

# Inappropriate thyrotropin secretion in the presence of a pituitary adenoma: a complex differential diagnosis made easier by thorough clinical evaluation – two teaching case reports

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## RESUMEN

La secreción inadecuada de tirotrópina es un hallazgo raro que puede relacionarse con diferentes diagnósticos diferenciales. La presencia de adenoma de hipófisis suele asociarse a un TSHoma, sin embargo, se debe considerar la posibilidad de incidentalomas y otros tumores. El diagnóstico diferencial requiere evaluación clínica cuidadosa y una historia clínica extensa, especialmente cuando los estudios confirmatorios más complicados no están disponibles. Presentamos dos casos, uno con un adenoma productor de TSH y otro con un adenoma no funcionante, que demuestran que no todos los estudios son necesarios para dar un diagnóstico y tratamiento adecuado si consideramos las herramientas clínicas.

**Palabras clave:** TSH inapropiada. Adenoma. Hipófisis. Resistencia hormonas.

## ABSTRACT

Inappropriate thyrotropin secretion is a rare laboratory finding that may be related to multiple differential diagnosis. The presence of a pituitary adenoma usually relates to a thyroid-stimulating hormone (TSH) producing adenoma; however, the possibility of incidentalomas and other tumors should be considered. Differential diagnosis requires careful clinical evaluation and family history evaluation, especially when the most complicated tests are unavailable. We present two cases, one with a TSH producing adenoma and other with a non-functioning pituitary adenoma and thyroid hormone resistance that was diagnosed using the available clinical data, showing that not all the tests are necessary to provide adequate treatment if the clinical tools are considered. (REV MEX ENDOCRINOL METAB NUTR. 2018;1:33-8)

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**Key words:** Inappropriate thyroid-stimulating hormone. Adenoma. Pituitary. Hormone resistance.

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## INTRODUCTION

The biochemical profile where high concentrations of serum thyroid hormones (free triiodothyronine (T3) or free thyroxine [FT4]) are accompanied by detectable (high, normal, or non-suppressed) thyrotropin is frequently referred to as inappropriate secretion of thyrotropin syndrome (ISTS)<sup>1</sup>. The differential diagnosis originally included only thyroid-stimulating hormone (TSH) secreting pituitary adenomas (TSHomas) and resistance to thyroid hormone action (THR); however, a new differential diagnosis such as antibodies against TSH, drugs, or protein metabolism disorders may account for the mismatching results<sup>2</sup>. The diagnostic algorithm to differentiate these entities includes special dynamic tests with both T3 and thyroid releasing hormone (TRH). These tests are expensive, complicated, some of them are not standardized and due to the potency of the hormones involved it may result dangerous in some cases. Another significant pitfall in the evaluation of these patients is the fact that the elements required for the tests are not available in most countries or public health facilities<sup>3</sup>. Even when all the elements are available, the scarce published data generates a lack of generalizable reference data for normal controls and subjects with ISTS, which questions the need to perform them in all the cases<sup>4</sup>. The basic algorithm for diagnosis proposes confirming the thyroid tests and its validity, using other biomarkers, genetic and dynamic tests as well as magnetic resonance imaging (MRI) or computed tomography scans. Even thyroid ultrasounds have been proposed to be useful in these scenarios<sup>5</sup>. However, the importance of thorough medical history and clinical examination are often taken for granted and the possibility of one patient having two different conditions that may resemble a rare occurrence is considered in the texts, but this is also usually overlooked. One must not forget the fact that patients with THR may also harbor incidental abnormalities on imaging, or that the patients with TSHomas can also have thyroid hormone receptor mutations, which could be the source of diagnostic confusion<sup>6-8</sup>. There are even reports of patients with both a TSHoma and THR<sup>9</sup>. Careful interpretation of the available tests along with the clinical evaluation may hallmark the differences.

We present two cases where a pattern of inappropriate TSH secretion accompanied a pituitary adenoma. The clinical presentation of the cases was helpful in the differential diagnosis even when the additional tests were not available.

