Physiopathology, Diagnosis, and Treatment of Secondary Hyperthyroidism

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Abstract

Thyrotropin-secreting pituitary adenomas (TSHomas) are a rare cause of secondary hyperthyroidism and account for less than 2% of all pituitary adenomas. In the last 30 years, the recognition of TSHomas has been facilitated by the routine use of ultrasensitive TSH immunometric assays, i.e., methods clearly able to distinguish between TSH concentration in normal controls and undetectable TSH levels in hyperthyroid patients, as well as by the direct measurement of circulating

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free thyroid hormones (FT4 and FT3). TSHomas must be promptly diagnosed whenever measurable levels of TSH in the presence of high FT4 and FT3 concentrations are documented. As similar biochemical picture is found in patients with thyroid hormone resistance (RTH), a differential diagnosis between the two disorders must be performed. Therefore, a correct diagnosis is fundamental in order to prevent dramatic consequences, such as improper thyroidectomy in patients with secondary hyperthyroidism due to TSHoma or unnecessary pituitary surgery in patients with RTH. The differential diagnosis between TSHomas and RTH mainly rests on dynamic testing, such as T3 suppression test, TRH tests, as well as injection of long acting somatostatin for 2 or more months.

First-line therapeutical approach to TSHomas remains pituitary neurosurgery, though in particular cases medical treatment should be considered. The medical treatment of TSHomas mainly rests on the administration of somatostatin analogs, such as octreotide and lanreotide, which are effective in reducing TSH secretion in the majority of patients with consequent normalization of FT4 and FT3 levels and restoration of the euthyroid state.

Keywords

Thyroid hyperfunction · TSH-induced · TSH-secreting pituitary adenomas (TSHomas) · Resistance to thyroid hormones · Thyrotropin (thyroid-stimulating hormone, TSH) · Pituitary glycoprotein hormone α-subunit (α-GSU) · Somatostatin analogs (octreotide, lanreotide) · Dopaminergic drugs (cabergoline, bromocriptine)

Introduction

Hyperthyroidism due to TSH-secreting pituitary adenoma (TSHoma) is a very rare disorder. In the past, it was estimated that less than 2% of all pituitary tumors are TSHomas with a prevalence of one case per million (Beck-Peccoz et al. 1996). However, recent data show that the prevalence of TSHomas is about 2–3 cases per million inhabitants and the incidence is about 0.2–0.3 cases per million per year (Raappana et al. 2010; Ónnestam et al. 2013).

Such a rare disorder is due to two different clinical situations, i.e., TSHomas and resistance to thyroid hormone action (RTH) (Refetoff et al. 1993; Gurnell et al. 2016). The main difference between these two syndromes consists in the presence of signs and symptoms of hyperthyroidism in patients with TSHoma, while RTH patients are in general euthyroid (so-called generalized RTH, GRTH). However, in a minority of RTH patients, features of hyperthyroidism may be present involving some organs, e.g., heart (tachycardia) and brain (nervousness, insomnia, attention deficit, hyperactivity) and not others. This particular form of RTH is termed pituitary RTH (PRTH). Both TSHomas and RTH are characterized by elevated serum circulating free thyroid hormone levels in the presence of measurable (normal or high) serum TSH concentrations. TSH secretion from the tumor is autonomous, whereas

thyrotropes of patients with RTH are refractory to the action of high levels of thyroid hormones, so that in both situations negative feedback mechanism is not operating (Beck-Peccoz et al. 1996; Refetoff et al. 1993; Foppiani et al. 2007; Kienitz et al. 2007; Ness-Abramof et al. 2007; Clarke et al. 2008; Gurnell et al. 2016; Beck-Peccoz et al. 2016). Moreover, the secretion by TSHomas is characterized by increase pulse frequency, delayed circadian rhythm, and increased basal secretion (Roelfsema et al. 2008).

Many years ago, Gershengorn and Weintraub (1975) suggested calling the above situations inappropriate TSH secretion, where "inappropriate" refers to the fact that, contrary to what happens in the classical hyperthyroidism, TSH is not inhibited in these particular forms of thyroid hyperfunction. Currently, we propose to classify TSHomas and PRTH as the two different forms of "central hyperthyroidism."

In the past, many patients with TSHoma were misdiagnosed as having a Graves' disease, and this mistake was due to the lack of sensitivity of the various assays for TSH measurement. Nowadays, serum TSH is routinely measured by ultrasensitive immunometric assays and circulating free thyroid hormones by direct immunoassays, a fact that greatly improved the diagnostic workup of hyperthyroid patients, allowing the recognition of the cases with unsuppressed TSH secretion and increased levels of free thyroid hormones. Therefore, central hyperthyroidism is now more often diagnosed earlier, and an increased number of patients with normal or elevated TSH levels in the presence of high free thyroid hormone concentrations have been recognized (Refetoff et al. 1993; Beck-Peccoz et al. 2016; Gurnell et al. 2016). When the diagnosis of central hyperthyroidism has been made, the differential diagnosis between TSHoma and RTH, particularly PRTH, is mandatory (Beck-Peccoz et al. 2013; Gurnell et al. 2016). Early diagnosis and correct therapeutic approach to patients with TSHomas may prevent the occurrence of neurological and endocrine complications, such as headache, visual field defects, and hypopituitarism, and should improve the rate of cure. Conversely, improper thyroid ablation or unnecessary pituitary surgeries in patients with RTH are the distressing consequences of the failure to recognize these different disorders.

