Thyrotropin-Secreting Pituitary Adenomas

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Normal or elevated thyrotropin (TSH) levels in hyperthyroid patients are characteristic of rare TSH-secreting pituitary adenoma (TSH-oma), which is easily detectable by computed tomographic (CT) scan or magnetic resonance imaging (MRI). Other diagnostic aids are an absent/impaired TSH response to thyrotropin-releasing hormone (TRH), discrepant TSH and α-subunit responses to TRH, high sex hormone–binding globulin (SHBG) levels, high α-subunit levels, and a high α-subunit/TSH molar ratio. Familial studies help rule out thyroid hormone resistance (RTH). Surgical removal of TSH-oma leads to clinical and biochemical remission in most patients. In surgical failures, radiotherapy and octreotide treatment have a high success rate. Undetectable TSH 1 week postsurgery suggests a definitive cure, backed up by tests for cosecreted hormones from the adenoma and dynamic tests of TSH suppression.

SINCE THE INTRODUCTION of ultrasensitive assays for thyrotropin (TSH) and direct methods for free thyroid hormone (FT_4 and FT_3) measurements as first-line tests of thyroid function, TSH-secreting pituitary adenomas (TSH-omas) have been recognized with increasing frequency.[1,2] At present, about 270 TSH-omas have been reported in the literature, and their occurrence in a surgical series during the period 1989 to 1991[3] accounts for 2.8% of all pituitary tumors, a figure fivefold to sixfold higher than those previously reported.[1,4] Signs and symptoms of hyperthyroidism are the clinical manifestations of the disease, which are no different from those occurring in the more conventional forms of thyroid hyperfunction such as toxic nodular goitre and autoimmune Graves' disease.[4] Some patients, especially those previously misdiagnosed as having Graves' disease and therefore subjected to therapies directed at the thyroid, present with signs and/or symptoms resulting from compression of the surrounding nervous structures. In approximately 30% of patients, the pituitary tumor secretes other hormones, usually growth hormone (GH) or prolactin (PRL).[1,2,4] Failure to recognize these clinical situations may result in dramatic consequences, such as inappropriate thyroid ablation, while early diagnosis and correct treatment prevent the appearance of signs of mechanical compression of the adjacent structures by the expanding tumor mass.

PATHOGENESIS AND PATHOPHYSIOLOGY

Approximately 90% of TSH-omas are macroadenomas (diameter > 1 cm). Any previous treatment involving either thyroid ablation (surgery and radioiodine) or antithyroid drug administration appears detrimental (Table 1). In fact, invasive macroadenomas have been found in 52% of treated patients, a percentage significantly higher than that recorded in untreated patients (~26%). Conversely, microadenomas or macroadenomas with minimal or no suprasellar extension were seen in about 48% of untreated patients and only in about 28% of those previously treated. Therefore, according to Weintraub et al,[5] previous thyroid ablation may induce an aggressive transformation of the tumor, as seen after adrenalectomy for Cushing's disease in Nelson's syndrome. Under light microscopy, tumoral cells appear polymorphous, with large nuclei and prominent nucleoli, often arranged in cords. Occasionally, monstrosities and mitoses are found, which may lead to the false diagnosis of pituitary malignancy or metastases from distant carcinomas.[6] It is noteworthy that only one pituitary TSH-secreting carcinoma characterized by several brain, bone, lung, and liver metastases has been described.[7] Immunostaining studies have shown the presence of TSH and its subunits in adenomatous cells from every type of TSH-oma, with few exceptions.[2] The finding of positive TSH immunostaining excludes the diagnosis of TSH carcinoma whenever monstrosities and mitoses are recorded and brain or distant metastases are excluded. Cells from adenomas cosecreting TSH and other pituitary hormones generally appear monomorphous by electron microscopy, and colocalization of TSH and other pituitary tropins in the same cell or even in the same secretory granule can be detected using techniques such as double-gold immunolabeling.[8,9]

Pharmacological studies performed both in vivo and in vitro suggest that several functioning receptors, except thyrotropin-releasing hormone (TRH) receptors, are expressed by TSH-omas. This finding accounts for the in vivo unresponsiveness to TRH seen with almost all TSH-omas. The presence of dopamine receptors was the rationale for therapeutic trials with dopaminergic agonists.[10,11] The existence of normal somatostatin receptors is strongly suggested by the good correlation between their binding capacity and their biological response as documented by restoration of patient euthyroid state.[12]

