-1 and Pit-1 (73). Rare is the occurrence of mixed TSH/gonadotropin adenoma, while no association with ACTH hypersecretion has been documented to date, probably due to the distant origin of corticotrope and thyrotrope lineages. Nonetheless, positive immunohistochemistry for one or more pituitary hormone does not necessarily correlate with its or their hypersecretion *in vivo* (9, 71, 74). Accordingly, clinically and biochemically silent thyrotropinomas have been reported (9, 75, 76). Moreover, true TSH-secreting tumors associated with Hashimoto's thyroiditis and hypothyroidism have been documented (2, 39, 77, 78). Finally, an isolated pituitary gangliocytoma producing TSH and TRH has been recently reported (78a).

Microadenomas, with a diameter <1 cm, were recorded in less than 15% of the cases before 1996 (22), but their prevalence among all the TSH-omas is progressively increasing due to improved testing of thyroid function and awareness among endocrinologists and general practitioners. Consistently, in the series recently published by our Institution (79), up to 30% of TSH-omas were microadenomas. In this view, a recent structured review of 533 cases of adult TSH-omas confirmed that 23.1% of them were microadenomas the remaining 76.9% being macroadenoma with a mean diameter of 21.5 ± 7.9 mm (59a). Most TSH-omas had been diagnosed at the stage of macroadenomas and showed localized or diffuse invasiveness into the surrounding structures, especially into the dura mater (1, 8, 15, 22, 71). Extrasellar extension in the supra- and/or parasellar direction were present in the majority of cases. The occurrence of invasive macroadenomas is particularly high among patients with previous

thyroid ablation by surgery or radioiodine (Figure 1) (2). This finding emphasizes the deleterious effects of incorrect diagnosis and treatment of these adenomas, and the relevant action on tumor growth exerted by the reduction of circulating thyroid hormone levels through an altered feedback mechanism. Such an aggressive transformation of the tumor resembles that occurring in Nelson's syndrome after adrenalectomy for Cushing's disease. Finally, some data suggest that

somatic mutations of the thyroid hormone receptor beta may be responsible for the defect in negative regulation of TSH secretion in some TSH-omas (56, 80-82). In addition, alteration in iodothyronine deiodinase enzyme expression and function may contribute to the resistance of tumor cells to the feedback mechanism of elevated thyroid hormone levels (83). However, these data were not confirmed by another study on this topic (84).
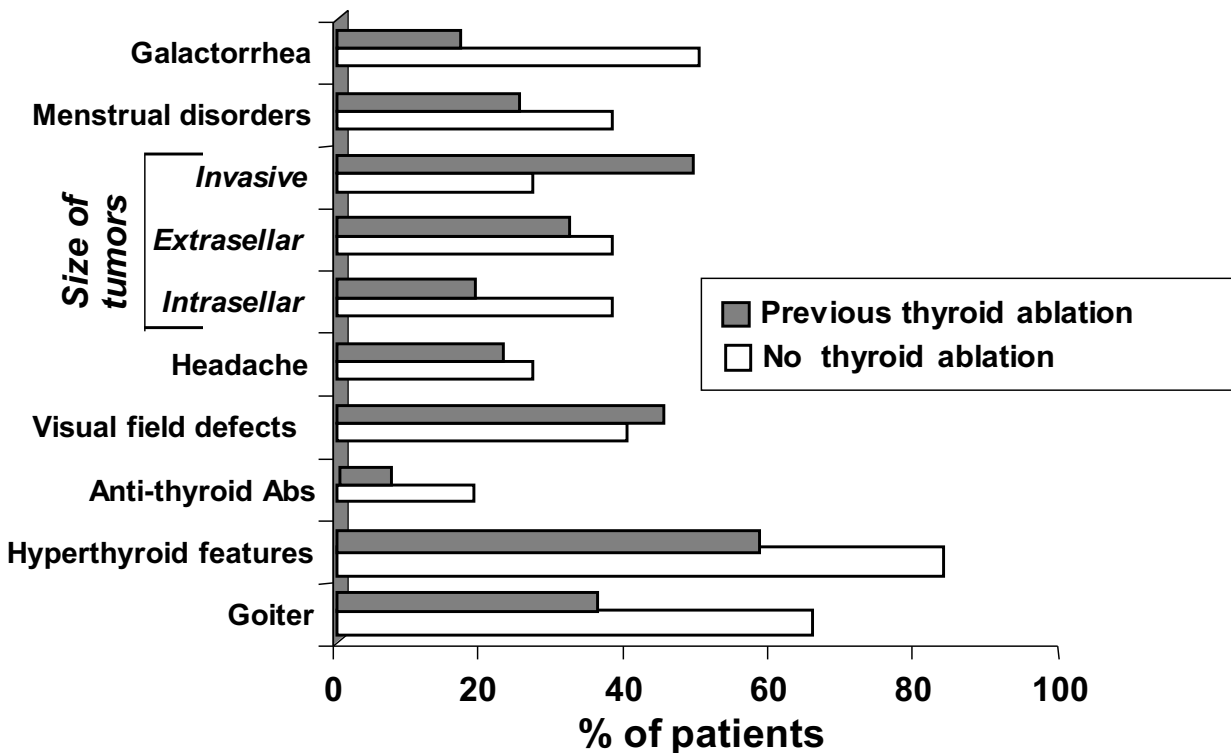
Figure 1. Clinical manifestations in patients with TSH-secreting adenomas. Patients have been divided into two categories according to previous thyroid surgery. The presence of goiter is the rule, even in patients with partial thyroidectomy. Hyperthyroid features may be overshadowed by those of associated hypersecretion/deficiency of other pituitary hormones. Invasive tumors are seen in about half of the patients with previous thyroidectomy and in 1/4 of untreated patients (P<0.01 by Fisher's exact test). Intrasellar tumors show an opposite distribution pattern.

