



Thyrotropinomas: Presentation of Three Cases and Review of Literature

CASE REPORT

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ABSTRACT

Thyrotropinomas are rare pituitary tumors that are difficult to diagnose due to their variety of clinical presentations. We describe three patients with thyrotropinoma and review the management of this disease based on current literature. Patient 1 had a typical acromegalic phenotype with a pituitary adenoma that secreted both growth hormone (GH) and thyroid-stimulating hormone (TSH). Patient 2 underwent pituitary surgery without antithyroid treatment; this tumor was also positive for both TSH and GH on pathological examination, and the patient experienced transient central hypothyroidism postoperatively. Patient 3, who had both a thyrotropinoma and autoimmune thyroiditis, underwent surgery after one year of treatment with lanreotide; the removed pituitary adenoma was positive only for TSH. To our knowledge, concomitant Graves' disease and thyrotropinoma is very rare, with only two patients previously reported. In conclusion, thyrotropinomas are increasingly being encountered when they are smaller, which has improved patient prognosis. Nevertheless, the diagnosis and perioperative management of thyrotropinomas remain challenging, which suggests that patients with such tumors should be managed by endocrinologists.

Keywords: Thyrotropinoma, Graves' disease, management

INTRODUCTION

Thyrotroph cells account for fewer than 5% of all pituitary cells (1), which may be the reason for the low incidence of thyrotropinomas (2). At present, thyrotropinomas account for fewer than 2% of all pituitary tumors (3, 4). However, the widespread application of magnetic resonance imaging (MRI) and the introduction of more sensitive assays for thyroid-stimulating hormone (TSH) have led to an increase in the frequency of the diagnosis of thyrotropinoma. Furthermore, earlier detection has resulted in a greater percentage of patients being diagnosed with smaller thyrotropinomas and milder hyperthyroidism (2).

The diagnostic differentiation of thyrotropin-secreting pituitary adenomas from other diseases is challenging, as is the management of thyrotropinomas. The goals of therapy include the complete removal of the adenoma and restoration of a euthyroid state (2, 3, 5-7). Transsphenoidal surgery has been the first-line treatment option for tumor removal (2, 3, 5-7), which makes it important to manage alterations in thyroid hormones before and after the pituitary operation.

This study retrospectively analyzed three patients with thyrotropinoma who underwent transsphenoidal surgery at Erciyes University Medical School since 2008 and who have been followed up post-surgery. The report emphasizes the challenges that were encountered during the diagnosis and perioperative management of patients with thyrotropinoma, as well as a review of the management of thyrotropinoma based on current literature.

CASE REPORTS

Patient 1: A 46-year-old male patient was admitted for the regulation of poorly controlled type 2 diabetes mellitus. The appearance of his face suggested acromegaly and he was found to have acral growth, increased sweating, frequent heart palpitations, and headache. Physical examination showed a typical acromegalic phenotype. No tremors were observed but his pulse rate was 102/minute. Other examinations, including visual field and thyroid palpation, were normal.

Immunoassays (Immulite 2000 XPi, Siemens, Germany) of his serum showed an insulin-like growth factor-1 (IGF-1) concentration of 705.5 ng/mL (normal range: 71–263 ng/mL for persons aged 40–50 years) and a growth hormone (GH) concentration of 74.4 µU/mL (normal range: 0.27–16 µU/mL). An oral glucose tolerance test (OGTT) was not performed because the patient was diabetic. His basal cortisol, prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone concentrations were normal. A thyroid function test,

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which was performed using an IRMA method, showed increased thyroid hormone but inappropriately normal TSH levels (Table 1). A triiodothyronine (T3) suppression test and measurements of the α -subunit level were not performed to differentiate between resistance to thyroid hormone (RTH) and a TSH-secreting pituitary tumor. A thyrotropin-releasing hormone (TRH) stimulation test showed that the TSH response was blunted. In addition, pituitary MRI revealed a 17 mm adenoma in the pituitary gland (Figure 1).

These findings indicated that the patient had a pituitary adenoma that was secreting both GH and TSH. Methimazole (20 mg/day) and propranolol (40 mg/day) were administered before surgery due to symptomatic hyperthyroidism. Immunohistochemical analysis of the removed tumor showed strong positive staining for both GH and TSH but negative staining for other hormones.