In the present chapter, we will focus on the pathophysiology, clinical features, diagnostic procedures, differential diagnosis, and treatment of thyroid hyperfunction due to the presence of TSH-secreting pituitary adenomas.

Pathophysiology

TSHomas arise from adenomatous transformation of thyrotroph cell type. They are benign tumors, and till now transformation of a TSHoma into a carcinoma with multiple metastases has been described in only three patients (Mixson et al. 1993; Brown et al. 2006; Lee et al. 2012). Loss of pituitary glycoprotein hormone alpha-subunit (α-GSU) has been reported in one patient (Mixson et al. 1993), while in another case TSH-secreting carcinoma developed from a previously nonfunctioning pituitary adenoma (Brown et al. 2006). The majority of benign TSHomas (74%) secretes TSH alone, though this is often accompanied by unbalanced hypersecretion

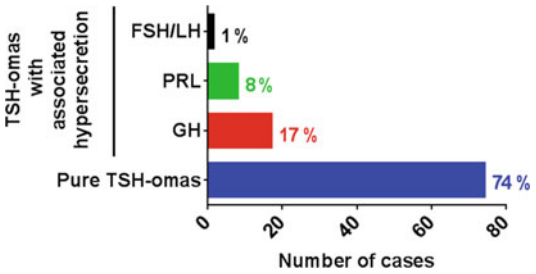

Fig. 1 Classification of TSH-secreting pituitary adenomas based on hormone secretion into circulation

of α-GSU, particularly in macroadenomas. Indeed, very few patients with TSH-secreting microadenomas present with hypersecretion of α-GSU (Socin et al. 2003).

About one-fourth of TSHomas are mixed adenomas and are characterized by concomitant hypersecretion of other anterior pituitary hormones, mainly growth hormone (GH) or prolactin (PRL), which are known to share with TSH common transcription factors, such as PROP-1, Pit-1 (POU1F1) and HESX-1 (Asa et al. 1993; Cohen and Radovick 2002; Mantovani et al. 2006; Pereira et al. 2016). Indeed, hypersecretion of TSH and GH is the most frequent association (17%), followed by hypersecretion of TSH and PRL (8%) and occasionally TSH and gonadotropins (Fig. 1). Interestingly, no mixed TSHomas were found to cosecrete ACTH molecules. Moreover, previous data have documented the existence of central hyperthyroidism due to a TSH-secreting adenoma, not associated with hypersecretion of other pituitary hormones, composed of two different cell types: one secreting α-GSU alone and another cosecreting α-GSU and TSH (Terzolo et al. 1991). Such an observation may explain the finding of an unbalanced release of α-subunit and TSH, responsible for very high α-subunit/TSH molar ratios, and why after therapy, certain thyrotroph adenomas recur only with α-GSU, and not TSH, hypersecretion (Kourides et al. 1977). Nonetheless, a positive immunohistochemistry for one or more pituitary hormone does not necessarily correlate with its or their hypersecretion in vivo (Bertholon-Grégoire et al. 1999; Pellegrini-Bouiller et al. 1997; Azzalin et al. 2016). Accordingly, clinically and biochemically silent thyrotropinomas have been reported (Banerjee et al. 2000; Lim et al. 2001; Rabbiosi et al. 2012; Tritos et al. 2013; Kirkman et al. 2014). Moreover, true TSH-secreting tumors associated with Hashimoto's thyroiditis and hypothyroidism have been documented (Iskandar et al. 2003; Losa et al. 2006; Ma et al. 2006; Beck-Peccoz et al. 2016).

In patients with confirmed biochemical findings of TSHoma and normal anterior pituitary gland, the presence of ectopic TSH secretion should be taken into consideration (Thompson et al. 2012). In fact, ectopic TSHoma occurring in the nasopharyngeal pituitary residue have been reported in six cases (Cooper and Wenig 1996; Pasquini et al. 2003; Collie and Collie 2005; Tong et al. 2013; Song et al. 2014; Wang et al. 2016).

Microadenomas (diameter < 1 cm) were recorded in less than 15% of the cases before 1996 (Socin et al. 2003), but their prevalence among the total number of TSHoma is progressively increasing due to improved testing of thyroid function and awareness among Endocrinologists and General Practitioners. Recently, the

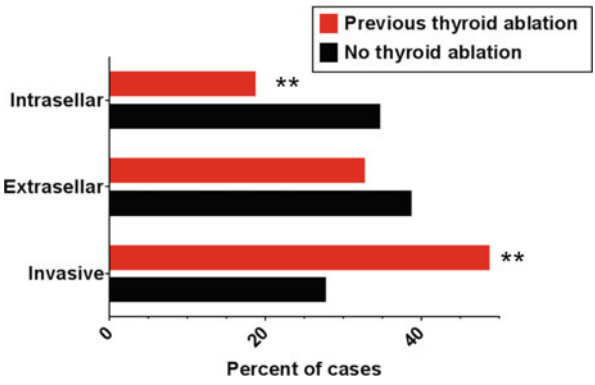

Fig. 2 Effects of previous thyroid ablation on the characteristic of TSHomas: "intrasellar" refers to both microadenomas and intrasellar macroadenomas, "extrasellar" to macroadenomas with suprasellar extension, and "invasive" to invasive macroadenomas. $^{**}P < 0.05$ by Fisher's exact test