The consistency of TSH-omas is usually very fibrous and sometimes so hard that they deserve the name of "pituitary stone" (85). Increased basic fibroblast growth factor (bFGF) levels were found in blood from

two patients with invasive mixed PRL/TSH-secreting adenomas characterized by marked fibrosis (86). The tumoral origin of bFGF was confirmed by the finding of specific transcript in the tissues removed at surgery,

suggesting a possible autocrine role for this growth factor in tumor development.

By light microscopy and appropriate staining, adenoma cells usually have a chromophobe appearance. Cells are often organized in cords, and they frequently appear polymorphous and characterized by large nuclei and prominent nucleoli. Ultrastructurally, the well differentiated adenomatous thyrotropes resemble the normal ones, while the poorly differentiated adenomas are composed of elongated angular cells with irregular nuclei, poorly developed RER, long cytoplasmic processes and sparse small secretory granules (50-200 nm) usually lining up along the cell membrane (9, 71). Generally, no exocytosis is detectable. Cells with abnormal morphology or mitoses are occasionally found which may be mistaken for a pituitary malignancy or metastases from distant carcinomas (87). Nevertheless, the transformation of a TSH-oma into a pituitary carcinoma with multiple metastases has seldom been reported (35, 59a, 60, 88). Future malignant behavior might be predicted by the finding of a concomitant, spontaneous and marked decrease of both TSH and alpha-GSU serum concentrations that might indicate that the tumor is becoming less differentiated. Finally, in a mouse model of TSH-oma, the activation of phosphatidyl-inositol 3-kinase promoted aberrant pituitary growth that may induce transformation of the adenoma into a carcinoma (89).

MOLECULAR AND *IN VITRO* SECRETION STUDIES

The molecular mechanisms leading to the formation of TSH-omas are presently unknown, as is true for the large majority of pituitary adenomas. X-chromosomal inactivation analysis demonstrated that most pituitary adenomas, including the small number of TSH-omas investigated, derive from the clonal expansion of a single initially transformed cell (43). Accordingly, the

general principles of tumorigenesis, which assume the presence of a transforming event providing gain of proliferative function followed by secondary mutations or alterations favoring tumor progression, presumably also apply to TSH-omas.

A large number of candidate genes, including common proto-oncogenes and tumor suppressor genes as well as pituitary specific genes, have been screened for mutations able to confer growth advantage to thyrotrope cells. In analogy with the other pituitary adenomas, no mutations in oncogenes commonly activated in human cancer, particularly *RAS*, have been reported in TSH-omas. In contrast, with GH-secreting adenomas in which the oncogene *gsp* (*GNAS* mutation) is frequently present, none of the TSH-oma screened has been shown to express activating mutations of genes encoding for G protein subunits, such as alpha s, alpha q, alpha 11 or alpha i2 (90). Similarly, no mutations in the TRH receptor or dopamine D2 receptor genes (90-91) have been reported in 9 and 3 TSH-omas, respectively, while these tumors were not screened for alterations in protein kinase C, previously identified in some invasive tumors. In consideration of the crucial role that the transcription factor Pit-1 exerts on cell differentiation and PRL, GH and TSH gene expression, the Pit-1 gene has been screened for mutations in 14 TSH-omas and found to be wild-type (2). By contrast, as occurs in GH-omas, Pit-1 was demonstrated to also be overexpressed in TSH-omas, although the proliferative potential of these findings remains to be elucidated (2, 71, 73).

In addition to activating mutations or overexpression of protooncogenes, tumors may originate from the loss of genes with antiproliferative action. As far as the loss of tumor suppressor genes is concerned, no loss of p53 was found in one TSH-oma studied, while the loss of retinoblastoma gene (Rb), which is unaltered in other pituitary adenomas, was not investigated in TSH-omas. Another candidate gene is *MEN1* coding

for menin. In fact, 3-30% of sporadic pituitary adenomas show loss of heterozygosity (LOH) on 11q13, where *MEN1* is located, and LOH on this chromosome seems to be associated with the transition from the non-invasive to the invasive phenotype. A screening study carried out on 13 TSH-omas using polymorphic markers on 11q13 showed LOH in 3, but none of them showed a *MEN1* mutation after sequence analysis (92). Interestingly, hyperthyroidism due to TSH-omas has been reported in five cases within a familial setting of multiple endocrine neoplasia type 1 syndrome (1, 2, 10). In addition, LOH and in particular polymorphisms at the somatostatin receptor type 5 gene locus, seem to be associated with an aggressive phenotype and resistance to somatostatin analogue treatment (93). Moreover, germline mutations in the aryl hydrocarbon receptor interacting protein (*AIP*) are known to be involved in sporadic pituitary tumorigenesis, but mutations were found in two patients with TSH-omas (52, 94). Finally, a recent study based on whole-exome sequencing identified several candidate somatic mutations and change in copy numbers in 12 sporadic TSH-omas, but with low number per tumor and without recurrence of mutations (95). A recent publication by Villa and others analyzing a series of secreting and non-secreting pituitary adenomas (including 6 TSH-omas) demonstrated a higher frequency of chromosomal alterations in TSH-omas, these alterations not being related to aggressiveness (95a). The same authors also demonstrated that POU1F1/PIT1-lineage tumors (including TSH-omas) were characterized by a global hypomethylation possibly inducing chromosomal alteration through the activation of transposable elements. Finally, transcriptosome analysis demonstrated that thyrotrope tumors cluster with sparsely granulated somatotroph adenomas and plurihormonal PIT1-positive adenomas, a group characterized by a higher high interferon-α and -γ gene expression (95a).