One day after surgery, the patient's serum TSH and fT3 concentrations were low but his fT4 concentration was in the normal range (Table 1). Five days after surgery, his fT3 and fT4 concentrations were nearly normal and the patient was discharged without thyroid hormone replacement. Thyroid function test results remained in normal ranges during the first three months postoperatively.

One year after pituitary surgery, however, his IGF-1 levels were above the normal range and MRI revealed a residual tumor invading the right cavernous sinus (Figure 1). The patient was started on

treatment with octreotide-LAR (20 mg per month); after two years, his IGF-1 levels remain under control. Although there has been no shrinkage in the size of the residual tumor, he has accepted neither radiotherapy nor reoperation for the residual tumor.

Patient 2: A 29-year-old male with a >1 year history of increased sweating, occasional palpitations, and weight loss was admitted to another hospital. Laboratory examination revealed inappropriately high TSH (6.69 μ U/L, normal range: 0.34–5.6 μ U/L), fT3 (5.6 pg/mL, normal range: 2.5–3.9 pg/mL), and fT4 (1.6 ng/mL, normal range: 0.6–1.1 ng/mL) concentrations. Because of his unsuppressed TSH level, he was referred to the Endocrinology Department of Erciyes University Medical School. His medical history was unremarkable and none of his relatives had any history of thyroid disease. On physical examination, his pulse rate was normal and no tremors were noted.

Thyroid function immunoassays (Advia Centaur XP, Siemens, Germany) on admission showed a normal TSH level, whereas fT3 and fT4 levels were elevated (Table 2). The IGF-1 level was also elevated (427 ng/mL, normal range 232–385 ng/mL for persons aged 20–30 years) but cortisol, prolactin, FSH, LH, and total testosterone levels were within normal ranges. Because of the high IGF-1 concentration, OGTT was performed; the patient's GH level was suppressed from 0.25 μ U/mL at baseline (normal range: 0.27–16 μ U/mL) to 0.013 μ U/mL. To rule out RTH, the α -subunit level (normal range: 0–1.6 IU/L) was measured manually by an IRMA assay at another laboratory (Duzen Laboratory, Ankara, Turkey). It was found to be normal (0.43 IU/L), as was the α -subunit/TSH molar ratio (0.86, normal: <5.7). In a TRH stimulation test, the TSH level did not increase sufficiently. Moreover, MRI revealed a 15 mm adenoma in the pituitary gland (Figure 2).

The findings in this patient of central hyperthyroidism, a negative family history, inappropriate levels of TSH, and a pituitary adenoma on MRI yielded a diagnosis of thyrotropinoma, for which the patient underwent a successful transsphenoidal operation. Pathological examination showed that the adenoma was not tough (fibrous) and immunohistochemical analysis showed strong positive staining for both TSH and GH.

Thyroid function tests two days after the operation showed low TSH and high thyroid hormone levels (Table 2). At discharge two weeks after surgery, the patient was started on thyroid hormone replacement therapy due to the development of secondary hypothyroidism. Three months after surgery, replacement therapy was stopped due to a normal result of a thyroid function test (Table 2). Nine months after the operation, pituitary MRI showed no tumor remnant (Figure 2); moreover, serum hormone concentrations had increased (Table 2). In addition, IGF-1 concentrations three and nine months after surgery were normal at 168 ng/mL and 181 ng/mL, respectively.

Patient 3: A 56-year-old female was admitted to another hospital for headaches. A brain MRI showed a pituitary adenoma and she was referred to our Endocrinology Department. In addition to headaches, she reported a several-year history of heat intolerance and occasional palpitations. She had occasionally been treated with antithyroid drugs due to thyroid disease. The patient's medical history also included type 2 diabetes mellitus and hypertension but there was no family history of thyroid disease. Physical examina-

Table 1. Thyroid function test results of patient 1

Time	TSH (μ U/L) (Normal range: 0.2–3.2)	Free T3 (pg/dL) (Normal range: 2.2–4.7)	Free T4 (ng/dL) (Normal range: 8–20)
At presentation	1.49	8.48	39.24
Pre-operation	0.20	4.25	23.39
1 day after surgery	0.09	1.81	12.58
5 days after surgery	0.01	2.17	12.98
3 months after surgery	0.67	2.98	12.97
1 year after surgery	1.02	3.19	13.76

