Learning Objectives:

- Explain how inappropriate (normal or increased) thyrotropin (TSH) secretion in the presence of hyperthyroidism can be a clue to a thyrotroph adenoma of the pituitary.
- Describe the clinical and endocrinological features of thyrotroph pituitary adenoma and how to distinguish it from other states of inappropriate TSH secretion.
- Define the roles of pituitary surgery, radiotherapy, and drug treatment in the management of thyrotroph pituitary adenoma.

Introduction

Physiological thyroid function is intricately controlled by an elegant interplay between stimulatory hypothalamic influences and a negative feedback system. The major stimulatory influence is hypothalamic thyrotrophin-releasing hormone (TRH), which induces thyroid-stimulating hormone (TSH) secretion by pituitary thyrotrophs. In turn, TSH is transported by the blood stream to the thyroid gland, where it promotes synthesis and release of the thyroid hormones, triiodothyronine (T₃) and thyroxine (T₄). Triiodothyronine is the most important physiologic inhibitor of TSH secretion. Increased circulating serum T₃ levels act at the hypothalamus and pituitary to down-regulate the hypothalamic–pituitary–thyroid axis. In addition to these major influences, dopamine, somatostatin, and corticosteroids possess TSH secretion-inhibiting properties, whereas epinephrine and estrogens have stimulatory effects [1]. Modern immunoassay techniques allow a clear differentiation between normal and subnormal serum TSH concentrations. Hyperthyroidism is most often caused by primary thyroid disease, such as autonomous hyperfunctioning nodular goiter or overstimulation by immunoglobulins (Graves disease). In these conditions, TSH secretion is clearly suppressed to...
subnormal levels. However, a small group of patients with hyperthyroidism have normal or even increased TSH levels, and in these conditions, it is TSH itself that is responsible for thyroid hyperstimulation. A normal or increased level of TSH observed in the presence of increased serum thyroid hormone indicates a disruption of feedback regulation and is termed inappropriate secretion of TSH [2, 3], TSH-induced hyperthyroidism, or central hyperthyroidism [4]. Inappropriate secretion of TSH may result either from a thyrotroph pituitary adenoma (TSH-secreting pituitary adenoma, thyrotropinoma) or from a selective resistance to thyroid hormone in which defective, but nonneoplastic pituitary thyrotrophs, are not sufficiently suppressed by increased circulating T3 levels. Careful radiological, laboratory, and clinical studies are required to differentiate between these two forms of inappropriate TSH secretion (i.e., neoplastic and nonneoplastic disease). It is also important to distinguish these conditions from pituitary thyrotroph hyperplasia resulting from chronic severe hypothyroidism. In such cases, the lack of adequate thyroid hormone feedback results in excess TSH secretion, and the consequent thyrotroph hyperplasia is a condition that may also result in a space-occupying pituitary lesion. The latter, however, is usually differentiated from adenoma, because in most cases hyperplasia will regress after regular substitution therapy with thyroid hormones.

Although this short review is focused on thyrotroph adenomas, the author considers it necessary to describe briefly the nonneoplastic conditions, because these require different management than that for thyrotropinomas. Differential diagnosis is therefore imperative for proper management. The terms thyrotroph adenoma, thyrotropinoma, TSH-secreting pituitary adenoma, and TSHoma are used synonymously.

### Inappropriate Secretion of Thyroid-Stimulating Hormone From Thyrotroph Adenoma

Historically, pituitary tumors producing TSH were considered exceptionally rare. Only when specific sensitive assays for TSH became available could this condition be diagnosed. Hamilton et al. [5] were the first to describe a case of hyperthyroidism secondary to a TSH-secreting pituitary adenoma diagnosed by modern radioimmunoassay techniques in 1970. Thyrotroph adenomas may arise from a de novo somatic mutation of a thyrotroph cell or may be caused by thyrotroph hyperplasia after hypothyroidism. Their incidence is actually low and ranges from 0.2% to 0.9% [6–8]. To date, however, more than 300 cases have been reported, mostly in small series or as anecdotal findings. Most cases of inappropriate secretion of TSH are caused by a thyrotropinoma.