percentage of microadenomas is ranging between 30% and 35% of all TSHomas (Malchiodi et al. 2014). Nonetheless, most TSHomas had been diagnosed at the stage of macroadenomas and showed localized or diffuse invasiveness into the surrounding structures, especially into the dura mater and bone (Brucker-Davis et al. 1999; Socin et al. 2002; Foppiani et al. 2007; Ness-Abramof et al. 2007; Clarke et al. 2008; Malchiodi et al. 2014; Beck-Peccoz et al. 2016). Extrasellar extension in the supra- and/or parasellar direction were present in the majority of cases. These findings highlight the deleterious effects of misdiagnosis and mistreatment of these adenomas, and the relevant action on tumor growth exerted by the reduction of circulating thyroid hormone levels through an altered feedback mechanism (Fig. 2).

The molecular mechanisms underlying the formation of TSHomas are presently unknown. Inactivation analysis of X-chromosome demonstrated that most pituitary adenomas, including the small number of TSHomas investigated, derive from the clonal expansion of a single initially transformed cell (Ma et al. 2003). Therefore, the presence of a transforming event providing gain of proliferative function followed by secondary mutations or alterations favoring tumor progression, presumably also apply to TSHomas. A number of proto-oncogenes, tumor suppressor genes, as well as pituitary specific genes, have been screened for mutations able to confer growth advantage to thyrotroph cells. As for other pituitary adenomas, no mutations in oncogenes commonly activated in human cancer, particularly *Ras*, have been reported in TSHomas. In contrast with GH-secreting adenomas in which the oncogene *gsp* is present in about 40% of cases, none of the screened TSHomas has been shown to express activating mutations of genes encoding for G protein subunits, such as αs, αq, α11, or αi2, or for TRH receptor (Dong et al. 1996). Negative results have also been reported when dopamine type 2 receptor gene was investigated (Friedman et al. 1994). Moreover, the transcription factor Pit-1 exerts a crucial role on cell differentiation and expression of PRL, GH, and TSH genes. Thus, Pit-1 gene has been studied and shown to be overexpressed, but not mutated, in 14 TSHomas (Pellegrini-Bouiller et al. 1997). As far as the possible loss of anti-oncogenes is concerned, no loss of *p53* was found in one TSHoma studied, while

loss of retinoblastoma gene (*Rb*) was not investigated in TSHomas. Another candidate gene is menin, whose mutations are responsible for multiple endocrine neoplasia type 1 (MEN1). In fact, about one-fourth of sporadic pituitary adenomas show loss of heterozygosity (LOH) on 11q13, where menin is located, and LOH on this chromosome seems to be associated with the transition from the noninvasive to the invasive phenotype. A recent screening study carried out on 13 TSHomas using polymorphic markers on 11q13 showed LOH in three, but none of them showed a menin mutation at sequence analysis (Asteria et al. 2001). Interestingly, hyperthyroidism due to TSHomas has been reported in five cases within a familial setting of MEN 1 (Beck-Peccoz et al. 1996; Taylor et al. 2000). Finally, germline mutations in the aryl hydrocarbon receptor interacting protein (AIP) are known to be involved in sporadic pituitary tumorigenesis, but mutations were found in a single patient with TSHoma (Barlier et al. 2007; Daly et al. 2010).

The extreme refractoriness of tumoral thyrotropes to the inhibitory action of thyroid hormones led to search for alterations in thyroid hormone receptor (TR) function (Gittoes et al. 1998; Tagami et al. 2011). Absence of TRα1, TRα2, and TRβ1 expression was reported in one TSHoma, but aberrant alternative splicing of TRβ2 mRNA encoding TRβ variant lacking T3 binding activity was recently shown as a mechanism for impaired T3-dependent negative regulation of both TSHβ and α-GSU in tumoral tissue (Ando et al. 2001a). Moreover, recent data suggest that somatic mutations of TRβ may be responsible for the defect in negative regulation of TSH secretion in some TSHomas (Ando et al. 2001b). Finally, it has recently been demonstrated that knock-in mutant mice harboring a mutation in the TRβ gene spontaneously develop TSHomas and that aberrant pituitary growth is due to activation of phosphatidylinositol 3-kinase signaling (Lu et al. 2008).

Finally, somatostatin receptor subtypes have been studied in some adenomas (Spada et al. 1985; Bertherat et al. 1992; Horiguchi et al. 2007; Gatto et al. 2011). The presence of subtypes 1, 2A, 3, and 5 were documented, a figure that may explain the high efficacy in blocking the hormone hypersecretion and tumor shrinkage during somatostatin analog treatment in the majority of patients with TSHoma (Horiguchi et al. 2007). Moreover, it has been shown that LOH and particular polymorphisms at the somatostatin receptor type 5 gene locus are associated with an aggressive phenotype and resistance to somatostatin analog treatment, possibly due to lack of somatostatin-induced inhibition of TSH secretion (Filopanti et al. 2004). Overexpression of basic fibroblast growth factor by some TSHomas suggests the possibility that it may play a role in the development of fibrosis and tumor cell proliferation of this unusual type of pituitary neoplasm (Sato et al. 1995; Ezzat et al. 1995). Moreover, the overexpression of basic fibroblast growth factor may explain the presence of some TSHomas defined “pituitary stone” (Webster et al. 1994).

