

TSH-induced hyperthyroidism caused by a pituitary tumor

Paolo Beck-Peccoz* and Luca Persani

SUMMARY

Background A 45-year-old man presented with frontal headache and visual disturbances to our clinic. For the previous 5 years, he had been receiving treatment for long-lasting mild hyperthyroidism with antithyroid therapy, but therapy had not been carefully followed. During the last 2 years he had also complained of erectile dysfunction and loss of libido. On physical examination, he had a small goiter, normal skin, no Graves' ophthalmopathy, normal BMI, and reduced testis volume and pubic hair.

Investigations Serum levels of free T₃ and T₄, serum prolactin, testosterone, serum gonadotropins, insulin-like growth factor 1, adrenocorticotrophic hormone, and cortisol were measured. MRI scan, TSH-releasing hormone test, and T₃ suppression test were carried out. Levels of pituitary glycoprotein hormone α -subunit and sex-hormone-binding protein were also measured.

Diagnosis Hyperthyroidism caused by a mixed pituitary adenoma that secretes prolactin and TSH.

Management Trans-sphenoidal resection of the pituitary tumor. After surgery, T₃ suppression test failed to completely suppress TSH secretion, which suggested a persistence of residual adenomatous cells. Hyperthyroidism and hypogonadism recurred after 5 years, therefore, treatment with lanreotide was initiated, and resulted in complete resolution of signs and symptoms of the disease.

KEYWORDS hyperthyroidism, pituitary adenoma, prolactin, somatostatin analogs, TSH

CME

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THE CASE

In 1998, a 45-year-old man presented with frontal headache and visual disturbances to the outpatient department of our clinic. He had been receiving treatment with antithyroid therapy (methimazole 15 mg per day orally) for the previous 5 years for long-lasting mild hyperthyroidism, but he followed the therapy erratically, and spontaneously stopped taking the drug 2 months before presentation. During the 2 years before presentation, he had experienced erectile dysfunction and loss of libido.

On physical examination, he had a small goiter, normal skin, heart rate of 78 beats per min, no Graves' ophthalmopathy, normal BMI (24.3 kg/m²), and reduced testis volume and pubic hair. Laboratory investigations revealed high levels of circulating free T₄ and T₃ (free T₄ 28.5 pmol/l, normal range 9–20 pmol/l; free T₃ 12.7 pmol/l, normal range 4–8 pmol/l) in the presence of measurable levels of serum TSH (3.2 mIU/l, normal range 0.3–4.0 mIU/l). These values unquestionably point to the presence of central hyperthyroidism. Moreover, serum prolactin levels were high (4,970 mIU/l, normal range <350 mIU/l), whereas serum testosterone concentrations were low (3.5 nmol/l, normal range 12–45 nmol/l), as were levels of serum gonadotropins (Table 1). Normal levels of serum growth hormone, insulin-like growth factor 1, adrenocorticotrophic hormone (ACTH), and cortisol were recorded in this patient.

MRI of the sella turcica showed a pituitary macroadenoma (diameter 3.5 cm) with suprasellar extension and optic chiasma compression causing bitemporal emianopsia. To exclude the association of a pituitary adenoma that secretes prolactin with a syndrome of 'resistance to thyroid hormone' (RTH), a TSH-releasing hormone (TRH) test was performed. Following the TRH test, TSH levels remained

Table 1 Results of hormone measurements before, during, and after treatment in the patient described.

Parameter	Normal range	Basal	6 months after surgery	3 years after surgery	5 years after surgery (recurrence)	6 months after treatment with cabergoline	During treatment with lanreotide
TSH (mIU/l)	0.3–4.0	3.2	0.5	1.4	2.9	2.8	0.5
Free T ₄ (pmol/l)	9–20	28.5	14.2	15.6	23.4	25.0	12.4
Free T ₃ (pmol/l)	4–8	12.7	5.1	5.3	9.7	9.1	4.3
α-GSU (μg/l)	<1.1	5.7	0.8	NR	2.3	2.1	0.7
TSH peak after TRH (mIU/l)	>3	0.1	NR	NR	1.6	NR	NR
TSH nadir after T ₃ suppression (mIU/l)	<0.0001	3.0	0.6	NR	2.4	NR	NR
PRL (mIU/l)	<350	4,970	210	290	2,560	1,650	220
Testosterone (nmol/l)	12–45	3.5	13.0	25.0	5.9	6.3	24.1
LH (IU/l)	2–10	0.2	NR	4.3	0.4	0.5	3.7
FSH (IU/l)	1–8	0.4	NR	5.1	0.6	0.7	2.8
SHBG (nmol/l)	<50	124	41	NR	129	NR	35