TSH: thyroid-stimulating hormone

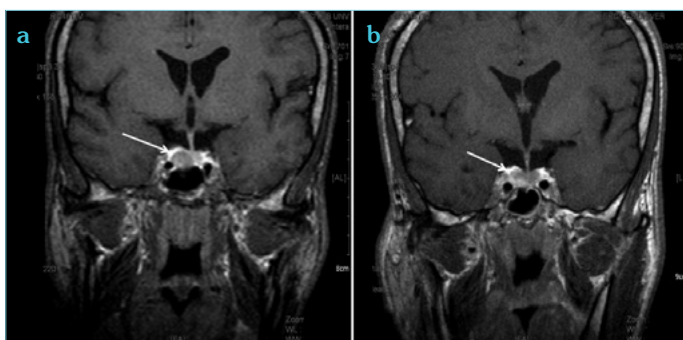


Figure 1. Magnetic resonance imaging scans of patient 1. (a) Preoperative image showing a 17×10 mm pituitary mass invading the right cavernous sinus. (b) One year after surgery, there is a remnant tumor still invading the right cavernous sinus

Table 2. Thyroid function test results of patient 2

Time	TSH (μ U/L) (Normal range: 0.57–5.6)	Free T3 (pg/dL) (Normal range: 2.3–4.2)	Free T4 (ng/dL) (Normal range: 0.88–1.72)
At presentation	4.32	6.97	2.08
2 days after surgery	0.15	4.36	3.09
2 weeks after surgery	0.08	2.26	0.90
3 months after surgery	0.86	3.18	1.19
9 months after surgery	1.30	3.28	1.27

TSH: thyroid-stimulating hormone

tion revealed no abnormalities; the thyroid gland was not enlarged and there were no nodules or tenderness upon palpation. Exophthalmos was absent and a visual field examination was normal.

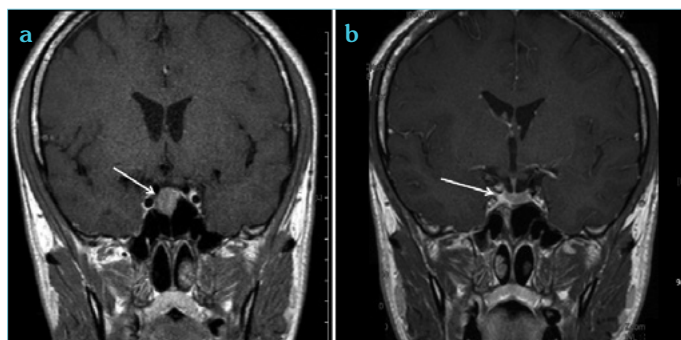
Thyroid function tests showed a high TSH level along with elevated thyroid hormone concentrations (Table 3). Her α -subunit concentration was 2 IU/L and the α -subunit/TSH molar ratio was 2.66 (normal: <1.0). There was a blunted TSH response to TRH stimulation and levels of thyroid autoantibodies (anti-TPO and anti-thyroglobulin) were elevated. MRI showed a pituitary adenoma measuring 10×8 mm on the sellar floor but basal cortisol, prolactin, IGF-1, FSH, and LH levels were within normal ranges (Figure 3). Thyroid ultrasound demonstrated a heterogeneous echotexture of the thyroid parenchyma with multiple thin internal septations bilaterally. Both thyroid lobes were of normal size.

These findings, including symptoms of hyperthyroidism, elevated serum concentrations of TSH, thyroid hormone, and thyroid autoantibodies, a high α -subunit/TSH ratio, thyroid ultrasound findings, and the adenoma that was revealed on MRI, suggested that this patient had two concurrent diseases, thyrotropinoma and autoimmune thyroiditis.

Transsphenoidal surgery was recommended but the patient refused and opted for medical therapy. Therefore, the patient was initially treated with 90 mg lanreotide Autogel per month. After one year of treatment, her thyroid test results were normal with no side effects but the patient reported continuing headaches and MRI did not show any decrease in tumor size. Surgery was again recommended. This time, the patient agreed and underwent pituitary surgery about six weeks after the last dose of lanreotide.