Patients with a thyrotroph adenoma of the pituitary gland usually present with signs of hormonal oversecretion. Goiter and signs of hyperthyroidism are the most frequent initial symptoms. Many of these patients then unfortunately undergo therapies targeted primarily to the thyroid. This is because the underlying cause of the disease remains unrecognized at this stage. Frequently, goiter recurs after subtotal surgical thyroidectomy or radioiodine therapy, at which point the diagnosis of a thyrotropinoma is established [4, 9]. Later, with progression of adenoma size, such symptoms as headache, visual disturbances, and other disturbances associated with a pituitary mass lesion (e.g., a third nerve palsy) become apparent and direct the clinical attention to the sellar region. Because most of these tumors are medium or large, some degree of hypopituitarism is commonly encountered. The patients lack stigmata of Graves disease, such as ophthalmopathy, pretibial edema, and acropathy. Unilateral exophthalmus, observed in the case reported by Yovos et al. [10], was the result of invasion of the orbit. Some patients who have plurihormonal adenomas present with acromegaly or symptoms consistent with the diagnosis of prolactinoma. The age of the patients reported to date ranged from 13 [11] to 84 [7] years. The most common age range of those coming to clinical attention was between 30 and 60 years [12]. In a total of four cases, there was an association between multiple endocrine neoplasia type 1 and a thyrotropinoma [13, 14]. In contrast to autoimmune hyperthyroidism, there is no sex predilection for thyrotroph adenomas.

### Endocrine Testing

It is characteristic of these tumors that the TSH level is not completely suppressed, although circulating levels of T3 and T4 are increased. Patients may have TSH levels that are either increased or within the normal range for euthyroid individuals, despite the presence of hyperthyroidism. A specific and sufficiently sensitive immunoassay needs to be used to document inappropriate secretion of TSH and, thus, central hyperthyroidism [4, 12, 15]. The presence of a pituitary mass lesion and the laboratory feature of inappropriate secretion of TSH are diagnostic. Theoretically, a hormonally inactive pituitary adenoma could coincide with primary hyperthyroidism. In the latter case, completely suppressed serum TSH concentrations would exclude the presence of a TSH-secreting adenoma. The magnitude of TSH increase in patients with TSH-secreting pituitary tumors has been reported to range from 1.1 to 568 mIU/L [7, 16]. The mean serum TSH levels have been found to be significantly higher in patients with a treated thyroid compared with those with an intact thyroid [17]. The biological activity of the TSH
produced by thyrotroph adenomas varies considerably. Immunoreactive TSH synthesized from a thyrotroph adenoma when partially purified by immunoaffinity chromatography showed a higher activity in stimulating adenylate cyclase from a human thyroid membrane preparation than normal TSH [18, 19]. Gel-filtration studies revealed that this “biologically hyperactive” TSH had a smaller apparent molecular weight than normal TSH. Increased biologic activity of tumor TSH was also found by using a cytotoxic bioassay [20]. Additionally, Kourides et al. [21] demonstrated that patients with TSH-secreting pituitary adenomas usually produce excess amounts of the common glycoprotein α-subunit (α-TSH), resulting in a molar ratio of greater than 1. Although all 27 patients in the study by Smallridge [22] fulfilled this criterion, a few patients with unequivocally documented thyrotropinomas had levels less than 1.0. [4, 7, 11, 13, 23, 24]. Furthermore, a few cases of thyrotropinomas with undetectable α-subunit levels have been reported [6, 7, 16, 24]. In the authors’ series, one of seven patients had an undetectable serum α-subunit. However, in two further patients with normal α-subunit levels, the α-subunit-to-TSH ratio was less than 1.0. Furthermore, the presence of α-subunit-to-TSH ratio as high as 5.7 in control subjects with normal levels of TSH and gonadotropins and 29.1 in euthyroid postmenopausal women indicate the need to compare the individual level with those of controls matched for TSH and gonadotropin levels before making any diagnostic conclusions [14]. Thus, although generally helpfully, the α-subunit-to-TSH ratio warrants some caution. The β-TSH levels are normal in patients with thyrotropinomas. Thyrotroph microadenomas may pose a much greater diagnostic problem, because they might escape imaging detection because of their minute size [25]. Sophisticated magnetic resonance imaging using thin-section techniques and gadolinium-enhanced images is required to document these lesions that have an excellent prognosis if submitted to transsphenoidal pituitary microsurgery.