Clinical Features

Signs and symptoms of hyperthyroidism are frequently associated with patients with TSHoma with those due to the compression of the surrounding anatomical structures, thus causing visual field defects, loss of vision, headache, and partial or

Table 1 Clinical features in patients with TSHoma (data from reports published until December 2016 and personal unpublished observations)

Clinical features	Patients with TSHoma
Age range (years)	8–86
Female/Male ratio	1.4
Previous thyroidectomy	28%
Severe thyrotoxicosis	15%
Goiter	85%
Thyroid nodule(s)	58%
Macroadenomas	72%
Visual field defects	30%
Headache	18%
Menstrual disorders	35%
Galactorrhea	25%
Acromegaly	17%

complete hypopituitarism (Table 1). Most patients have a long history of thyroid dysfunction, frequently misdiagnosed as Graves' disease, and about 30% of them had inappropriate thyroidectomy or radioiodine thyroid ablation (Beck-Peccoz et al. 1996; Brucker-Davis et al. 1999; Socin et al. 2003; Ness-Abramof et al. 2007; Varsseveld et al. 2014; Yamada et al. 2014; Beck-Peccoz et al. 2016). The deleterious effects of incorrect diagnosis are demonstrated by the finding that the occurrence of invasive macroadenomas is particularly high among patients with previous thyroid ablation by surgery or radioiodine (Fig. 2; Beck-Peccoz et al. 2016). This aggressive transformation of the tumor resembles that occurring in Nelson's syndrome after adrenalectomy for Cushing's disease.

TSHomas may be diagnosed at any age without sex preference (Nakayama et al. 2012; Yamada et al. 2014; Beck-Peccoz et al. 2016). The severity of hyperthyroidism is sometimes milder than expected on the basis of circulating thyroid hormone levels (Lim et al. 2001; Rabbiosi et al. 2012). In some acromegalic patients, signs and symptoms of hyperthyroidism may be clinically missed, as those of acromegaly overshadow them. Cardiotoxicosis with atrial fibrillation and/or cardiac failure and episodes of periodic paralysis are less frequent as compared to the frequency observed in patients with primary hyperthyroidism. The diagnosis of TSHoma may be delayed when autoimmune hypothyroidism is coexistent with the pituitary tumor (Langlois et al. 1996; Idiculla et al. 2001; Ma et al. 2003; Losa et al. 2006). In such a situation, the inadequate suppression of TSH during LT4 replacement therapy may suggest the presence of an autonomous TSH hypersecretion from the pituitary tumor.

Goiter is present in 85% of patients, even in those previously thyroidectomized, as thyroid residue may regrow as a consequence of TSH hyperstimulation (Table 1). Occurrence of uni- or multinodular goiter is frequent (about 58% of reported cases), whereas differentiated thyroid carcinomas were documented in a few cases (Gasparoni et al. 1998; Kishida et al. 2000; Ohta et al. 2001; Poggi et al. 2009; Ünlütürk et al. 2013). Progression towards toxic nodular goiter is very rare

(Abs et al. 1994). In contrast to what is observed Graves' disease, the occurrence of circulating antithyroid autoantibodies is similar to that found in the general population, being about 8%. However, Graves' hyperthyroidism may coexist with TSHoma in some patients (Kamoi et al. 1985; Kamoun et al. 2014). Bilateral exophthalmos occurred in a few patients who subsequently developed autoimmune thyroiditis, while unilateral exophthalmos due to orbital invasion by pituitary tumor was reported in three patients with TSHomas (Kourides et al. 1980; Yovos et al. 1981; Beck-Peccoz et al. 2016).

Disorders of the gonadal axis are frequent, menstrual disorders being present in all females with mixed TSH/PRL tumors and in one-third of those with pure TSHoma (Table 1). Central hypogonadism, delayed puberty, and decreased libido were also found in a number of males with TSHomas and/or mixed TSH/FSH adenomas.

Diagnostic Procedures

The finding of elevated levels of circulating thyroid hormones in the presence of measurable TSH concentrations is the biochemical hallmark of central hyperthyroidism. However, attention should be paid to the presence of circulating factors, such as antibodies against TSH or thyroid hormones, as well as abnormal forms of albumin or transthyretin that may interfere in the measurement methods of both TSH and thyroid hormones, giving spuriously high hormone levels and possibly simulating the biochemical characteristics of central hyperthyroidism (Koulouri et al. 2013; Koulouri and Gurnell 2013; Beck-Peccoz et al. 2016). Particular attention should be paid to the measurement of FT4, as only the "two-step" immunometric assays are to be employed, i.e., methods able to avoid possible interference due to the contact between serum interfering factors and the tracer (Schoenmakers et al. 2014).