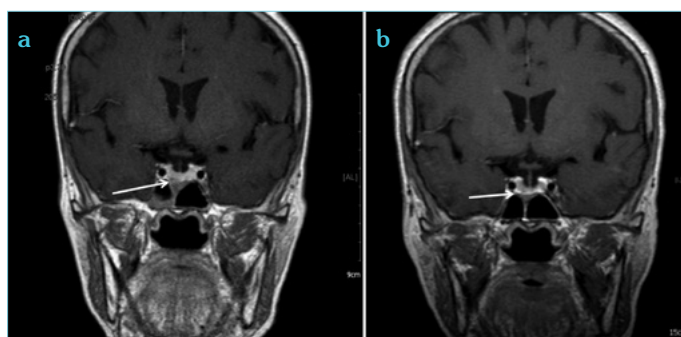
Histopathological examination of the pituitary tumor showed fibrosis but no complications occurred during the transsphenoidal operation. Immunohistochemical analysis of the resected pituitary adenoma showed staining only for TSH, whereas the remaining stains were negative. Two weeks postoperatively, her thyroid functions had normalized and she was discharged without further medical therapy (Table 3).

Nine months after surgery, MRI showed no tumor remnant in the pituitary gland (Figure 3). Her thyroid hormone concentrations were within normal ranges, which indicated that her thyrotropi-

**Figure 2.** Magnetic resonance imaging scans of patient 2. (a) Preoperative image, 15×7 mm pituitary mass extending to the sphenoid sinus. (b) Nine months after surgical resection, no tumor remnant**Table 3.** Thyroid function test results of patient 3

Time	TSH (μ U/L) (Normal range: 0.57–5.6)	Free T3 (pg/dL) (Normal range: 2.3–4.2)	Free T4 (ng/dL) (Normal range: 0.88–1.72)
At presentation	7.50	17.68	4.47
Preoperation	2.13	3.10	2.15
4 days after surgery	0.012	3.41	2.27
2 weeks after surgery	0.006	2.40	1.34
4 months after surgery	0.52	2.34	1.07
1 year after surgery	0.35	2.50	1.06

TSH: thyroid-stimulating hormone

**Figure 3.** Magnetic resonance imaging scans of patient 3. (a) Preoperative image showing 10×8 mm pituitary mass extending inferiorly along the septation of the sphenoid sinuses. (b) Nine months after pituitary tumor resection, no apparent residual tumor

noma was in remission (Table 3). In contrast, thyroid function tests one year after surgery showed sustained subclinical hyperthyroidism. Thyroid scintigraphy showed results that were compatible with Graves' disease.

DISCUSSION

Patients with thyrotropinoma usually present with symptoms of hyperthyroidism, including elevated T3 and T4 hormone levels

and inappropriately high or normal TSH levels. Other features may include goiter (80–94%), deterioration of vision (42%), headache (17–39%), menstrual cycle disorders (30%), and loss of libido (5). Although most thyrotropinomas secrete only TSH and its α -subunit, 16% also secrete GH and 11% secrete prolactin, with the secretion of other hormones being rare (7). The presence of an acromegalic phenotype or galactorrhea may therefore cause diagnostic confusion in patients with thyrotropinomas.

As seen in the patients described here, thyrotropinomas can present with a wide variety of features. Patient 1 had an obvious acromegalic phenotype but unfortunately his acromegaly has not been cured completely. Thyrotropinoma was not incidental in patient 2 but findings such as slightly elevated IGF-1, low GH, normal GH response to OGTT, and positive staining of the pituitary adenoma for GH and TSH made a diagnosis of acromegaly unclear. In addition, there was no evidence of acromegaly in the patient's history or physical examination and postoperative IGF-1 levels were within the normal range. This vague clinical picture was likely due to low secretion of GH by the pituitary adenoma.

Patient 3 had both thyrotropinoma and autoimmune thyroiditis. Thyroid test results, particularly the postoperative persistence of low TSH levels and elevated thyroid antibodies, as well as findings on thyroid ultrasound and scintigraphy, indicated a diagnosis of Graves' disease. Another possible diagnosis, hashitoxicosis, could be excluded by thyroid function findings after pituitary surgery, with neither decreased thyroid hormones nor elevated TSH concentrations observed. In addition, the scintigraphy results were not compatible with hashitoxicosis.