The extreme refractoriness of neoplastic thyrotropes to the inhibitory action of thyroid hormones indicates mutant forms of thyroid hormone receptors (TR) as other potential candidate oncogenes. Absence of TR alpha1, TR alpha2 and TR beta1 expression was reported in two TSH-omas (82, 96), but aberrant alternative splicing of thyroid hormone receptor beta2 (*THRB*) mRNA encoding TR beta variant lacking T3 binding activity and other *THRB* mutations were shown as a mechanism for impaired T3-dependent negative regulation of both TSH and alpha-GSU in tumoral tissue (80, 81). Moreover, an aberrant expression of a novel thyroid hormone receptor β isoform (TRβ4) may partly contribute to the inappropriate secretion of TSH in TSH-omas (56). Several patients with *THRB* mutation and an PRTH phenotype have been described to bear pituitary lesions at imaging of the sella region, raising diagnostic and therapeutic dilemmas (30, 97-99). The results of dynamic testing of TSH secretion were consistent with PRTH, rather than TSH-omas, indicating that these lesions are likely to be pituitary incidentalomas, whose prevalence in not selected autopsy series reaches 20%.

Pharmacological manipulations in short-term cultures of TSH-omas indicate that these tumors express a large number of functioning receptors. Although *in vivo* TSH response to TRH is usually absent, several *in vitro* studies showed either the presence or the absence of TSH response, indicating that the majority of tumors possess TRH receptors (2). Similarly, somatostatin binding experiments indicate that almost all TSH-omas express a variable number of somatostatin receptors, the highest somatostatin-binding site densities being found in mixed GH/TSH adenomas (57, 100, 101). Since somatostatin analogues are highly effective in reducing TSH secretion by neoplastic thyrotropes (12, 13, 102, 103), the inhibitory pathway mediated by somatostatin receptors appears to be largely intact in such adenomas. Consistently, there is a good correlation

between somatostatin binding capacity and maximal biological response, as quantified by inhibition of TSH secretion and *in vivo* restoration of euthyroid state (57, 102-104). The presence of dopamine receptors in TSH-omas was the rationale for therapeutic trials with dopaminergic agonists, such as bromocriptine (57, 105, 106). Several studies have shown a large heterogeneity of TSH responses to dopaminergic agents, either in primary cultures or *in vivo* (1, 41, 107, 108). The effects of these two inhibitory agents should be nowadays re-evaluated in light of the demonstration of the possible heterodimerization of somatostatin receptor subtype 5 (sst5) and dopamine D2 receptor (109).

CLINICAL FINDINGS

Patients with TSH-omas present with signs and symptoms of hyperthyroidism that are frequently associated with those related to the pressure effects of the pituitary adenomas, causing loss of vision, visual field defects, headache, and/or loss of anterior pituitary function (Figure 1) (22, 49, 63, 110). TSH-omas may occur at any age and, in contrast with the common thyroid disorders, there is no preferential incidence in females (2, 8, 22, 59, 59a). Due to the long history of thyroid dysfunction, many patients had been mistakenly diagnosed as having primary hyperthyroidism (Graves' disease or multinodular goiter), and about one third had inappropriate thyroid ablation by thyroidectomy and/or radioiodine. True coexistence of Graves' disease and TSH-oma has been reported in 14 cases (54, 111, 111a, 111b). The majority of these cases were females (aged between 25 and 53 years old) and the dual diagnosis was confirmed within 3 years from the original diagnosis in all cases. When Graves' disease is diagnosed initially, it has been speculated that antithyroid medications may promote the growth of a TSH-oma via the positive feedback system (111c).

Clinical features of hyperthyroidism are present in up to 75% of patients (59a), sometimes milder than expected given the level of thyroid hormones, probably due to their longstanding duration (112). Interestingly, only two cases of TSH-oma complicated with a thyroid storm peri- or post-operatively have been published (112a, 112b). Consistently, several untreated patients with TSH-oma were described as clinically euthyroid (59, 113). Moreover, hyperthyroid features can be overshadowed by those of acromegaly in patients with mixed TSH/GH adenomas (59a, 79, 114-118), thus emphasizing the importance of the systematic measurement of TSH and FT4 in patients with pituitary tumors. Acromegaly itself can often be associated with multinodular goiter, presenting a further possible differential diagnostic scenario.

Cardiotoxicosis with atrial fibrillation, cardiac failure, massive pleural and pericardial effusions have been reported in sporadic cases (119-123). Thyrotoxic heart failure and atrial fibrillation were found to be present in 11.1% of cases (59a). Typical episodes of periodic paralysis have also been described in two patients (20, 124). A high prevalence of radiological vertebral fracture has been recently documented in a series of patients with TSH-omas (125) thus confirming the deleterious effects of thyrotoxicosis on bone health.

The presence of a goiter is the rule, even in the patients with previous partial thyroidectomy, since thyroid residue may regrow as a consequence of TSH hyperstimulation. The occurrence of uni- or multinodular goiter is frequent (about 72% of reported cases), but progression towards functional autonomy seems to be rare (126, 127). The monitoring of the thyroid nodule(s) and the performance of fine needle aspiration biopsy are indicated in TSH-omas since differentiated thyroid carcinomas were documented in several patients (1, 11, 55, 59a, 128-131). A recent publication evaluating sixty-two patients who underwent surgery for TSH-oma demonstrated an

estimated incidence of thyroid carcinoma of 4.8%, thus suggesting a possible role of TSH hypersecretion in the development of thyroid tumors (130). The prevalence of circulating antithyroid autoantibodies (anti-thyroglobulin: Tg-Ab, and anti-thyroid peroxidase: TPO-Ab) is similar to that found in the general population, but some patients developed Graves' disease after pituitary surgery and a few others presented bilateral exophthalmos due to autoimmune thyroiditis (2, 55, 132), while unilateral exophthalmos due to orbital invasion by the pituitary tumor has also been reported (3, 133).