No difference in basal values of TSH and free thyroid hormone levels was seen between patients with TSHoma and those with RTH (Fig. 3). However, an unbalanced hypersecretion of circulating free α-GSU levels and elevated α-GSU/TSH molar ratio are merely detected in patients with TSHoma (Table 1; Terzolo et al. 1991; Brucker-Davis et al. 1999; Socin et al. 2003). The calculation of α-GSU/TSH molar ratio increases the diagnostic sensitivity of hormone measurement, if such a calculation is done taking into account the serum levels of TSH and gonadotropins (Beck-Peccoz et al. 1992). Nevertheless, in a recent series of TSHomas, normal α-GSU levels and α-GSU/TSH molar ratio were observed in about 60% of the cases and more frequently in macroadenomas than in microadenomas (Socin et al. 2003). These findings are probably related to the fact that a higher number of microadenomas are diagnosed nowadays. Indeed, these data show a relationship between multiple hypersecretion and tumor volume: the bigger the tumor, the higher the number and the amount of hormones secreted in excess (Socin et al. 2003). It is worth noting that the bioactivity of secreted TSH may be enhanced or reduced in some patients with TSHoma (Beck-Peccoz and Persani 1994). These findings

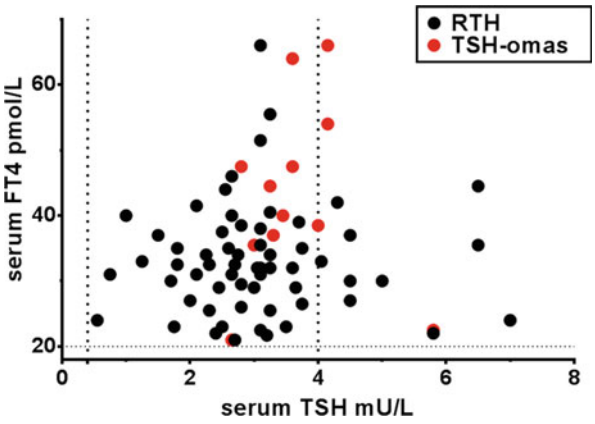

Fig. 3 Serum levels of Free Thyroxine (FT4) and TSH in patients with TSH-secreting pituitary adenoma (TSHomas) as compared to those with resistance to thyroid hormone action (RTH). Horizontal dashed line indicates the upper limit of FT4 normal range. The vertical dashed lines indicate the TSH normal range. No significant difference between RTH and TSHomas was found

explain the lack of correlation between serum TSH and FT3 circulating levels in patients with TSHoma.

In addition, measurements of several parameters of peripheral thyroid hormone action have been proposed to quantify the degree of tissue hyperthyroidism (Beck-Peccoz et al. 2016). In particular, bone (carboxyterminal cross-linked telopeptide of type I collagen, ICTP) and liver (sex-hormone binding globulin, SHBG) parameters may help in differentiating hyperthyroid patients with TSHoma from those with PRTH (Beck-Peccoz et al. 1990; Persani et al. 1997). In fact, as it occurs in the common forms of hyperthyroidism, such as Graves' disease or toxic goiter, patients with TSHoma have high ICTP and SHBG levels, while they are into the normal range in patients with hyperthyroidism due to PRTH (Table 2).

Dynamic testing is mandatory in the diagnosis of TSHoma, in particular the T3 suppression test (80–100 μg/day per 8–10 days). A complete inhibition of TSH secretion after T3 suppression test has never been recorded in patients with TSHoma (Table 2), particularly in those previously thyroidectomized (Brucker-Davis et al. 1999; Socin et al. 2003; Beck-Peccoz et al. 2016). In this latter condition, T3 suppression seems to be the most sensitive and specific test in assessing the presence of a TSHoma. However, this test is contraindicated in elderly patients or in those with coronary heart disease. Therefore, TRH test (200 μg iv) has been widely used in the work-up of these adenomas. In the vast majority of patients, TSH and α-GSU levels do not increase after TRH injection (Table 2). In patients with hyperthyroidism, discrepancies between TSH and α-GSU responses to TRH are pathognomonic of TSHomas cosecreting other pituitary hormones (Terzolo et al. 1991).

As most TSHomas maintain the sensitivity to native somatostatin and its analogs (octreotide and lanreotide) (Bertherat et al. 1992; Chanson et al. 1993; Gancel et al. 1994; Kuhn et al. 2000), we have recently treated a series of patients with TSHomas or PRTH with multiple injections of long-acting somatostatin analogs documenting a marked decrease of FT3 and FT4 levels in all patients but one with pituitary adenoma, while all patients with PRTH did not respond

Table 2 Parameters useful in differentiating patients with TSH-secreting pituitary adenomas (TSHomas) from those with resistance to thyroid hormones (RTH). Only patients with intact thyroid were taken into account. Data are obtained from patients followed at our Institution and are expressed as mean ± SE or percent

Parameter	TSHomas	RTH	*P*
	(n = 52)	(n = 84)	
Serum TSH mU/L	2.9 ± 0.8	2.4 ± 0.7	NS
High α-GSU levels	64%	3%	<0.0001
High α-GSU/TSH m.r.	78%	2%	<0.0001
Serum FT4 pmol/L	41.4 ± 5.3	36.2 ± 3.1	NS
Serum FT3 pmol/L	15.5 ± 1.7	13.9 ± 1.1	NS
Serum SHBG nmol/L	138 ± 25	54 ± 8	<0.0001
Serum ICTP μg/L	9.2 ± 5.2	3.1 ± 1.1	<0.001
Abnormal TSH response to			
T3 suppression[a]	100%	100%[b]	NS
Blunted TSH response			
To TRH test	90%	3%	<0.0001

Abbreviations: *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). 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 the majority of RTH patients

(Mannavola et al. 2005). Thus, administration of these long-acting analogs for at least 2 months can help in the differential diagnosis of problematic cases of central hyperthyroidism. Nevertheless, since none of these tests is of clear-cut diagnostic value, it is recommend the use of both T3 suppression and TRH test whenever possible, because the combination of their results increases the specificity and sensitivity of the diagnostic workup.