To our knowledge, the co-occurrence of Graves' disease and thyrotropinoma is incidental and very rare. In some previously reported patients, Graves' disease and thyrotropinoma occurred consecutively, not concomitantly, because there was insufficient evidence of thyrotropinoma at the time that Graves' disease was detected (8–10). Two previous patients, however, seemed to have concomitant Graves' disease and thyrotropinoma (11, 12), which was similar to our findings in patient 3.

Furthermore, it may also be difficult to distinguish between thyrotropinoma and RTH. RTH is a rare disorder, which is characterized by reduced sensitivity of the pituitary gland and/or peripheral target tissues to thyroid hormone. RTH has been associated with various gene mutations, particularly in the gene encoding thyroid hormone receptor- β . Patients with RTH have goiter and normal or elevated serum TSH concentrations, along with increased levels of thyroid hormones, but have no symptoms or metabolic indications of excess thyroid hormone (13). Thyrotropinoma is more likely than RTH if the following are present: pituitary tumor on MRI, elevated α -subunit level, elevated α -subunit/TSH molar ratio, high concentration of sex-hormone-binding globulin (SHBG), inappropriate responses to TRH stimulation and T3 suppression tests, negative family history, and no mutations of the thyroid hormone receptor gene in the blood. However, as none of these findings alone can lead to a correct diagnosis, they should be evaluated together. In addition, screening first-degree relatives of subjects with RTH by a thyroid function test, which is a cheap and practical method, might be beneficial for the diagnosis of RTH.

Thyrotropin-releasing hormone stimulation tests include serial measurements of TSH after intravenous injection of TRH, with a normal result indicated by a $>200\%$ or $>5 \mu\text{IU/L}$ increase over baseline. T3 suppression tests are performed by administering 80–100 $\mu\text{g/day}$ T3 orally for 8–10 days followed by measurements of TSH concentration, with a normal TSH response consisting of suppression to $\leq 10\%$ of baseline (6). In addition, the α -subunit/TSH molar ratio can be calculated by dividing the α -subunit concentration by the TSH concentration and multiplying the result by 10, with a normal ratio depending on the concentrations of TSH and gonadotropin (Table 4).

The increased incidence and earlier detection of thyrotropinomas have resulted in an increase in the percentages of smaller-sized tumors that secrete lower amounts of α -subunit and thyroid hormones than in the case of larger tumors (2, 5, 6, 14). This may explain, at least in part, the findings in patient 2, who had normal α -subunit and lower thyroid hormone levels, because the time between presumed disease onset and diagnosis was shorter in this patient than in the other two.

The optimal initial treatment of thyrotropinomas, whether with somatostatin analogs or pituitary surgery, is unclear. Although surgery has traditionally been the first-line treatment, somatostatin analogs may be an alternative for patients which do not have certain indications for operation, including those with huge macroadenomas, pituitary apoplexy, optic nerve compression, or cavernous sinus invasion (2, 3, 15–17). The main advantage of medical treatment with somatostatin analogs is avoiding any complications of pituitary surgery. However, although most patients show normalizations of both thyroid functions and α -subunit levels, only about half show tumor shrinkage after treatment with somatostatin analogs (2, 3, 15). Other disadvantages of somatostatin analog treatment include its high costs, the necessity for prolonged treatment, and rare side effects, such as tachyphylaxis, cholelithiasis, and carbohydrate intolerance (3, 15). Patient 3 showed improvements in thyroid hormone levels after treatment with a somatostatin analog but there was no change in the tumor size or her intensity or frequency of headaches. These headaches, which were regarded as associated with the tumor, improved after surgery.

Somatostatin analogs can also be used as adjuvant therapy for patients with active disease after pituitary surgery. In addition, ergot alkaloids have been shown to be effective for pituitary tumors that secrete both TSH and prolactin (18). However, the effectiveness of ergot alkaloids is not clear in patients with pure thyrotropinomas that are resistant to both surgery and somatostatin analogs. In addition to medical therapy, radiotherapy, in particular gamma-knife radiosurgery, may be effective in patients with persistent thyrotropinomas (16).