### Case 1: THR+ clinically non-functioning pituitary adenoma

A 47-year-old woman presented to the hospital with complaints of a headache and visual alterations. An MRI showed a large tumor in the clivus initially considered to be a chordoma. She was referred to the endocrinology department because she had been diagnosed with subclinical hypothyroidism 3 years before and had taken different doses of levothyroxine with failure to reach normal thyroid hormone concentrations (Table 1). She and her family members were otherwise healthy, she was not taking any other medication, and she complained of hair loss, mild constipation, and cold intolerance. She had a BMI of 31 kg/m<sup>2</sup>, a pulse of 62 per min, blood pressure of 130/80 mmHg. The general laboratory workup showed no anemia, normal proteins and electrolytes and the rest was irrelevant. She had no goiter. Other pituitary hormones were normal for age and gender: Luteinizing hormone (LH) 39.16 mUI/mL (7.7-58 mUI/mL), follicle stimulating hormone (FSH) 63.23 mUI/mL (25.8-134 mUI/mL), prolactin 6.72 ng/mL (3.4-24.1 ng/mL), and cortisol 21.65 mcg/dL (5.0-25.0 mcg/dL).

Considering the similar behavior of the thyroid tests with different doses of thyroid hormone, and suppression with supraphysiologic doses, the lack of clinical symptoms of thyrotoxicosis and evaluating that the patient's technique for pill intake was adequate, we considered the possibility of THR and took a serum sample from one of her sons. His thyroid function tests were also similar to hers (Table 1). We did not have the possibility to determine alpha subunit or perform a TRH or T3 test in our center.

We adjusted de levothyroxin therapy to the dose were the FT4 was in the upper limit of normal and authorized the surgery. The final pathology report revealed an invasive pituitary adenoma, Ki-67 <1%, with immunohistochemistry positive for prolactin

Table 1. The most important thyroid function tests from case 1

	Initial	Levothyroxine 0.7 mcg/kg	Levothyroxine 1.4 mcg/kg	Levothyroxine 2.8 mcg/kg	Before surgery 1.4 mcg/ kg	After surgery 1.4 mcg/ kg	Son's tests without treatment
TSH 0.270-4.200 mIU/mL	12.610	16.69	7.960	2.100	11.990	26.060	3.010
FT4 0.930-1.700 ng/dL	1.42	1.400	1.35	0.098	1.410	1.160	2.310

TSH: thyroid-stimulating hormone; FT4: free thyroxin.