Dysfunction of the gonadal axis is not rare, with menstrual disorders present in one third of the reported cases, mainly in the mixed TSH/PRL adenomas. In this respect, a recent report described a case of a 37-year-old woman who had experienced galactorrhea and menstrual disorder and undergone infertility treatment in 1 year before TSH-oma was identified (133a). Central hypogonadism, delayed puberty, and decreased libido were also found in a number of males with TSH-omas and/or mixed TSH/FSH adenomas (1, 107, 134, 135).

Because of suprasellar extension or invasiveness, signs and symptoms of an expanding tumor mass are predominant in many patients. Partial or total hypopituitarism was seen in about 25% of cases, headache reported in 20-25% of patients, and visual field defects are present in about 50% of patients (Figure 1).

BIOCHEMICAL FINDINGS

High concentrations of circulating free thyroid hormones in the presence of detectable TSH levels characterize the hyperthyroidism secondary to TSH-secreting pituitary adenomas. In a review of 533 cases of TSH-omas it has been shown that the median TSH at diagnosis was 6.75 (4.02–11.90) mU/L in the case series and 5.16 (3.20–7.43) mU/L in the case reports whereas FT4 averaged 35.7 ± 8.5 and 41.5 ± 15.3 pmol/L, respectively (59a). Interestingly, normal levels of total T4 were recorded in several patients with TSH-omas despite the presence of clinical signs and symptoms of hyperthyroidism. This observation indicates that the measurement of circulating free thyroid hormones (FT4 and FT3) is mandatory. In fact, these measurements show the highest sensitivity for the correct diagnosis of central hyperthyroidism and prevent misclassification in the case of excess of circulating levels of thyroxine-binding globulin (26). Many different physiological or clinical conditions, such as pregnancy or PRTH, may present with hyperthyroxinemia and detectable serum TSH levels, and should be distinguished from TSH-omas. Most of these conditions may be recognized on the basis of either a patient's clinical history or by measuring the concentrations of FT4 and FT3 with direct "two-step" methods, i.e., the methods able to avoid possible interference due to the contact between serum factors and tracer at the time of the assay (e.g., equilibrium dialysis+RIA, adsorption chromatography+RIA, and back-titration) (136, 137). In fact, some factors may interfere with the measurement of either thyroid hormones or TSH. The presence of anti-iodothyronine autoantibodies (anti-T4 and/or anti-T3) or abnormal albumin/transthyretin forms, such as those circulating in familial dysalbuminemic hyperthyroxinemia, may cause FT4 and/or FT3 to be overestimated, particularly when "one-step" analog methods are employed (137, 138). The more common factors interfering in TSH measurement and giving spuriously high levels of TSH are the circulating heterophilic antibodies, i.e., antibodies directed against mouse gamma-globulins (36, 139).

About 30% of TSH-oma patients with an intact thyroid gland showed TSH levels within the normal range (2). In this respect, it is worth noting that TSH with "reflex FT4 strategy" (i.e., measurement of FT4 test only in the presence of an abnormal TSH result) fails to

recognize both central hypo and hyperthyroidism thus leading to TSH deficiency or TSH-oma misdiagnosis (140, 141). The diurnal rhythm is preserved in TSH-omas and TSH secretion shares many characteristics (cross-approximate entropy, cross-correlation and cosinor regression) of other pituitary hormone-secreting adenomas (142). Interestingly, a case of TSH-oma with cyclic fluctuations in serum TSH levels has recently been reported (143).

Furthermore, despite the TSH-dependent origin of hyperthyroidism, there is no direct correlation between free thyroid hormone and immunoreactive TSH levels (Figure 2). An increased biological activity of secreted TSH molecules likely accounts for the finding of normal TSH in the presence of high levels of FT4 and FT3 (114). TSH molecules secreted by pituitary tumors are heterogeneous and may have either a normal, reduced, or increased ratio between their biological and immunological activities, probably due to modification of glycosylation processes secondary to alterations of the post-translational processing of the hormone within the tumor cell (144, 145). Interestingly, TSH levels in patients previously treated with thyroid ablation were 6-fold higher than in untreated patients, though free thyroid hormone levels were still in the hyperthyroid range (115). Moreover, tumoral thyrotropes may undergo more active cellular proliferation in response to even small reductions in circulating thyroid hormone levels, as documented by the higher number of invasive macroadenomas found in previously treated patients (Figure 1), beyond the increase of TSH secretion.
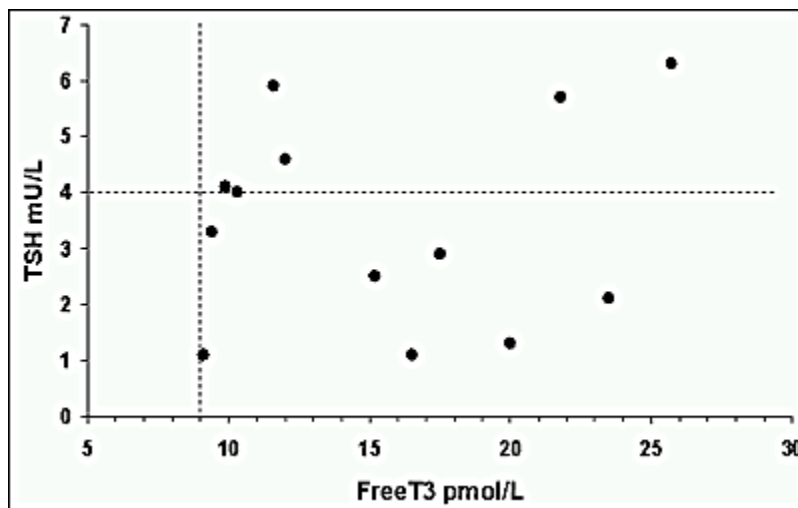
Figure 2. Absent correlation between immunoreactive concentrations of circulating TSH and FT3 in 14 patients with TSH-secreting adenomas. Dotted lines indicate the upper limits of normal ranges for both parameters.