Finally, high-resolution computed tomography (CT) and nuclear magnetic resonance imaging (MRI) are nowadays the preferable tools for the visualization of a TSHoma. Most TSHomas were diagnosed at the stage of macroadenomas with frequent suprasellar extension or sphenoidal sinus invasion. Microadenomas are now reported with increasing frequency, accounting for 30–35% of all recorded cases in both clinical and surgical series (Socin et al. 2003; Kienitz et al. 2007). Recently, pituitary scintigraphy with radiolabeled octreotide (octreoscan) has been shown to successfully localize TSHomas expressing somatostatin receptors (Losa et al. 1997; Foppiani et al. 2007). However, the specificity of octreoscan is low, since positive scans can be seen in the case of a pituitary mass of different types, either secreting or nonsecreting. Such a procedure may be useful in the recognition of the possible ectopic localization of a TSHoma, as six cases of TSHomas were found in the nasopharyngeal region (Cooper and Wenig 1996; Pasquini et al. 2003; Collie and Collie 2005; Tong et al. 2013; Song et al. 2014; Wang et al. 2016).

Differential Diagnosis

The possible presence of Graves' disease, uni- or multinodular toxic goiter or activating mutations of TSH receptor, is ruled out by the finding of measurable levels of circulating TSH. Once the existence of central hyperthyroidism is confirmed and the presence of methodological interferences excluded (Koulouri et al. 2013; Koulouri and Gurnell 2013; Beck-Peccoz et al. 2016), several diagnostic steps have to be carried out to differentiate a TSHoma from RTH, particularly PRTH (Fig. 4). Indeed, the presence of neurological signs and symptoms (e.g., visual defects and headache) or clinical features of concomitant hypersecretion of other pituitary hormones (acromegaly, amenorrhea/galactorrhea) points to the presence of a TSHoma. Furthermore, an alteration of the pituitary gland at MRI or CT scan strongly supports the diagnosis of TSHoma. Nevertheless, the differential diagnosis with PRTH may be difficult when the pituitary adenoma is very small, or in the case of confusing lesions, such as ectopic tumors, empty sella, or pituitary incidentalomas, the latter lesion being frequently found in the general population. In these cases, elevated α-GSU concentrations or high α-GSU/TSH molar ratio, high circulating levels of parameters of peripheral thyroid hormone action (SHBG, ICTP),

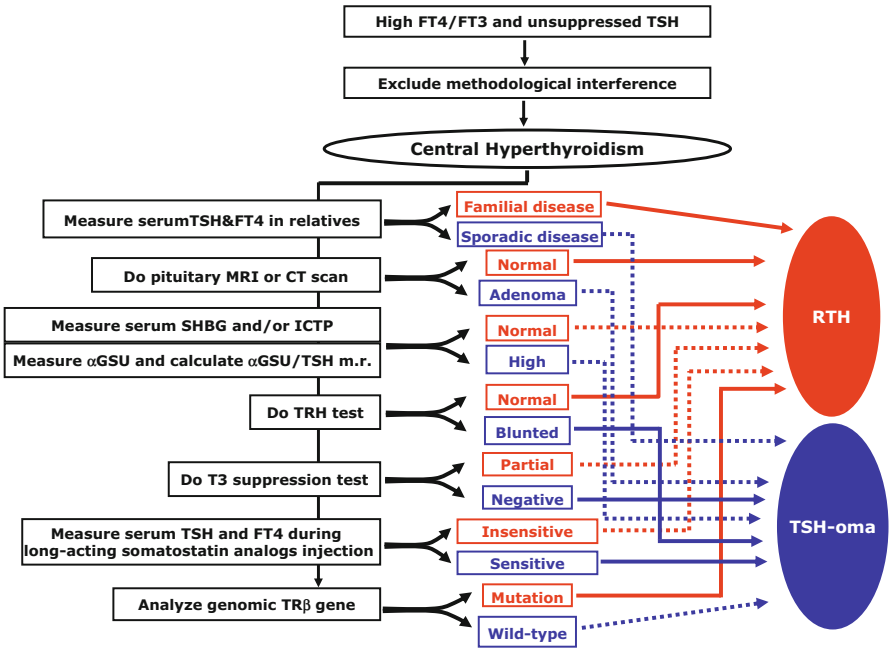

Fig. 4 Flow-chart for the differential diagnosis between resistance to thyroid hormone (RTH) and TSH-secreting pituitary adenoma (TSHoma). After exclusion of methodological interference, central hyperthyroidism is confirmed. A series of clinical, biochemical, and genetic tests may be necessary to reach the final diagnosis (modified from Beck-Peccoz et al. 2013)

TSH unresponsiveness to TRH stimulation or to T_3 suppression tests, decrease of TSH and free thyroid hormones during injection of long-acting analogs for at 2–3 months favor the presence of a TSHoma (Beck-Peccoz et al. 2013¸ Gurnell et al. 2016; Beck-Peccoz et al. 2016). Moreover, the finding of similar biochemical data in relatives definitely points to the presence of RTH, as familial cases of TSHomas have not been documented. 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 (Ando et al. 2001a; Ando et al. 2001b); thus, the occurrence of TSHoma in patients with RTH should be carefully taken into account (Watanabe et al. 1993; Safer et al. 2001; Teng et al. 2015).