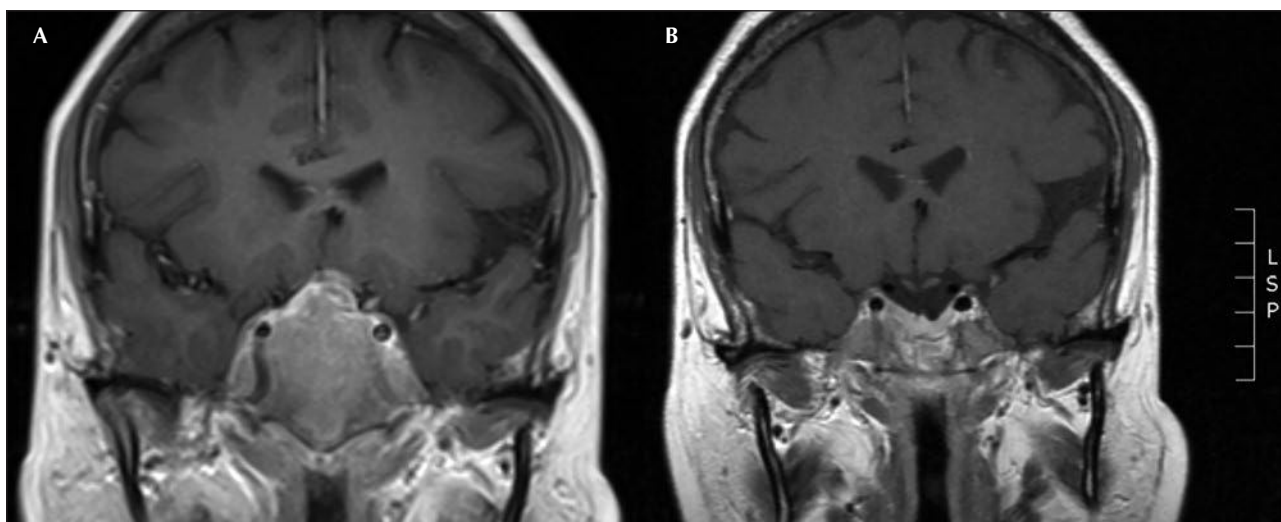


Figure 1. A: Initial magnetic resonance imaging (MRI). B: MRI after surgery.

(1+) and ACTH (1+), negative for TSH and GH. The tumor eroded the bone and was very invasive; therefore, it was not possible to remove it completely. The debulking; however, improved her visual field and headache (Fig. 1). She has been under treatment with 1.5 mg/week of cabergoline for 4 months considering the immunohistochemistry profile, and the tumor remnant reduced an additional 5%. The thyroid function tests remain unchanged, and the patient is waiting for an evaluation to determine if she is a candidate for radiotherapy. At the time of writing this article, she has been followed for 10 months after surgery.

### Case 2: TSH producing pituitary adenoma

A 44-year-old woman with a history of “difficult to control hyperthyroidism” presented for evaluation.

She was diagnosed 10 years before, during her last pregnancy, and was started on methimazole and propranolol. However, the patient failed to attend follow-up visits. 6 years later she started showing signs of goiter and amenorrhea, but she did not request for a medical evaluation. 1 year ago, after some unusual hot flashes, nervousness, dizziness, and palpitations she went to a private physician who noticed the inappropriate TSH pattern and decided to order additional tests and referred her to our hospital (Table 2). The patient had lost approximately 10 kg in the past 2 years, she had a pulse of 128 per minute, a blood pressure of 140/70, a large goiter (6 times the normal size), distal tremor, intolerance to heat and sweating. She denied having family or personal history of thyroid or autoimmune disease; she was not taking any medication. She mentioned having occasional mild transient headaches, insomnia, and amenorrhea for the past 2

Table 2. The most important thyroid function tests from case 2.

	Initial	Confirmation	Before surgery with medical treatment	After surgery without other treatment	Before octreotide	Last evaluation with octreotide
TSH 0.270-4.200 mIU/mL	12.480	7.650	17.510	2.180	2.870	5.430
FT4 0.930-1.700 ng/dL	6.700	5.240	3.820	1.140	2.140	1.510

TSH: thyroid-stimulating hormone; FT4: free thyroxin.