Abbreviations: α-GSU, pituitary glycoprotein hormone α-subunit; FSH, follicle-stimulating hormone; LH, luteinizing hormone; NR, not reported; PRL, prolactin; SHBG, sex-hormone-binding protein; TRH, TSH-releasing hormone.

within the normal range. Levels of pituitary glycoprotein hormone α-subunit (α-GSU) and sex-hormone-binding protein (SHBG) were also measured and found to be elevated (5.7 μg/l, normal range <1.1 μg/l, and 124 nmol/l, normal range <50 nmol/l, respectively; Table 1). The diagnosis of hyperthyroidism and hypogonadotropic hypogonadism caused by a mixed pituitary tumour that secretes TSH and prolactin was, therefore, made. The patient's visual disturbances rapidly worsened and he underwent trans-sphenoidal surgery. Serum thyroid hormone and prolactin levels normalized 1 week after trans-sphenoidal surgery, but TSH was still measurable (0.5 mIU/l).

MRI was repeated 3 months after surgery and showed a partial, empty sella without evidence of tumor remnant. A T₃ suppression test (100 μg liothyronine daily for 10 days) showed a lack of a complete suppression of TSH levels, which suggested that a very small portion of the adenoma was still present. Because of a 6-month stable normalization of both thyroid hormone and prolactin levels, in addition to the disappearance of all clinical signs and symptoms (including impotence), no medical therapy was initiated at this point in time. The patient underwent follow-up every 6–12 months after surgery to check that thyroid and prolactin levels remained in the normal range. In 2003, 5 years after surgery, both serum thyroid hormone and prolactin levels

increased (Table 1), and a small tumor residue was seen at high-field MRI. Other pituitary functions, in particular ACTH secretion, were normal. The patient was subsequently treated with cabergoline for 6 months, but no beneficial effect was observed (Table 1). Treatment with 20 mg lanreotide intramuscularly every 45 days was subsequently started, and levels of serum thyroid hormones and prolactin normalized in the patient after 3 months. In 2006, a high-field MRI showed the disappearance of the tumor residue.

DISCUSSION OF DIAGNOSIS

Pituitary adenomas that secrete TSH are a rare cause of hyperthyroidism and have a prevalence of 1 case per million persons worldwide.¹ The majority of these cases (72%) concern adenomas that secrete TSH alone, although this secretion is often accompanied by an unbalanced hypersecretion of α-GSU. An elevated serum α-GSU level and, in particular, a high α-GSU:TSH molar ratio are present in about 80% of patients with pituitary adenomas (mainly macroadenomas) that secrete TSH.¹ A hallmark of this tumor is the biochemical finding of high concentrations of circulating free thyroid hormones in the presence of measurable serum TSH levels. About a quarter of cases of pituitary adenomas that secrete TSH are mixed adenomas, characterized by concomitant hypersecretion of other anterior

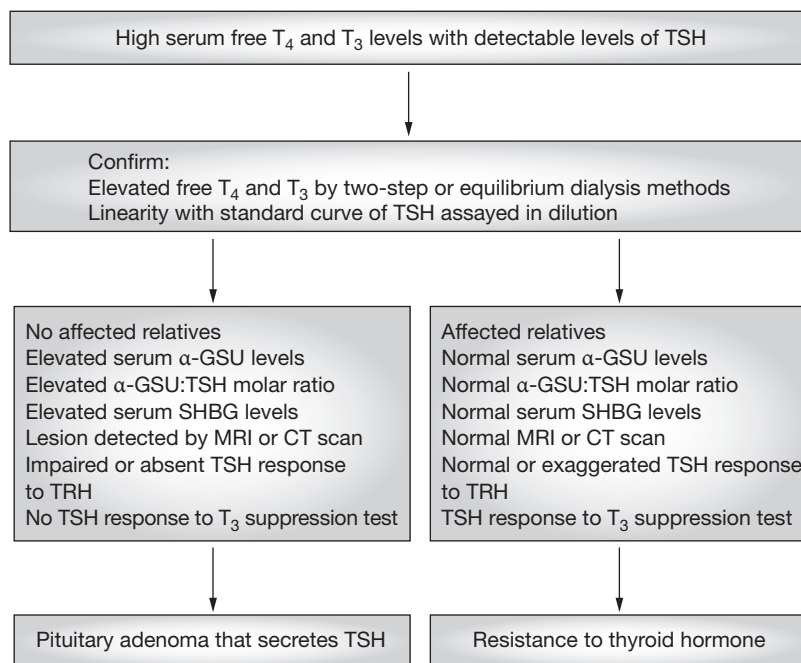


Figure 1 The main clinical parameters that are useful in the differential diagnosis between pituitary adenomas that secrete TSH and syndromes of thyroid hormone resistance. Abbreviations: α -GSU, pituitary glycoprotein hormone α -subunit; SHBG, sex-hormone-binding protein; TRH, TSH-releasing hormone.

pituitary hormones, mainly growth hormone or prolactin.