During the past 30 years, many patients with TSH-secreting pituitary adenomas underwent a variety of provocative and suppressive tests. The TRH stimulation test is generally believed to be the most important of them, and it was originally attributed major importance in the discrimination of tumorous and nontumorous inappropriate TSH secretion. Although basal TSH levels were measurable with thyrotropinomas, only 25% of these patients exhibited a greater than 100% increase from basal values after intravenous TRH administration [4, 15, 16]. However, 39% of thyrotropinoma patients had a significant response of TSH after TRH administration [22, 26]. Thus, a lack of TSH response to TRH is consistent with a TSH-secreting pituitary adenoma. However, a positive test result does not totally exclude neoplastic TSH secretion from a thyrotroph adenoma. Most patients with thyrotroph pituitary tumors have at least some response of TSH after TRH administration. Despite the variable response of TSH to TRH in these patients, α-TSH usually parallels the TSH response [21, 25, 27, 28].

The influence of basal thyroid hormones on TSH secretion can be indirectly deduced from the response of TSH to thyrostatic medical treatment. For example, in 70% of thyrotropinoma cases, an increase of TSH levels occurs when antithyroid medical treatment is instituted to control hyperthyroidism [22]. It is not yet clearly elucidated whether this increase in serum TSH after thyrostatic drug administration is caused by increased secretion by the normal or adenomatous thyrotrophs. Low basal TSH levels that lack stimulation after TRH administration, however, support the concept that normal thyrotrophs are suppressed in this condition and that they only regain function some time after resection of the TSH-secreting adenoma. Ectopic TRH secretion has not yet been reported. Testing for antithyroglobulin and antимicrosomal antibodies yields negative results in patients with thyrotroph adenomas, unless there is a co-existing thyroid immunopathy.

Despite the fact that the vast majority of patients with TSH-secreting adenomas exhibit an oversecretion of only TSH (and α-subunit), several patients with thyrotropinomas were found to have a co-secretion of TSH and other pituitary hormones [14, 17]. Frequently, this multihormonal potency is expressed by concomitant excessive growth hormone and prolactin secretion. Many instances of TSH hypersecretion associated with acromegaly have been reported [16, 19, 29, 30]. The combination was found in 13 patients in the reviews by Smallridge [22] and in seven patients reviewed by Faglia et al. [4]. Acromegaly is frequently the cardinal clinical feature of these patients. Other patients have hyperprolactinemia concomitant to TSH hypersecretion; the highest incidence of this combination (77%) in a single series was reported by Gesundheit [16].

**In Vitro Studies and Morphology**

Because of their rarity, there are few studies on the behavior of thyrotroph adenomas in vitro compared with other hormone-secreting pituitary adenomas. Nevertheless, a number of reports from various groups in the literature demonstrate consistent findings from which some conclusions can be drawn concerning the in vitro characteristics of thyrotropinomas. In an early report, pituitary tumor material from a 36-year-old woman with increased serum TSH and T₄ levels was found to secrete only TSH.
Absence of activating mutations in the 
Gaq, G11, and thyrotropin-releasing hormone receptor genes [36]. None of these six tumors examined by us contained gsp oncogenes, indicating that these specific defects, commonly present in growth hormone-secreting tumors and some functionless tumors, are unlikely to be a common causative factor in thyrotropinomas [6, 35].

Thyrotropinomas originate from thyrotroph cells of the anterior pituitary. Although benign, they have a tendency to invade adjacent structures more often than other pituitary adenomas [37–39]. Thus, their biological behavior is similar to adrenocorticotrophic hormone-secreting adenomas associated with Nelson syndrome; growth of these adenomas is also promoted by a deficient negative feedback system [37].