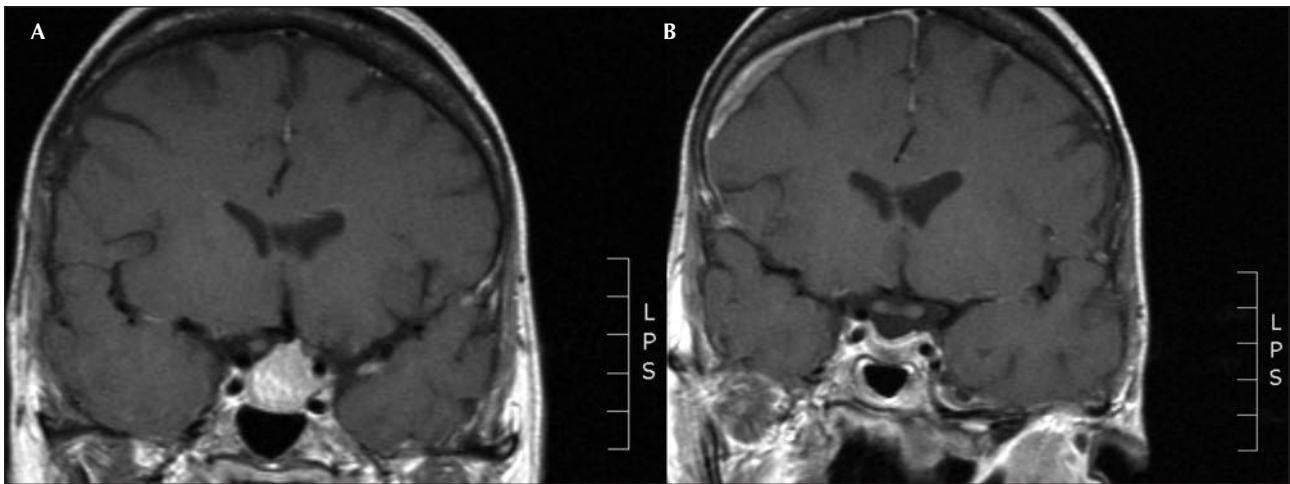


Figure 2. **A:** Initial magnetic resonance imaging (MRI). **B:** MRI after surgery

years, no galactorrhea, or orbitopathy was present. The other pituitary hormones were normal for her gender and age: LH 36.19 (7.7-58 mIU/mL), FSH 33.68 (25.8-134 mIU/mL), prolactin 6.49 (3.4-24.1 ng/mL), estradiol 20.2 (12.5-498 pg/mL), and cortisol 12.2 (5.0-25.0 mcg/dL).

The initial MRI showed a large intra-sellar tumor that was starting to invade the right cavernous sinus, and she was started on 20 mg of long-acting octreotide every 4 weeks, starting 3 months before surgery with a mild reduction of FT4 but continued to be hyperthyroid (Fig. 2). The patient had to travel a long distance to the center and considering her history of missed medical appointments, we decided to hospitalize her and treat her hyperthyroidism aggressively before surgery. She received Lugol's solution 10 drops tid, propranolol 40 mg/qid, methimazole 10 mg tid, cholestyramine 4 g after every meal, and hydrocortisone 50 mg tid. The FT4 made an initial descent but it failed to reach normal concentrations, her pulse was 62/min and blood

pressure reduced to 110/65 and before iodine escape ensued, the surgery was performed uneventfully; however, the patient presented severe persistent hypocalcemia associated with hungry bone syndrome with serum calcium of 6.8 mg/dL (normal 8.4-10.2 mg/dL), magnesium of 1.2 mg/dL (normal 1.6-2.6 mg/dL), and phosphorus 1.5 mg/dL (normal 2.7-4.5 mg/dL) that mandated prolonged hospital stay. After the surgery the patient's symptoms improved, the goiter reduced by half the size 6 weeks later and she stopped taking calcium and Vitamin D. The immunohistochemistry showed positivity for TSH (3+) and alpha subunit and was negative for other pituitary hormones; Ki-67 was 1%. The thyroid function tests remained normal for a month; however, subsequent evaluation showed a small tumor remnant in the cavernous sinus (Fig. 2), and the FT4 increased again, the patient was started on long-acting octreotide and showed improvement of the hormone concentrations after 3 months. She is

Table 3. Main differences between thyroid hormone resistance and TSHoma

Test	THR	TSHoma
Serum TSH	Usually < 10 mU/L	Usually > 10 mU/L
Normal TSH circadian rhythm	Preserved	Absent
TSH response to supraphysiologic thyroid hormone	Suppression	No suppression
TRH test	Normal or exaggerated response	No response
Alpha subunit	Normal	High
Alpha subunit/TSH ratio	Normal	Increased
Steroid hormone binding globulin	Normal	Increased
Clinical information	Normal/ hypothyroidism or hyperthyroidism symptoms	Hyperthyroidism
Family history	Members with unspecified or difficult to treat thyroid problems or THR	Usually none relevant

TSH: thyroid-stimulating hormone. Adapted from Olateju, et al.<sup>14</sup>

now being considered for radiotherapy after a total follow-up of 1 year.

## DISCUSSION

The correct interpretation of thyroid function tests is not an easy or straightforward task in many cases. It requires thoughtful consideration of the pitfalls in the laboratory testing, the patient's characteristics and the confounding factors at the time of the sampling. The most common answer to these "odd" tests is a laboratory mistake or non-compliance with therapy<sup>10</sup>. Truly contradictory tests are rare, but they should not be forgotten, given the interesting differential diagnosis that needs to be evaluated on them, which includes TSHomas and RTH.