Clinical signs and symptoms in patients with pituitary adenomas that secrete TSH are caused by either hyperthyroidism or the mass effect of an expanding intracranial tumor. Most of these patients have a long history of thyroid dysfunction, often mistakenly diagnosed as Graves' disease, and a third of these patients undergo an inappropriate thyroidectomy or radioiodine thyroid ablation.¹ In general, clinical features of hyperthyroidism are sometimes milder than those expected from the levels of circulating thyroid hormones. Moreover, individual patients with untreated pituitary adenomas that secrete TSH were reported to be clinically euthyroid.^{1–4} This finding emphasizes the importance of systematic measurement of TSH and free T_4 levels in all patients with pituitary tumors, to disclose those with central hyperthyroidism or hypothyroidism. Severe thyrotoxic features, such as atrial fibrillation, cardiac failure, and episodes of periodic paralysis, are observed in a quarter of cases.^{1,5}

The TRH stimulation test and the T_3 suppression test are the most reliable screening tests for pituitary adenomas that secrete TSH, although they are not pathognomonic. The TSH response

to TRH (200 μ g intravenously) is absent or impaired in about 85% of patients with pituitary adenomas that secrete TSH. On the contrary, a complete inhibition of both basal and TRH-stimulated TSH secretion after a T_3 suppression test (80–100 μ g per day of liothyronine for 8–10 days) has never been recorded in patients with pituitary adenomas that secrete TSH. In patients who have undergone previous thyroid ablation, the T_3 suppression test is the most sensitive and specific in documenting the possible presence of a pituitary adenoma that secretes TSH. High doses of liothyronine, however, are contraindicated in elderly patients or in patients with coronary heart disease. In 2005, a study demonstrated that 2–3 months of treatment with long-acting somatostatin analogs in patients with pituitary adenomas that secrete TSH resulted in a clear decrease in levels of circulating thyroid hormones, as a consequence of the inhibition of TSH secretion,⁶ variation of its biological activity,^{7,8} or both.

Finally, the measurement of several parameters of peripheral thyroid hormone action might help to quantify the degree of peripheral hyperthyroidism, particularly in patients with mild clinical signs and symptoms. In particular, measurement of serum SHBG and carboxy-terminal crosslinked telopeptide of type I collagen (ICTP) levels might help to differentiate patients who are hyperthyroid and patients with adenomas that secrete TSH (all of whom have elevated levels of ICTP and SHBG) from those who have RTH (these patients have the same range of SHBG and ICTP levels as those observed in patients who are euthyroid).^{9,10}

DIFFERENTIAL DIAGNOSIS

In a patient with signs and symptoms of hyperthyroidism, the presence of elevated or detectable TSH levels rules out primary hyperthyroidism. Once the existence of central hyperthyroidism is confirmed, and the presence of methodologic interferences excluded,¹ several diagnostic steps have to be carried out to differentiate a pituitary adenoma that secretes TSH from the syndromes of RTH, particularly the 'selective' pituitary form (Figure 1).

Indeed, the possible presence of neurologic signs and symptoms (e.g. visual defects and headache) or clinical features of concomitant hypersecretion of other pituitary hormones points to the presence of a pituitary adenoma that secretes TSH; furthermore, the presence

Table 2 Results of pituitary surgery alone, surgery plus irradiation, and somatostatin analog treatment of patients with pituitary adenomas that secrete TSH.^a

Effect of treatment	Surgery (n = 144)	Surgery and irradiation (n = 59)	Somatostatin analogs (n = 102)
Proportion of patients with resolution of clinical symptoms (%)	57	62	94
Proportion of patients with a complete reduction of tumor mass (%)	36	28	0
Proportion of patients with a partial reduction of tumor mass (%)	30	41	51
Proportion of patients with no reduction of tumor mass (%)	34	31	49