Treatment

The therapeutical approach to TSHomas is the transsphenoidal or subfrontal adenomectomy, the choice of the route depending on the tumor volume and its suprasellar extension and invasiveness (Beck-Peccoz et al. 2013). The primary objectives of the treatment are in effect the removal of the pituitary tumor and the restoration of euthyroidism. The operation may be difficult as the tumor may present a marked fibrosis, possibly related to high expression of basic fibroblast growth factor (Ezzat et al. 1995). In addition, these tumors may be locally invasive involving the cavernous sinus, internal carotid artery, or other structures, thus rendering complete resection of the tumor either impractical or dangerous. Antithyroid drugs (methimazole or propylthiouracil, 20–30 and 200–300 mg/day, respectively) or somatostatin analogs, such as octreotide (100 μg sc, bid or tid), along with propranolol (80–120 mg/day orally) can be administered in order to restore euthyroidism before surgery (Wallace et al. 2015). However, this approach may cause TSH secretion from normal, nonadenomatous thyrotropes to be reactivated, so that one may lose a useful parameter to judge the complete removal of the adenoma, i.e., the unmeasurable levels of circulating TSH few days after successful surgery (Losa et al. 1996). If surgery is contraindicated or declined, pituitary radiotherapy (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) should be considered (Mouslech et al. 2016). A successful experience of an invasive TSHoma associated with an unruptured aneurysm treated by two-stage operation and gamma knife has been reported (Ohki et al. 1999).

With the above therapeutic approaches, normalization of thyroid hormone circulating levels and apparent complete removal of tumor mass was observed in one-third of patients who may therefore be considered apparently cured (follow-up ranged from 2 to 121 months). Indeed, only the complete suppression of TSH secretion during T3 suppression test permits to document the total removal of the TSHoma (Fig. 5; Losa et al. 1996). An additional one-third of patients were judged improved, as normalization of thyroid hormone circulating levels was achieved in all, though there was no complete removal of the adenoma. Together these findings indicate that about two-thirds of TSHomas are under control with surgery and/or

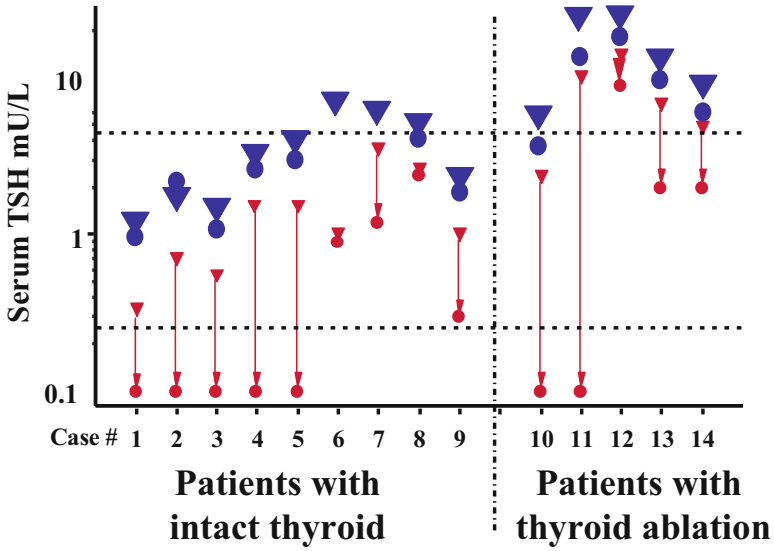

Fig. 5 Results of T3 suppression test carried out before (blue triangles and circles) and after (red triangles and circles) pituitary surgery in patients with TSH-secreting pituitary adenoma. Cases #1–9 had an intact thyroid, while patients #10–14 had a previous thyroid ablation. Horizontal dashed lines indicate serum TSH normal range. Note the lack of TSH suppression in all patients before pituitary tumor resection. Complete suppression of TSH levels, i.e., complete removal of the adenoma, was seen in about half of patients after surgery, independent of previous thyroid ablation

irradiation. In the remaining patients, TSH hypersecretion was unchanged after treatment, a fact that undoubtedly reflects the large size of the tumor and its invasiveness. Previous thyroid ablation or antithyroid drug treatments did not significantly affect the results of surgery and/or radiotherapy. Postsurgical deaths were reported in few cases. Evaluation of pituitary function, particularly ACTH secretion, should be carefully investigated soon after surgery and checked again every year, especially in patients treated with radiotherapy. In addition, in the case of surgical cure, postoperative TSH is undetectable and may remain low for weeks or even months, causing central hypothyroidism. A permanent central hypothyroidism may also occur due to the compression exerted by the tumor on the surrounding pituitary cells or the pituitary stalk or to surgical damage of the normal thyrotropes. Thus, transient or permanent L-T4 replacement therapy may be necessary. Finally, in few patients total thyroidectomy was performed after pituitary surgery failure, as the patients were at risk of thyroid storm.