In recent years, molecular biological approaches have provided several important insights into the pathogenesis of pituitary adenomas. TSH-omas are monoclonal in origin, as are the majority of pituitary tumors.[13] Genetic abnormalities such as activating mutations that could result in transcriptional activation have been poorly investigated in TSH-omas. In fact, there are no data available on the expression of either the *gsp* oncogene, which frequently occurs in GH-secreting adenomas, or the *ras* oncogene, which has been found in highly invasive prolactinomas and adenocarcinomas, or on protein kinase C mutations.[14-17]

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Table 1.Effects of Previous Treatment With Antithyroid Drugs or Thyroidectomy on the Size of the TSH-oma

Patients	No.	Micro- or Macroadenomas With No Suprasellar Extension	Macroadenomas With Suprasellar Extension	Macroadenomas (invasive)
Untreated	79	38 (48.1%)	19 (24.0%)	22 (27.9%)
Treated	87	23 (26.4%)*	19 (21.8%)	45 (51.8%)*

*$P < .01$ *v* untreated patients (Fisher's exact test).

Preliminary studies indicate that the expression of Pit-1 (a nuclear transcription factor that has an important regulatory role in the expression of PRL, GH, and TSH genes) is higher in tumors hypersecreting PRL, GH, or TSH than in the normal pituitary. These data are compatible with a role for Pit-1 in adenomatous cell proliferation.[18]

DIAGNOSIS

Analysis of all reported TSH-omas revealed no preferential distribution between sexes and indicated that the disease may occur at any age (Table 2). Two thirds of all patients presented with a long history of thyroid dysfunction, mistakenly diagnosed as Graves' disease and inappropriately treated. In fact, several clinical features of hyperthyroidism, including diffuse goiter, tachycardia, weight loss, and other features, are present in both conditions. Contrary to the situation found in Graves' disease, the incidence of circulating antithyroid autoantibodies in patients with TSH-oma was similar to that found in the general population, and thyroid-stimulating autoantibodies were found to be elevated in only three of 72 patients who had Graves' disease or developed it after pituitary surgery. Graves-associated bilateral exophthalmos was reported in three patients, and unilateral protrusion due to orbital invasion by the pituitary tumor was seen in three further subjects.[2,4] Multinodular goiter was observed in a few TSH-omas, and in one case was associated with thyroid follicular carcinoma,[21] suggesting a possible role of long-standing TSH hypersecretion in nodule formation and tumorigenesis. Concomitant GH hypersecretion was accompanied by typical acromegalic features, while hyperprolactinemia usually presented with amenorrhea and galactorrhea. In most patients, signs and symptoms due to the expanding tumor mass prevail over those due to thyroid hyperfunction, since the majority of TSH-omas are macroadenomas. Visual field defects were recorded in half, headache in a sixth, and menstrual disorders in a third of the reported cases. Central hypogonadism and delayed puberty were found in a few patients.

Table 2. Clinical and Biochemical Indices Useful in Differentiating Patients with TSH-oma From Those With RTH

Feature	TSH-oma	RTH
Age (yr)	11-84	0.1-80
Sex (F/M)	1.4/1	1.2/1
Familial (%)	0	78
Previous thyroid ablation (%)	39	49
CT scan or MRI lesions (%)	97	2
Mean TSH levels*	3.0 ± 4.0	1.8 ± 1.1
Mean FT_4 levels*	35.2 ± 5.1	31.2 ± 7.7
Mean FT_3 levels*	13.5 ± 4.0	11.8 ± 3.0
Serum TSH levels in the normal range (untreated patients) (%)	35	59
High serum α-subunit levels (%)†	89	2
High serum α-subunit/TSH molar ratio (%)†	85	2
Elevated SHBG (%)‡	95	0
Normal and/or exaggerated TSH response to TRH (%)	15	96
Qualitatively normal TSH response to T_3 (%)§	15	100

*Our series. Normal range for TSH, 0.26 to 4.0 mU/L; for FT_4, 9 to 18 pmol/L; for FT_3, 4 to 8 pmol/L.

†Normal values vary depending on the circulating TSH and gonadotropin levels of the subject.[19]

‡Normal values vary depending on the age and sex of the subject.[20]

§Werner's test (80 to 100 μg of T_3 for 8 to 10 days). Quantitively normal responses to T_3, ie, complete inhibition of both basal and TRH-stimulated TSH levels, have never been recorded in either group of patients.