^aData collected from Beck-Peccoz *et al.*¹

of alterations of the pituitary gland at MRI or CT scan strongly supports this diagnosis. Nevertheless, the differential diagnosis might be difficult when the pituitary adenoma is undetectable by CT or MRI scan, or in the case of confusing lesions, such as empty sella, pituitary incidentalomas, or ectopic tumors.^{2,11} In these cases, elevated levels of α -GSU or a high α -GSU:TSH molar ratio, plus levels of TSH that are unresponsive to either TRH stimulation, a T₃-suppression test, or both, favor the diagnosis of a pituitary adenoma that secretes TSH. Moreover, the finding of similar biochemical data in a member of the patient's family definitely points to the presence of RTH, as familial cases of adenomas that secrete TSH have not been documented. Finally, an apparent association between adenomas that secrete TSH and syndromes of RTH has been recently reported,¹² and somatic mutations in the thyroid hormone receptor have been found in some adenomas that secrete TSH;¹³ therefore, the occurrence of pituitary adenomas that secrete TSH in patients with RTH should be carefully considered.

TREATMENT AND MANAGEMENT

The primary goal of treatment of pituitary adenomas that secrete TSH is to remove the pituitary tumor and restore euthyroidism. The first therapeutic approach to treating this condition should, therefore, be trans-sphenoidal or subfrontal adenomectomy. Antithyroid drugs, somatostatin analogs, or even iopanoic acid (in the case of unresponsiveness to the first two drugs) should be administered to restore euthyroidism before surgery. If surgery is contraindicated or declined, pituitary radiotherapy should be considered.¹ Normalization of circulating

levels of thyroid hormones and apparent complete removal of the tumor mass was observed in 36% of patients with pituitary adenomas that secrete TSH who underwent adenomectomy; these patients might, therefore, be considered as apparently cured.^{1,4,5} An additional 30% of patients were judged as improved, as normalization of circulating levels of thyroid hormones was achieved, although the removal of the adenoma was partial. These findings indicate that symptoms in approximately two-thirds of patients with this condition are brought under control with surgery, irradiation, or both (Table 2). Evaluation of other pituitary functions, particularly ACTH secretion, should be carefully undertaken soon after surgery, and checked again every year, especially in patients treated with radiotherapy, because of possible iatrogenic hypopituitarism.

A third of all patients with pituitary adenomas that secrete TSH undergo pituitary surgery that is unsuccessful and, therefore, medical therapy is indicated. The presence of dopamine and somatostatin receptors in pituitary adenomas that secrete TSH was the rationale for therapeutic trials with dopaminergic agonists, such as bromocriptine and cabergoline, and with somatostatin analogs, such as octreotide and lanreotide in patients with these tumors. Although dopamine agonists, in some cases, are able to inhibit TSH secretion and cause shrinkage of the adenoma, medical treatment of pituitary tumors relies today on the administration of long-acting somatostatin analogs.^{14,15} In 73 patients with pituitary adenomas that secrete TSH, treatment with octreotide (50–750 μ g two or three times daily) was effective in the reduction of TSH and α -GSU secretion

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Competing interests

The authors declared they have no competing interests.

in 92% and 93% of cases, respectively; restoration of the euthyroid state was also achieved in 85% of these patients.¹ In addition, 75% and 50% of these patients experienced improvement in vision and shrinkage of the pituitary tumor mass, respectively.¹ In patients with mixed adenomas that secrete TSH in addition to growth hormone or prolactin, treatment with octreotide resulted in the disappearance of signs and symptoms of acromegaly and hypogonadism in almost all patients. Resistance to somatostatin analog treatment, true escape of TSH secretion from the inhibitory effects of the drugs, or discontinuation of treatment because of side effects was documented in a few cases. Patients taking somatostatin analogs have to be carefully monitored as untoward side effects, such as cholelithiasis and carbohydrate intolerance, might manifest themselves. The dose of these analogs administered should be tailored for each patient, depending on their therapeutic response and tolerance.

CONCLUSION

In conclusion, this case shows the possible multiform clinical appearance of pituitary adenomas that secrete TSH, a pituitary–thyroid disorder, which is otherwise easily diagnosed from biochemical findings of elevated thyroid hormone concentrations in the presence of measurable TSH levels. Surgery represents the first therapeutic approach to this disease, and pituitary irradiation might be considered in the case of incomplete removal of the tumor. It remains to be established whether somatostatin analog treatment might be an alternative to surgery and pituitary irradiation. The therapeutic success rate of somatostatin analogs (octreotide or lanreotide) in patients treated for pituitary adenomas that secrete TSH has been documented as more than 90%.^{1,14} Somatostatin analogs, therefore, represent a useful tool for the long-term treatment of this rare pituitary tumor

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