Independently of previous thyroid ablation, circulating free alpha-GSU levels and alpha-GSU/TSH molar ratio were clearly elevated in the majority of patients with TSH-oma, either due to unbalanced secretion of the subunit or to the presence of a mixed TSH/alpha-GSU adenoma (72). The calculation of the alpha-GSU/TSH molar ratio increases the diagnostic sensitivity of hormone measurement, and an alpha-GSU/TSH molar ratio above 1.0 was associated with the presence of a TSH-secreting pituitary adenoma (2, 8). However, data from our group show that the individual values must be compared with those of control groups matched for TSH and gonadotropin levels before drawing any diagnostic conclusions.

Controls with normal levels of TSH and gonadotropins may have alpha-GSU/TSH molar ratios as high as 5.7, and values as high as 29.1 can be found in euthyroid postmenopausal women (146). Indeed, hypersecretion of alpha-GSU is not unique to TSH-omas, being present in the majority of true gonadotropinomas, in a subset of non-functioning pituitary adenomas, and in a number of GH- or PRL-secreting tumors. Moreover, high alpha-GSU levels may be observed in conditions other than pituitary adenomas, such as in patients with inflammatory bowel disease (e.g., ulcerative colitis, Crohn disease) or with other neuroendocrine tumors (e.g., carcinoids) (146).

PARAMETERS OF THYROID HORMONE ACTION

Patients with central hyperthyroidism may present with mild signs and symptoms of thyroid hormone overproduction. Therefore, the measurements of several parameters of peripheral thyroid hormone action have been proposed to quantify the degree of tissue hyperthyroidism (2, 5-8, 98). Some of them are measured *in vivo* (basal metabolic rate, cardiac systolic time intervals, "Achilles" reflex time) and others *in vitro* (sex hormone-binding globulin: SHBG, cholesterol, angiotensin converting enzyme, soluble interleukin-2 receptor, osteocalcin, carboxyterminal cross-linked telopeptide of type I collagen (ICTP), etc.). Liver (SHBG) and bone parameters (ICTP) have been successfully used to differentiate hyperthyroid patients with TSH-omas from those with pituitary RTH (Figure 3). In fact, as seen in the common forms of hyperthyroidism, patients with TSH-omas have high SHBG and ICTP levels, while they are in the normal range in patients with hyperthyroidism due to PRTH (147, 148).
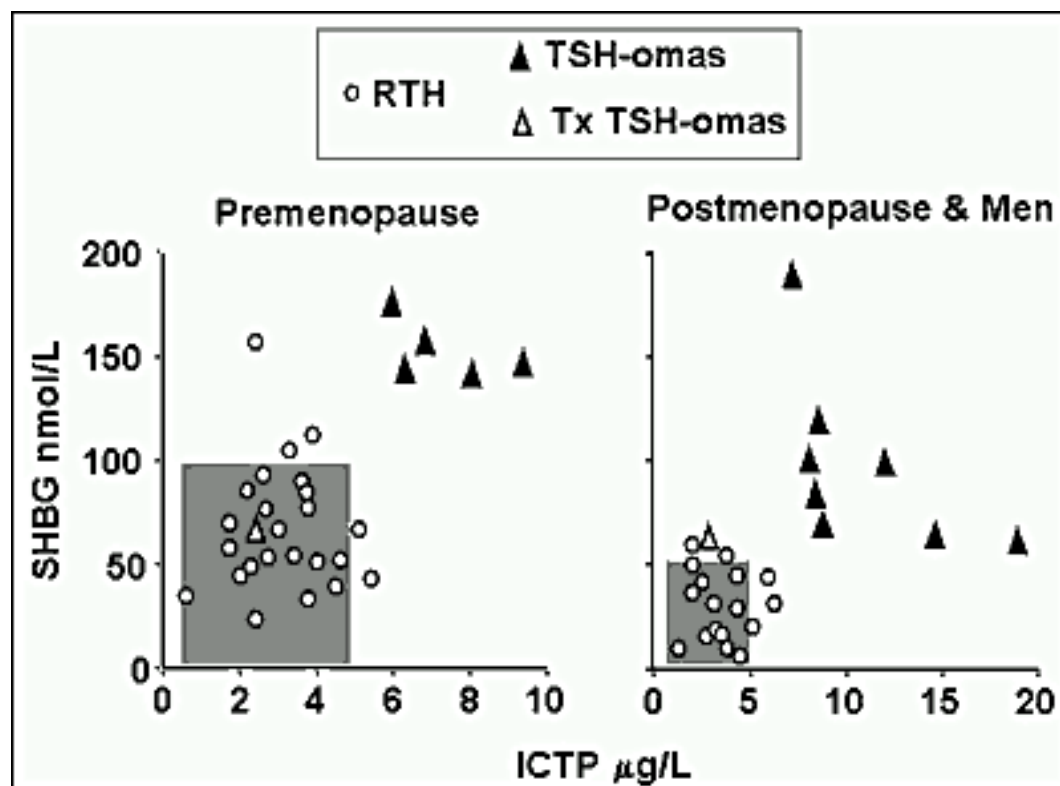
Figure 3. Values of sex hormone-binding globulin (SHBG) and carboxyterminal cross-linked telopeptide of type 1 collagen (ICTP) in patients with PRTH or TSH-omas. Shaded areas represent the normal ranges either in premenopausal women or in postmenopausal women and men. The combined measurement of parameters from different tissues may be useful for the differential diagnosis and by-pass possible interference by different factors (age, liver or bone diseases, combined alteration of pituitary functions, treatments, etc.). Tx TSH-omas, treated TSH-omas.