Thyrotroph adenomas are chromophobic and contain a few small PAS-positive cytoplasmic granules or, less frequently, large PAS-positive lysosomal globules. Immunohistochemistry reveals the presence of TSH and α-TSH in most, but not all, tumors [40, 41]. Frequently, the plurihormonality of these tumors is reflected by immunohistochemistry, which most frequently documents growth hormone and prolactin. Occasionally, it also documents gonadotropins. A double-staining study showed that β-TSH and α-TSH were frequently co-localized in the same cell, but some cells were found to stain only for α-TSH [40].

Terzolo et al. [42] could detect α-TSH immunohistochemically in all cells of their tumor. Using double immunolabeling, they found that only a few cells stained positively for both α-TSH and β-TSH, and they concluded that their tumor was composed of two different cell types.

Ultrastructurally, many of these adenomas are monomorphic and consist of cells with the characteristics of thyrotrophs [41, 43]. Electron microscopy reveals that the tumors are composed of medium or large, well-differentiated cells. The cytoplasm contains a well-developed, rough, endoplasmatic reticulum. The Golgi complexes are present in a variable degree. The secretory granules are usually spherical and small, measuring 100 to 200 nm in their largest diameter. Occasionally, these adenomas have larger secretory granules that measure up to 400 nm in diameter.

Recently, Mixsons et al. [39] reported the first case of a thyrotropin-secreting pituitary carcinoma.

Surgery

Selective adenectomy is considered the treatment of choice for TSH-secreting adenomas. The characteristics applied to define "remission" and "success" vary considerably and are controversial [6, 17, 22, 38, 44, 45]. In the earlier literature, a success rate of only 31% (19 of 62 patients) was reported for a compiled series [4]. Once postoperative irradiation was added, the "normalization rate" increased to 42%. Grisoli et al. [38] found only five cures achieved by transcranial surgery in 16 patients when they reviewed the literature one decade ago. Early reports on surgical treatment were discouraging. Failure to normalize the hormone excess and to eradicate the entire tumor mass were frequent. McCutcheon et al. [45] reported a 50% mortality rate (2 of 4) from surgical treatment of large and invasive thyrotroph adenomas. The clinical outcome of these patients was adversely influenced by delay in establishing the correct diagnosis and improper first-line treatments. In the National Institutes of Health series [16], the average delay between documentation of clinical hyperthyroidism and the diagnosis of a thyrotropinoma was 6.2 ± 4.8 (standard deviation) years. Four of these patients with a poor surgical outcome and in whom invasive macroadenomas developed had been treated for primary hyperthyroidism for a period as long as 18 years. More recent series [6, 7, 17, 40, 44] report more promising figures, with normalization rates of 75% to 100% (dependent on the criteria for normalization). Subnormal serum TSH levels are the best indicators of successful surgery in patients with an intact thyroid gland. In patients who underwent successful operation, TSH and α-TSH levels normalized quickly, as demonstrated by perioperative and postoperative measurements. In the authors’ series, normal values for both serum
parameters were achieved within 500 minutes after tumor resection in the patients who underwent successful transsphenoidal surgery for thyrotropinoma [35]. However, this time interval is clearly dependent on the degree of TSH excess before surgery. Beckers et al. [7] observed the recurrence of inappropriate TSH secretion and thyroid hormone increases as early as 10 days after initial normalization of the parameters after surgery of an invasive macroadenoma. The plasma clearance rates may, however, vary because of different glycosylation rates. The α-TSH and TSH secreted by thyrotroph tumors have a plasma half-life of 50 to 80 minutes [46]. It is important to perform the postoperative assessment when the patient is in a steady-state condition. Losa et al. [44] favor the T₃ suppression test as the most stringent criterion for a complete postoperative remission. The results of transsphenoidal surgery are particularly favorable for thyrotroph microadenomas (≤10 mm), which are uncommon [11, 13, 14, 17, 25, 31, 44, 45, 47, 48]. However, the surgery can have an unfavorable outcome because of tumor invasion. The biological behavior of the neoplasms in terms of their invasive nature directly correlates with previous thyroid ablation [14, 44]. A primary therapy targeted to the thyroid gland seems to increase the proportion of large and invasive adenomas. In these, the main goal of surgery, whether via the transsphenoidal or transcranial approach, is to debulk the tumor to obtain a more promising outcome after subsequent irradiation.