LABORATORY FINDINGS

High concentrations of circulating thyroid hormones in the presence of detectable TSH levels characterize the disease. It must be emphasized that it is necessary to use direct methods of measurement and not those based on the analog technique, so that the free moiety of circulating thyroid hormones is measured rather than the total, to prevent possible misinterpretation due to variation of normal or abnormal thyroid hormone transport proteins.[2] Serum TSH levels, as well as FT_4 and FT_3 concentrations, showed a broad range of values (Table 2). About a third of untreated and a quarter of treated patients with TSH-oma showed TSH levels within the normal range, and no correlation between free thyroid hormone and TSH levels was found. Variations in the biological activity of secreted TSH molecules most likely account for such findings.[8] In the majority of patients with TSH-oma, and regardless of previous thyroid ablation, circulating α-subunit levels, as well as the α-subunit/TSH molar ratio, were clearly elevated. Either an unbalanced secretion of the subunit or the presence of a mixed TSH/α-subunit adenoma[22] may account for these results.

Although previous studies have suggested that an α-subunit/TSH molar ratio greater than 1.0 is indicative of the presence of a TSH-secreting pituitary adenoma,[1] the finding of α-subunit/TSH molar ratios as high as 5.7 in normal subjects and 29.1 in postmenopausal women indicates the need to compare the individual values with those recorded in control groups matched for TSH and gonadotropin levels before drawing any diagnostic conclusion.[19]

The measurement of several parameters of peripheral thyroid hormone action both in vivo and in vitro may help in quantifying the degree of peripheral hyperthyroidism. We have found levels of sex hormone–binding globulin (SHBG) in the hyperthyroid range in more than 80% of patients with TSH-oma,[20] an observation that led us to propose that such a measurement may distinguish patients with TSH-omas from those with thyroid hormone resistance (RTH). Several stimulatory and inhibitory tests have been used to evaluate TSH secretory dynamics in patients with TSH-

oma. Of these, TRH levels appear to be the most useful, as an absent TSH response, as well as dissociation between the TSH and α-subunit responses, is frequently recorded. Treatment with antithyroid drugs was followed by a clear increase in TSH levels in approximately 60% of patients. In most of them, a possible reduction of FT_4 and FT_3 into the hypothyroid range may have caused additional TSH secretion from the normal thyrotropes surrounding the pituitary tumor. However, the adenoma appears very sensitive to even small reductions in circulating levels of FT_4 and FT_3, as observed during close follow-up evaluation of one patient in whom a TSH increase was manifest when both FT_4 and FT_3 were still in the upper limit of the normal range.[2] These data indirectly corroborate the hypothesis that the classical negative feedback loop is functional in TSH-omas only in response to decrements of circulating thyroid hormone levels. Finally, a normal response to the T_3 suppression test in TSH-omas (Table 2) has never before been reported.

DIFFERENTIAL DIAGNOSIS

The finding of unsuppressed TSH in the presence of elevated FT_4 and FT_3 levels definitively differentiates hyperthyroidism due to a TSH-secreting pituitary adenoma from Graves' disease and other forms of thyrotoxicosis. Furthermore, the existence of a TSH-oma is suggested by a computed tomographic (CT) scan or magnetic resonance image (MRI) showing an alteration of pituitary content, as well as by the possible presence of neurological signs and symptoms (visual defects and headache) or clinical features of concomitant hypersecretion of other pituitary hormones (acromegaly, galactorrhea, and amenorrhea). Nevertheless, the differential diagnosis between hyperthyroidism from a TSH-oma and that from pituitary RTH may be difficult when the pituitary adenoma appears to be undetectable by CT and MRI, or doubtful pituitary lesions (empty sella or imaging artifacts) are present. No significant differences in age, sex, previous misdiagnosis followed by thyroid ablation, TSH levels, or free thyroid hormone concentrations were found between patients with TSH-oma and those with RTH (Table 2).[23] However, contrary to the situation usually found in RTH patients, familial cases of TSH-oma have never been documented. Serum TSH levels within the normal range are more frequently found in RTH, where increased bioactivity of the secreted molecules is consistently found.[24] Moreover, the findings of elevated α-subunit concentrations and/or a high α-subunit/TSH molar ratio, absent/impaired TSH responses to TRH administration and to the T_3 suppression test, and values of circulating SHBG in the hyperthyroid range (Table 2) favor the presence of a TSH-oma.