DYNAMIC TESTING

Although both stimulatory and inhibitory tests had been proposed for the diagnosis of TSH-omas, none of them is of clear-cut diagnostic value. Classically, T3 suppression test has been used to assess the presence of a TSH-oma. A complete inhibition of TSH secretion after T3 suppression test (80-100 mcg/day for 8-10 days) has never been recorded in patients with TSH-oma. T3 suppression test can be combined with TRH testing, where normal subjects and TSH-oma patients do not show elevation of TSH in response to TRH, while PRTH patients show a brisk elevation (1). In patients with previous thyroid ablation,

T3 suppression seems to be the most sensitive and specific test in assessing the presence of a TSH-oma (2, 8, 98). However, this test is strictly contraindicated in elderly patients or in those with coronary heart disease.

TRH testing has been widely used to investigate the presence of a TSH-oma. In the vast majority of patients, TSH and alpha-GSU levels do not increase after TRH injection. In patients with hyperthyroidism, discrepancies between TSH and alpha-GSU responses to TRH (i.e., higher alpha-GSU than TSH response) are pathognomonic of TSH-omas co-secreting other pituitary hormones. Such a discrepancy is also found in an opposite clinical

condition, i.e., the congenital hypothyroidism due to a TSH beta gene mutation (149).

The majority of TSH-omas maintain sensitivity to native somatostatin and its analogues. Indeed, administration of native neuropeptide or its analogues (octreotide or lanreotide) induces a reduction of TSH levels in the majority of cases, and these tests may be predictive of the efficacy of long-term treatment (30, 89, 102, 104). Recently, it has been confirmed that a positive somatostatin test result is suggestive for a TSH-oma even before positive findings become apparent on pituitary imaging (104a).

As suggested by ETA 2013 guidelines we recommend the use of both T3 suppression and TRH tests whenever possible, because the combination of their results increases the specificity and sensitivity of the diagnostic work-up (158).

IMAGING STUDIES AND LOCALIZATION OF THE TUMOR

As for other tumors of the region of the sella turcica, nuclear magnetic resonance imaging (MRI) is nowadays the preferred tool for the visualization of a TSH-oma. High-resolution computed tomography (CT) is the alternative investigation in the case of contraindications, such as patients with pacemakers. Most TSH-omas have been diagnosed in the past at the stage of macroadenomas, and various degrees of suprasellar extension or sphenoidal sinus invasion are seen in two thirds of cases.

Microadenomas are now reported with increasing frequency, accounting for about 20-30% of all recorded cases in both clinical and surgical series. Pituitary scintigraphy with radiolabeled octreotide (*Octreoscan*) has been shown to successfully localize TSH-omas that express somatostatin receptors (8, 150, 151). However, the specificity of the *Octreoscan*

is low, since positive scans can be seen in the case of a pituitary mass of different types, either secreting or non-secreting.

Finally, ectopic localization of a TSH-oma has been reported by different groups who found a nasopharyngeal mass in few patients with clinical and biochemical features of central hyperthyroidism (21, 32, 152-157a). Histological and immunohistochemical studies of both specimens collected during the operation showed unequivocally that the tumor was a TSH-oma, and the resection of the mass restored TSH and alpha-GSU levels to normal. Interestingly, in these cases either Octreoscan or Gallium 68 DOTATATE Positron Emission Tomography/Computed Tomography might be helpful in identifying an ectopic lesion (157a).

DIFFERENTIAL DIAGNOSIS

If FT4 and FT3 concentrations are elevated in the presence of measurable TSH levels, it is important to exclude methodological interference due to the presence of circulating autoantibodies (e.g., against T3 and T4) or heterophilic antibodies (e.g., for TSH). A recent publication by Campi and others indicated assay interference as the main source of error due to the widespread use of high-throughput platforms based on one-step assays that increased the frequency of assay artifact, due to interference from biotin, circulating heterophilic antibodies, or abnormal binding proteins (157b). In this respect, in an asymptomatic patient with elevated FT4/FT3 and detectable TSH levels, the so called Familial dysalbuminemic hyperthyroxinemia should be taken into account. FSH is a familial autosomal dominant condition caused by an abnormal albumin molecule with an increased affinity for serum thyroxine thus leading to a false increase of FT4 and FT3 while TSH levels are normal (138, 157c). In a patient with signs and symptoms of hyperthyroidism, the confirmed

presence of elevated FT4/FT3 and detectable TSH levels rules out Graves' disease or other forms of primary hyperthyroidism. In patients on levothyroxine replacement therapy, the finding of measurable TSH in the presence of high FT4/FT3 levels may be due to poor compliance or to an incorrect high L-T4 dosage, probably administered before blood sampling.

When the existence of central hyperthyroidism is confirmed, several diagnostic steps have to be carried out to differentiate a TSH-oma from PRTH (Table 2) (1, 5-8, 30, 97, 98, 158). The presence of neurological signs and symptoms (visual defects, headache) of an expanding intra-cranial mass or clinical feature of concomitant hypersecretion of other pituitary hormones (acromegaly, galactorrhea/amenorrhea) points to the presence of a TSH-oma. The presence of alterations of the pituitary content on MRI or CT scanning strongly supports the diagnosis of a TSH-oma. Nevertheless, the differential diagnosis may be difficult when the pituitary adenoma is very small, or in the case of confusing lesions, such as an empty sella. Moreover, the possibility of pituitary incidentalomas should always be considered, due to their high prevalence. In our series, about 20% of PRTH patients have a pituitary lesion on MRI.