Radiation Therapy

Conventional external irradiation of the adenoma using a fractionation scheme that delivers approximately 45 Gy over the course of 4 to 5 weeks to the tumor has commonly been used to supplement surgery in patients in whom surgery has failed to eradicate the tumor mass and to normalize TSH secretion [22]. Rarely, radiation is used as the primary treatment [49]. One would expect that, like with other pituitary tumors, irradiation would cause a progressive decrease of excessive hormone secretion. There is little documentation that this occurs in thyrotroph adenomas. The author has observed the normalization of TSH-secretion in an 11-year-old girl with an invasive giant thyrotropinoma who had incomplete transcranial surgery 8 years after external postoperative radiotherapy [6]. In a previous compilation of therapy results [22], for patients treated by external irradiation, only one of eight patients had disease cured; however, 11 of 24 patients (46%) who underwent both surgery and postoperative irradiation had disease cured and no sign of disease for a follow-up period ranging between 3 and 36 months. Thus, irradiation of residual tumor is recommended once surgery fails to eradicate the tumor mass completely or if inappropriate secretion of TSH persists postoperatively.

Medical Therapy

Because patients with thyrotropinomas usually have hyperthyroidism, some form of medical therapy is usually required to achieve euthyroidism before pituitary surgery. This medical therapy can be directed toward either the thyroid or the pituitary gland. The conventional approach is to administer inhibitors of thyroid hormone synthesis, namely thiamines or potassium iodide as a short-term medical treatment to prepare the patient for surgery [12]. In some cases, the symptoms can be controlled by β-adrenergic blockers alone. Because decreasing thyroid hormones may promote pituitary tumor growth, long-term administration of antithyroid drugs should be avoided, as should surgical or radioiodine-induced thyroid ablation. Therapies directed at the thyroid may cause an increase in circulating serum TSH concentrations. In addition, therapy directed at the thyroid may increase the proliferative potential of these tumors. In addition, permanent thyroid-directed therapy complicates the follow-up of the patient after pituitary surgery, because recurrence of the thyrotropinoma can no longer be recognized by recurrent hyperthyroidism [12]. Medical therapy with dopamine agonists has proved to be generally unsuccessful in these tumors [22, 50].

In contrast, octreotide, a long-acting somatostatin analogue, is a valuable medical treatment option for TSH-secreting pituitary adenomas [33]. A rapid suppression of TSH and α-TSH levels occurs, and subsequently, with prolonged therapy, so does a decrease in increased thyroid hormones [51]. Administration of a single dose of 50 to 100 μg of octreotide subcutaneously led to a significant decrease of TSH levels in all but one of the 21 patients tested by Chanson and Warnet [50]. Fischler and Reinhart [52] have documented rapid tumor shrinkage and recovery from hyperthyroidism within 3 weeks of octreotide treatment in a patient with a large macroadenoma. Long-term treatment with octreotide has been shown to normalize TSH secretion in 78% of patients [50]. In some cases, octreotide also produces a reduction in tumor size, which leads to an improvement in visual function [50, 53] and to a radiologically detectable regression of the tumor mass [7, 54–57], possibly reflecting its direct mode of action. This therapy is also associated with side effects. Also, at least initially, most patients experience some abdominal discomfort and diarrhea after initiation of octreotide. Gallbladder sludge and stones can occur during long-term treatment. Because the drug tends to restore euthyroidism, it should be the drug of choice during both the preoperative [58] and postoperative [59] pe-
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Inappropriate Secretion of Thyroid-Stimulating Hormone Without Pituitary Tumor