TREATMENT

The goal of treatment of TSH-omas is to remove the pituitary adenoma or, alternatively, to block TSH secretion and cell replication, and restore a euthyroid state. Therefore, the first therapeutic approach to TSH-secreting pituitary adenomas should be to surgically debulk the tumor by trans-sphenoidal or subfrontal adenomectomy. If there are contraindications to the surgery, pituitary irradiation (using no less than 45 Gy fractionated at 2 Gy/d or 10 to 25 Gy in a single dose if a gamma knife is available) and subsequent somatostatin analog administration should be considered. The combined use of surgery and radiotherapy resulted in normalization of circulating thyroid hormone levels and complete removal of tumor mass in 40% of recorded patients, who may therefore be considered to have been completely cured. An additional 33% of patients may be judged to have improved, as normalization of circulating thyroid hormone levels was achieved in all, although there was no complete removal of the adenoma. Together, these findings indicate that approximately two thirds of TSH-omas are brought under control by surgery and/or irradiation. In the remaining patients, TSH hypersecretion was unchanged after these treatments, a fact that undoubtedly reflects the large size and the invasiveness of the tumor. Evaluation of other pituitary functions, particularly corticotropin (ACTH) secretion, should be carefully undertaken soon after surgery and checked again every year, especially in patients treated by radiation.

The evaluation of the efficacy of surgery or radiotherapy may be made more difficult by previous thyroid ablation and, even in patients with normal free thyroid hormone concentrations, doubts may exist over the complete removal or destruction of all tumoral cells. In our experience,[25] the most sensitive, specific, and predictive factors that resolve this problem are the findings of unmeasurable TSH levels both 1 week after surgery and after a T_3-suppression test. Only patients in whom TSH secretion is completely blocked are truly cured. In the others, additional treatment with irradiation and/or somatostatin analogs or, alternatively, careful monitoring by pituitary imaging, should be undertaken in order to prevent or detect further increases in tumor size and recurrence of hyperthyroidism.

Modern medical treatment of TSH-omas is by the administration of somatostatin analogs, ie, octreotide or lanreotide (Table 3).[26-28] In fact, octreotide was effective in reducing TSH and α-subunit secretion in 90% of our cases, with normalization of TSH in 75% and restoration of the euthyroid state in the majority. In 45% of patients, a clear shrinkage of tumor mass could be demonstrated, and vision improvement was observed in 80%. Tachyphylaxis occurred in 25% of patients and responded to increasing octreotide doses, whereas escape from the inhibitory effects was recorded in 12% of cases. In only 4% of cases has a true resistance to octreotide treatment been documented.[28]

Table 3. Medical Treatment (octreotide, 50-500 μ two or three times daily, subcutaneously) of Patients with TSH-oma: Results of Long-Term Studies

Effect of Octreotide	% of Patients
Normalization of thyroid hormone secretion	92
TSH reduction (> 50% vs. basal)	90
α-subunit reduction	90
Vision improvement	80
Tumor mass shrinkage	45
True escape	12
Discontinuation of therapy due to side effects	6

Interestingly, in almost all patients with mixed TSH/GH hypersecretion, signs and symptoms of acromegaly concomitantly disappeared. Patients on octreotide have to be carefully monitored, as untoward side effects, such as cholelithiasis and carbohydrate intolerance, may become manifest. In some of our cases, the marked suppression of TSH secretion and consequent biochemical hypothyroidism required L-thyroxine substitution. Whether somatostatin analog treatment may be an alternative to surgery and irradiation in patients with TSH-oma remains to be established.

CONCLUSIONS

Detection of normal or elevated TSH levels, measured by ultrasensitive assays, in hyperthyroid patients should raise suspicion of a TSH-oma. Confirmation by CT scan or MRI leads to recognition of these rare lesions, even at an initial stage of tumor development. Additional diagnostic factors in equivocal situations are an absent or impaired TSH response to TRH, discrepancies between the TSH and α-subunit responses to the tripeptide, high levels of SHBG, high levels of α-subunit, and a high α-subunit/TSH molar ratio. Familial studies are useful in ruling out the presence of RTH. Surgical removal of the TSH-oma is the best therapeutic option, leading to prompt clinical and biochemical remission of hyperthyroidism in most patients. In cases of surgical failure, radiotherapy and octreotide treatment are advised, owing to the high success rate obtained with this drug, both in terms of restoration of euthyroidism and shrinkage of tumor mass. Undetectable TSH levels 1 week after surgery are highly predictive of a definitive cure. Conversely, normalization of thyroid function after surgery does not necessarily mean complete removal of the tumor. Therefore, more comprehensive criteria of cure based on the behavior of cosecreted hormones, as well as dynamic testing such as TSH suppression by T_3, should be used. The recurrence rate of TSH-omas does not appear to be high, at least in the first years after successful pituitary surgery.

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