No significant differences in age, sex, previous thyroid ablation, TSH levels or free thyroid hormone concentrations were seen between patients with TSH-oma and those with PRTH. However, in contrast to PRTH patients, familial cases of TSH-oma have never been documented. Serum TSH levels within the normal range are more frequently found in PRTH, while elevated alpha-GSU concentrations and/or a high alpha-GSU/TSH molar ratio are typically present in patients with TSH-omas. Moreover, TSH unresponsiveness to TRH stimulation and/or to T3 suppression tests favors the presence of a TSH-oma. We have shown that chronic administration of long-acting somatostatin analogues in patients with central hyperthyroidism caused a marked decrease of FT3 and FT4 levels in all patients but one with TSH-oma, while patients with PRTH did not respond at all (30). Thus, administration of long-acting somatostatin analogues for at least 2 months can be useful in the differential diagnosis in problematic cases of central hyperthyroidism (30, 157b) (Table 2).

Indexes of thyroid hormone action at the tissue level (such as SHBG or ICTP levels) are in the hyperthyroid range in most patients with TSH-oma, while they are generally normal/low in PRTH (Figure 3). Exceptions are the findings of normal SHBG levels in patients with mixed GH/TSH adenoma, due to the inhibitory action of GH on SHBG synthesis and secretion, and of high SHBG in PRTH patients treated with estrogens or showing profound hypogonadism. Genetic analysis of the TR beta gene may be useful in the differential diagnosis, as TR beta mutations in leukocyte DNA have been found only in patients with PRTH (Table 2).

Table 2. Differential Diagnosis Between TSH-Secreting Adenomas (TSH-omas) and Resistance to Thyroid Hormones (RTH).			
Parameter	TSH-omas	RTH	P
Female/Male ratio	1.3	1.4	NS
Familial cases	0 %	85 %	<0.0001
TSH mU/L	3.0 ±0.4	2.3 ±0.3	NS
FT4 pmol/L	38.8 ±3.9	29.9 ±2.3	NS
FT3 pmol/L	14.0 ±1.2	11.3 ±0.8	NS
Lesions at CT or MRI	99 %	23 %	<0.0001
Germline THRB mutation	0%	84%	<0.0001
High biological activity of circulating serum TSH	38%	90%	NS
High alpha-GSU levels	69 %	3 %	<0.0001
High alpha-GSU/TSH molar ratio	81 %	2 %	<0.0001
Elevated SHBG and/or ICTP	90%	8%	<0.0001
Blunted TSH response to TRH test (cutoff <3 mU/L in males and <5 mU/L in females)	87 %	2 %	<0.0001
Abnormal TSH response to T3 suppression[a]	100 %	100 % [b]	NS
FT4/FT3 reduction/normalization during long-acting somatostatin analog[c]	92%	0%	<0.0001

[a] Werner's test (80-100 µg T3 for 8-10 days). Quantitatively normal responses to T3, i.e., complete inhibition of both basal and TRH-stimulated TSH levels, have never been recorded in either group of patients.

[b] Although abnormal in quantitative terms, TSH response to T3 suppression test was qualitatively normal in 45/47 PRTH patients.

[c] Two or more injections of somatostatin analogues (e.g., Octreotide-LAR 20-30 mg every month or Lanreotide Autogel 120 mg every 6-8 weeks)

Only patients with intact thyroid were taken into account. Data are obtained from patients followed at our department and are expressed as mean ± SE.

TREATMENT AND OUTCOME

As stated in 2013 guideline by European Thyroid Association (158), surgical resection is the recommended therapy for TSH-secreting pituitary tumors, with the aim of removing neoplastic tissue and restoring normal pituitary/thyroid function. However, radical removal of large tumors, that still represent the majority of TSH-omas, is particularly difficult because of the marked fibrosis of these tumors and the local invasion involving the cavernous sinus, internal carotid artery, or optic chiasm. Considering this high invasiveness, surgical removal or debulking of the tumor by transsphenoidal or subfrontal adenomectomy, depending on the tumor volume and its suprasellar extension, should be undertaken as soon as possible (158a). According to the review of

535 cases of TSH-omas by De Herdt and others, surgical resection of the adenoma was performed in 87.7% of patients of which 33.5% had residual pituitary adenoma (59a). Particular attention has to be paid to presurgical preparation of the patient, particularly in the preanesthetic period (159): antithyroid drugs or octreotide along with propranolol should be used, aiming at restoration of euthyroidism. In patients with very severe hyperthyroidism, the administration of iopanoic acid may be successfully employed (25). Though the preoperative treatment with somatostatin analogues may be useful to reduce hyperthyroid signs and symptoms in a significant number of patients, as well as the adenoma size (160-161a), no correlations between FT4/FT3 normalization and a higher rate of remission has been demonstrated (68). However, a recent multicenter, single-arm, phase 3 study in Japan confirmed in a series of TSH-omas that preoperative lanreotide autogel treatment was effective in normalizing thyroid function in 10/13 patients and to induce a -23.8% median percent change in pituitary tumor size from baseline at final assessment (161b). Finally, a single report on the efficacy of pasireotide in the pre-operative treatment of a TSH-omas has been so far published (161c).

It is worth noting that somatostatin analogues may lead to a condition of TSH deficiency. In this respect, in the series published by Illouz and others TSH deficiency appeared in 15% of 46 treated TSH-omas after a median time of 4 weeks, the TSH deficiency occurring after one to three injections of long-acting somatostatin analogues (161d). These data suggest that thyrotropic function should be reassessed after the first three injections of somatostatin analogues in order to diagnose TSH deficiency and to reduce the frequency of injections when control of thyrotoxicosis is the aim of the treatment.

After surgery, partial or complete hypopituitarism may result (162, 163). However, a case of thyroid storm after pituitary surgery was documented (164).