Hyperthyroidism resulting from inappropriate secretion of TSH is described in several patients without evidence of a pituitary tumor. In these patients, the hyperthyroidism is thought to be caused by a selective resistance of the pituitary to thyroid hormones. A selective pituitary resistance to thyroid hormone is mandatory for this clinical manifestation, because hyperthyroidism can only occur if the pituitary gland is more resistant to thyroid hormone than peripheral tissues [26]. This group comprises approximately 25% of patients with inappropriate secretion of TSH. In 1975, Gershengorn and Weintraub [2] reported the first case of nonneoplastic hypersecretion of TSH. To date, the total number of patients reported with this condition is approximately 200. The mechanism of resistance usually is related to point mutations in the ligand-binding domain of TR-B1 that preclude normal T₃ binding [22]. Selective pituitary resistance to thyroid hormone is less frequent than generalized resistance of all tissues to thyroid hormone. The latter, however, does not produce clinical symptoms. It is of paramount importance to differentiate nonneoplastic inappropriate secretion of TSH from the thyrotroph adenoma, because the appropriate therapies differ significantly [4, 62]. Clinically, hyperthyroidism is a consistent finding in patients with selective pituitary resistance. These patients lack ophthalmopathy and pretibial edema, as do patients with a TSH-secreting pituitary tumor. High-resolution imaging of the sella turcica is probably the most important and reliable diagnostic tool. Poor-quality imaging in the past has obscured a clear differentiation of these pathogenetic entities and has led to misdiagnosis of several cases. Tests for thyroid antibodies and thyroid-stimulating antibodies are usually negative. During endocrine testing, these patients exhibit a suppression of TSH by thyroid hormones, somatostatin, and dopamine agonists [4, 12, 26]. After TRH stimulation, an exaggerated response is usually found, which is a clearly different response than that of most patients with thyrotropinomas. The suppression of TSH after high doses of exogenous glucocorticoids, however, is similar in patients both with and without tumors. The α-subunit level is usually normal, as is the α-subunit-to-TSH ratio, which is less than 1.0. Primary therapy should be aimed at medical suppression of TSH hypersecretion. Octreotide is variably effective. Although an intravenous infusion readily suppressed TSH secretion, the effects of prolonged subcutaneous injection were weak and did not last long [63]. A T₃ analog called 3,5,3'-triiodoacetic acid binds to nuclear receptors with higher affinity than T₃, has negligible metabolic effects, and can inhibit TSH secretion [64]. Both T₃ and T₄ are known to suppress TSH secretion, but a normalization of TSH is rarely achieved. Furthermore, the medications cause hyperthyroidism. Long-term therapy with glucocorticoids is not recommended because of the side effects.

There are a few other conditions that can be confused with TSH-induced hyperthyroidism. These result from abnormalities in pituitary and thyroid physiology and misinterpretations of laboratory data: 1) laboratory artifacts; 2) inhibition of T₄ to T₃ conversion; 3) abnormal thyroid hormone binding to serum proteins; and 4) disequilibrium (nonsteady state) of thyroid hormones and TSH [4, 12].

Hypothyroidism and Pituitary Tumor

In chronic hypothyroidism, pituitary mass lesions can result from the lack of thyroid hormone feedback. In this context, it does not matter whether hypothyroidism is congenital or induced by iatrogenic thyroid ablation, antithyroid drugs, or x-ray exposure of the thyroid. In an autopsy study of pituitary glands from patients with chronic hypothyroidism [65], thyrotrroph hyperplasia was found in almost all the glands. Significant mass effect was rare [66]. Hyperplasia was diffuse. In 25% of the specimens, nodular thyrotrroph hyperplasia was detected and five tiny microadenomas staining for TSH were found. In 20% of these pituitaries, lactotroph hyperplasia was present.

Pituitary mass lesions in the presence of hypothyroidism have important clinical implications. Their management differs completely from the management of thyrotrrophin-secreting adenomas.

The key diagnostic finding is hypothyroidism. This occurs more commonly in women than in men and is frequently a result of autoimmune thyroiditis. Thyroid antibodies will commonly be found in the serum. Congenital hypothyroidism and poor compliance with thyroid hormone substitution therapy are other common causes. Hypothyroidism is usually asymptomatic once it causes thyrotrroph hyperplasia of the pituitary. A few patients have symptoms of hyperprolactinemia resulting from mixed thyrotrroph hyperplasia [34]. Occasionally, a patient will be completely asymptomatic. Unexplained weight gain, cold intolerance, fatigue, and headache are the most frequent presenting symptoms. In children, thyrotrroph hyperplasia from hypothyroidism has been reported in association with preco-
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