Pituitary adenomas account for 15% of the intracranial neoplasms;<sup>11</sup> however, TSH producing adenomas represent usually < 1% of most case series. Thyroid hormone resistance is also rare, with a prevalence of 1:40,000 inhabitants; however, it may be underdiagnosed given its heterogeneous and sometimes subtle behavior<sup>12</sup>. The combination of a pituitary tumor and inappropriate thyroid hormone secretion poses a challenge for endocrinologists since the possibility of a TSHoma versus an incidentaloma carries the risk of unnecessary treatments including pituitary surgery or thyroid ablation. There are few reported cases in which a pituitary

adenoma is present in the context of a proven thyroid hormone resistance;<sup>13</sup> however, there are reports of pituitary incidentalomas and pituitary hyperplasia following inappropriate thyroid ablation may cause diagnostic difficulties<sup>14</sup>. Some biochemical differences between TSHoma and THR are mentioned in table 3.

Despite the apparently different characteristics, the tests are not always unequivocal: 30% of TSHomas show normal serum alpha-subunit, and this may happen more frequently with microadenomas, steroid hormone binding globulin may be affected by other physiological or pathological conditions. In some cases, both THR and TSHomas have been associated with autoimmune thyroid disease which may change the clinical presentation and goiter is a common finding in both entities. Ten percent of the TSHomas may present normal or increased responses to TRH stimulation, but TSH suppression has never been reported in these tumors with the T3 test using 80-100 µg/day divided into three administrations for 10 days (sampling at 0, 5, and 10 days). Twenty percent of the TSHomas may have a normal alpha-subunit/TSH ratio, and postmenopausal women normally have high concentrations of the subunit<sup>15</sup>. Therefore, it is not useful to rely in only one result to conclude a diagnosis. There aren't any validated reports of neither sensitivity nor specificity nor an ideal cutoff point for each test, which translates into a lack of reliable confirmatory algorithms. This is because these tests are

not specifically designed or validated to prove one condition and discard the others, more likely they give some idea of the way that the disease is behaving and increases the chances of having one or the other, but the evidence available cannot be translated into a specific odds ratio or probability at this point.

We present two cases with these characteristics. In both these cases there was no question whether the tumor should be removed, given their large size; however, perioperative evaluation and treatment were very different: In the case with thyroid hormone resistance we used levothyroxine to correct some of the tissue-specific hormone deficiencies and improve symptoms as well as quality of life, while in the TSHoma we did the opposite in preparation for surgery. Surgical risk may also be different, since patients with THR may have lower risks even if they are not treated; however, there are no guidelines on the appropriate line of perioperative management of THR<sup>16</sup>. TSH producing adenomas, on the other hand, are associated with clear signs and symptoms of hyperthyroidism which encompass more predictable complications, such as thyroid storm and arrhythmia<sup>17</sup>. The possibility of a hungry-bone syndrome, for example, is a complication expected only in true long-term thyroid hormone excess that may put the patient's life at risk if the medical team had not been aware of it. Treating physicians should also explain their colleagues, nurses, and trainees about the implications of an altered thyroid test in each patient, because the rarity of these events may be the cause of confusion and delays among untrained personnel. Finally, the aggressiveness of the surgical and medical treatment after the initial therapy may depend on the nature of the ISTS; while the patient with THR may be treated like any other patient with non-functioning tumors, where a large and stable remnant may not be of concern once the visual field and compressive symptoms have resolved, a TSHoma will require second-line therapy and probably lifetime treatment in most of the cases, even if the tumor remnant is small.

## CONCLUSIONS

Inappropriately normal or high TSH in the context of elevated free thyroid hormones and a pituitary tumor is not always indicative of a TSHoma. Performing extensive laboratory tests will be a mainstay in the differential diagnosis; however, they do not supersede the value of careful medical history and clinical evaluation.

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