Evaluation of pituitary function, particularly ACTH secretion, should be carefully undertaken soon after surgery and hormone replacement therapy initiated, if needed. In case of failure of pituitary surgery and in the presence of life-threatening hyperthyroidism, total thyroidectomy or thyroid ablation with radioiodine is indicated (165).

According to the largest published series, pituitary surgery is effective in restoring euthyroidism in 75% to 83% of patients with TSH-omas (61, 79, 165a) and a recent metanalysis by Cossu and others showed that the pooled rate of postoperative biochemical remission was 69.7% and a gross total resection was observed in 54% of patients. As expected, the extent of resection was significantly increased in microadenomas and cavernous sinus invasion was predictive of lower gross total resection (68).

If pituitary surgery is contraindicated or declined, as well as in the case of surgical failure, pituitary radiotherapy and/or medical treatment with somatostatin analogues (octreotide or lanretotide) are valid alternatives (158). In the 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 knife is available (158, 166). Radiotherapy and radiosurgery are effective in normalizing thyroid function in 37% of patients within 2 years (79). The successful experience of an invasive TSH-oma associated with an unruptured aneurysm treated by two-stage operation and gamma knife has been reported (167). Although earlier diagnosis has improved the surgical cure rate of TSH-omas, several patients have required medical therapy in order to control the hyperthyroidism. Dopamine agonists, and particularly cabergoline, have been employed in some TSH-omas with variable results, positive effects being mainly observed in some patients with mixed PRL/TSH adenoma (121, 168, 169). Today, the medical treatment of TSH-omas relies on long-acting somatostatin analogues, such as octreotide or

lanreotide (12, 13, 85, 158, 170-172). Indeed, many papers suggest the use of somatostatin analogues as first-line therapy for patients with TSH-omas, particularly for invasive macroadenomas (173-176). Treatment with these analogues lead to a reduction of TSH and alpha-GSU secretion in almost all cases, with restoration of the euthyroid state in the majority of them and it is safe even during pregnancy (18, 24, 177, 178). In some cases, inhibition of tumoral TSH secretion may be so profound that hypothyroidism may even be seen. During somatostatin analogues therapy tumor shrinkage occurs in about 50% of patients and vision improvement is seen in 75% (61, 79, 179). Very rapid shrinkage of the tumor has been described (34). Resistance to octreotide treatment has been documented in a few cases. Patients on somatostatin analogues have to be carefully monitored, as untoward side effects, such as cholelithiasis and carbohydrate intolerance, may become manifest. The dose administered should be tailored for each patient, depending on therapeutic response. Tolerance is usually very good, as gastrointestinal side effects are transient with long-acting analogues (12, 13, 57, 179, 180). As a whole, post-operative treatment with a somatostatin analogue induces a biochemical remission in 76% of patients (68) and led to a stable disease in 81.3% of the cases with residual tumor (59a).

CRITERIA OF CURE AND FOLLOW-UP

Due to the rarity of the disease and the great heterogeneity of the methods used, the criteria of cure of patients operated or irradiated for TSH-omas has not been clearly established. Previous thyroid ablation makes some of these criteria inapplicable (Table 3).

Table 3. Criteria for the Evaluation of the Outcome of Treatment	
Criteria	**Comments**
Remission from hyperthyroid manifestations (clinical and biochemical)	Clinical improvement may be transient No predictive value
Disappearance of neurological manifestations (adenoma imaging, visual field defects, headache)	May be transient Poor predictive value
Normalization of free thyroid hormone levels	Biochemical remission may be transient Poor predictive value
Normalization of circulating TSH levels	Not applicable to patients with normal TSH Poor predictive value
Undetectable TSH one week after neurosurgery	Applicable to hyperthyroid patients that stopped treatments at least 10 days before surgery Good prognostic value
Normalization of alpha-GSU levels and alpha-GSU/TSH molar ratio	Not applicable to patients with normal values before neurosurgery Lack of sensitivity
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

In untreated hyperthyroid patients, it is reasonable to assume that cured patients have clinical and biochemical reversal of thyroid hyperfunction. However, the findings of normal free thyroid hormone concentrations or indices of peripheral thyroid hormone action (SHBG, ICTP, etc.) are not synonymous with complete removal or destruction of tumoral cells, since transient clinical remission accompanied by normalization of thyroid function is possible (62, 63, 67, 98, 115). Disappearance of neurological signs and symptoms is a good prognostic event, but lacks both sensitivity and specificity, as even an incomplete debulking of the tumor may cause visual field defects and headache to vanish. The resolution of specific neuroradiological abnormalities is confusing, since the pituitary imaging performed soon after surgery is often difficult to interpret. 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 experience, undetectable TSH levels one week after surgery are likely to indicate complete adenomectomy, provided that the patient was hyperthyroid and presurgical treatments were stopped before surgery (115). A recent publication from a Korean group analyzing the outcome of adenomectomy in a series of 31 TSH-omas found that immediate postoperative TSH level at 12 hours after

surgery was the strongest predictor of cure, with a 0.62 µIU/mL cutoff (165a). Normalization of alpha-GSU and/or the alpha-GSU/TSH molar ratio is in general a good index for the evaluation of therapy efficacy (8, 115). 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 remains, in the absence of contraindication, the T3 suppression test (115). In fact, only patients in whom T3 administration completely inhibits basal and TRH-stimulated TSH secretion, appear to be truly cured.

Few data on the recurrence rates of TSH-oma in patients judged cured after surgery or radiotherapy have been reported. However, the recurrence of the adenoma does not appear to be frequent, at least in the first years after successful surgery (62, 115). In general, the patient should be evaluated clinically and biochemically 2 or 3 times the first year postoperatively, and then every year. Pituitary imaging should be performed every two or three 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, as visual function could be threatened. Emergency surgical decompression is not always able to reverse even a recent visual deficit.

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