Although the surgical cure rate of TSHomas is today improved due to an early diagnosis, some patients require medical therapy in order to control the hyperthyroidism or may be even treated medically as first-line therapy (Fliers et al. 2012; Gatto et al. 2015; Rimareix et al. 2015). Somatostatin analogs are highly effective in reducing TSH secretion by neoplastic thyrotropes (Beck-Peccoz et al. 1989; Orme et al. 1991; Bertherat et al. 1992; Chanson et al. 1993; Gancel et al. 1994; Kuhn et al. 2000;

Tayloret al. 2000; Horiguchi et al. 2007; Rabbiosi et al. 2012; Rimareix et al. 2015; Gatto et al. 2015), thus supporting the fact that the inhibitory pathway mediated by somatostatin receptors appears to be intact in such adenomas. Consistently, there is a good correlation between SRIH binding capacity and maximal biological response, as quantified by inhibition of TSH secretion and in vivo restoration of euthyroid state (Bertherat et al. 1992; Horiguchi et al. 2007). The presence of dopamine receptors in TSHomas was the rationale for therapeutic trials with dopaminergic agonists, such as bromocriptine or cabergoline (Chanson et al. 1984; Zuniga et al. 1997; Mulinda et al. 1999). Several studies have shown a large heterogeneity of TSH responses to dopaminergic agents both in primary cultures and in vivo, the best results having been achieved in mixed TSH/PRL adenomas (Spada et al. 1985). Effects of these two inhibitory agents should be nowadays re-evaluated in light of the demonstration of possible heterodimerization of somatostatin receptor type 5 and dopamine D2 receptor (Rocheville et al. 2000). Nonetheless, the medical treatment of TSHomas today rests on long-acting somatostatin analogs, such as octreotide LAR or lanreotide SR or lanreotide Autogel. Treatment with these analogs leads to a reduction of TSH and α-GSU secretion in almost all cases, with restoration of the euthyroid state in the majority of them. Circulating thyroid hormone levels normalized in more than 95% of patients. Goiter size was significantly reduced by somatostatin analog therapy in one-fifth of cases. Vision improvement was documented in two-third of patients and pituitary tumor mass shrinkage occurred in about 40% of them. Resistance to somatostatin analog treatment, true escape of TSH secretion from the inhibitory effects of the drugs or discontinuation of treatment due to side effects was documented in a minority of cases. Of interest are the findings of octreotide treatment in pregnant women, which was effective in restoring euthyroidism in the mother and had no side effects on development and thyroid function of the fetuses (Blackhurst et al. 2002; Chaiamnuay et al. 2003). Moreover, in almost all patients with mixed TSH/GH hypersecretion, signs and symptoms of acromegaly concomitantly disappeared. Patients on somatostatin analogs have to be carefully monitored, as untoward side effects, such as cholelithiasis and carbohydrate intolerance, may become manifest. The administered dose should be tailored for each patient, depending on therapeutic response and tolerance (including gastrointestinal side effects). The tolerance is usually very good, as gastrointestinal side effects are transient with long-acting analogs. The marked somatostatin-induced suppression of TSH secretion and consequent biochemical hypothyroidism seen in some patients may require a reduction of somatostatin analog doses or even an L-T4 substitution. Finally, no data have been reported on somatostatin analog treatment of TSHomas in patients who underwent thyroid ablation by thyroidectomy or radioiodine. Since aggressive and invasive macroadenomas are more frequently found in these patients (Beck-Peccoz et al. 2016), it is mandatory to treat them in order to block further growth of pituitary tumor mass.

The recurrence rate of TSHomas appears to be uncommon (Socin et al. 2003; Brucker-Davis et al. 1999; Losa et al. 1996, Malchiodi et al. 2014). Clinical and biochemical evaluation should be done two or three times after operation and then

every year. Pituitary imaging and visual field should be performed every 2–3 years, but should be done quickly if serum TSH and free thyroid hormone levels increase (Beck-Peccoz et al. 2013).

Summary

Patients with TSHoma present with a characteristic biochemical picture: high levels of circulating free thyroid hormones in the presence of normal/high concentrations of TSH. Such a biochemical picture may be caused by methodological interference in the measurement methods of both TSH and free thyroid hormones. Therefore, it is mandatory to check the results using different methods of measurement and to establish a close collaboration with the Institution laboratory.

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) due to compression on the surrounding anatomical structures by the pituitary tumor.

T3 suppression and TRH tests, as well as injection for 2 or 3 months of long acting somatostatin, appear to be useful in the differential diagnosis between TSHomas and syndromes of thyroid hormone resistance. In addition, the findings of several parameters of peripheral thyroid hormone action in the hyperthyroid range may help in differentiating TSHoma from RTH.

Since the primary objectives of the treatment are the removal of the pituitary tumor, the restoration of euthyroidism and the prevention of neurological symptoms, such as headache, visual field defects, and hypopituitarism, the first 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, the medical treatment is indicated and based on long acting somatostatin analog administration, such as octreotide or lanreotide, which are successful in the majority of patients with TSHoma.

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