Table 4. Normal values of α -subunit/TSH molar ratio

	In Normogonadotropic Patients	In Hypergonadotropic Patients
NORMAL TSH	<5.7	<29.1
HIGH TSH	<0.7	<1.0
TSH: thyroid-stimulating hormone		

Because huge macroadenoma forms of thyrotropinomas are less frequently encountered, medical and surgical treatments have become more effective. In addition, their complication ratios have decreased significantly and complete remission rates have become higher (2, 6, 7, 14). Although thyrotropinomas are generally fibrous and invasive (4, 15, 19), many smaller tumors are less fibrous and invasive and are therefore easier to remove (2). This feature of smaller adenomas likely contributes to their high remission rates after surgery. All three patients that are described in this study had small macroadenomas, not giant adenomas. Furthermore, the tumors in patients 1 and 3 were more fibrous than the tumor in patient 2, perhaps because of the longer time between disease onset and operation in patients 1 and 3.

Preoperative antithyroid drugs such as methimazole or propylthiouracil are not recommended to stabilize patients with severe thyrotoxicosis because they may trigger elevated TSH levels and increase tumor size when used for a long time (5, 15). Euthyroidism prior to surgery can be achieved by treatment with a short-acting octreotide ampule (200–300 µg/day subcutaneously) along with propranolol (40–120 mg/day orally) and this regimen should be initiated at least one week before pituitary surgery (15, 16). Because their symptoms were not severe, we did not treat patients 2 and 3 with any antithyroid agents prior to surgery. However, patient 1, who had severe hyperthyroidism, was preoperatively treated with an antithyroid agent because short-acting octreotide was not available. Patient 3 was almost euthyroid preoperatively, which was most likely because of the prolonged effect of long-acting lanreotide, which was stopped six weeks before pituitary surgery.

Criteria that demonstrate the success of surgery are the absence of residual tumor on MRI, improvement in hyperthyroidism, normalization of other secreted hormones, and absence of surgical complications. Thyroid function tests 1–7 days after surgery can evaluate the risk of thyroid storm and the success of surgery. If the tumor is completely removed, the early postoperative serum TSH level will be very low, even undetectable (16). In patients 2 and 3, the postoperative TSH concentration decreased immediately after surgery, followed by decreases in thyroid hormone levels. This was not observed in patient 1, however, because he received preoperative antithyroid treatment.

The early postoperative results in patient 2, which were measured two days after surgery, were not indicative of primary hyperthyroidism or thyroid storm but rather of the recovery phase of secondary hyperthyroidism. Although the initial decrease in TSH levels coupled with elevations in thyroid hormones may be interpreted as primary hyperthyroidism, this patient had no symptoms of hyperthyroidism, and antithyroid drugs were not administered. Moreover, the removal of the source of excess TSH was expected to result in normal concentrations of free thyroid hormones over the following days. Subsequent thyroid function test results were compatible with hypothyroidism. If, however, thyroid hormone levels are very high and severe symptoms of hyperthyroidism are present in the early postoperative interval, this should be regarded as thyroid storm.

Two weeks after surgery, patient 2 showed evidence of central hypothyroidism, which was based on the concentrations of TSH, fT3, and fT4 relative to those on postoperative day 2. This was con-

firmed by the results of thyroid tests performed three months after surgery because thyroid hormone treatment would have resulted in hyperthyroidism. Thyroid hormone treatment was stopped three months after surgery due to higher TSH levels, with this decision confirmed by the results that were obtained at nine months. Transient central hypothyroidism can be initially explained by tumoral damage and subsequently by surgical damage to non-tumoral thyrotrophs (6, 7). The time required for the recovery of non-tumoral thyrotrophs is approximately 3–12 months, whereas a longer recovery time may indicate permanent central hypothyroidism.

CONCLUSION

Thyrotropinomas are rare tumors but are now being diagnosed earlier and more frequently, which makes them smaller at diagnosis and improves patient prognosis. However, the diagnosis and perioperative management of thyrotropinomas remain difficult, which suggests that patients with these tumors should be managed by endocrinologists.

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