ISSN: 2755-015X

Journal of Surgery & Anesthesia Research

SCIENTIFIC Research and Community

Review Article

Open Access

TSH-Secreting Pituitary Tumors: A Case Series and Literature Review

Alcaraz Gaytan Liliana[1], Munuzuri Camacho Marco Antonio[2], Balderrama Soto Adriana[1] and Portocarrero Ortiz Lesly Aminta[1*]

[1]Neuroendocrine Unit, National Institute of Neurology and Neurosurgery, Mexico City, Mexico

[2]Neurosurgery Department, National Institute of Neurology and Neurosurgery, Mexico City, Mexico

ABSTRACT

Objectives: To present a series of 3 patients with TSHomas and a brief literature review.

Background: TSH-secreting pituitary neuroendocrine tumors (PitNETs) account for <1% of all adenomas observed in surgical series. Most are macroadenomas, and diagnosis can be delayed by up to 9.5 years. Early diagnosis and appropriate treatment can prevent the occurrence of neurological and endocrinological complications. Surgical resection is the first-line treatment. A literature review will be presented to summarize current evidence.

Methods: A retrospective multi-center case series of three patients with confirmed histopathologic and immunohistochemical diagnosis of thyrotropin-secreting PitNET. Information was obtained from physical and electronic records.

Results: Three patients were described: male (100%), mean age 34 (±9) years, with a diagnosis of TSH-secreting PitNET and macroadenomas (100%). The mean tumor volume was 12 cm3. Transsphenoidal endoscopic surgery was performed in 66.6% of the patients, one of whom underwent partial resection and required adjuvant radiosurgery. One patient refused the surgical procedure and was offered radiosurgery as initial therapy. Remission was achieved at 100%.

Conclusion: Thyrotropin-secreting pituitary adenomas are an uncommon cause of hyperthyroidism. Presurgical treatment with somatostatin analogs might be effective in reducing TSH-oma size. Surgery can effectively restore euthyroidism (>80%). Radiotherapy is an alternative treatment option. The T3 suppression test is the most sensitive and specific test for confirming complete removal of the adenoma. Recurrence appears infrequent.

***Corresponding author**

Portocarrero-Ortiz Lesly Aminta, Neuroendocrine Unit, National Institute of Neurology and Neurosurgery, Mexico City, Mexico.

Received: February 13, 2024; **Accepted:** February 20, 2024; **Published:** March 01, 2024

Keywords: TSH, Pituitary Tumor, Endoscopic Transnasal Surgery, Radiotherapy

Background

Pituitary adenomas secreting thyroid-stimulating hormone (TSH), also known as thyrotropinomas, are among the least prevalent pituitary tumors, accounting for 0.9-1.5% of all pituitary adenomas in surgical series.

Thyrotropinomas are observed in patients ranging from 8 to 84 years of age, primarily in the fifth and sixth decades of life. The prevalence of tumors does not seem to differ between men and women [1,2].

Thyrotropinomas are typically considered when the TSH level is inappropriately elevated or normal in a hyperthyroid patient with elevated serum T4 levels, regardless of the presence of a visible tumor on imaging. The mean TSH concentration varies from normal to very high, which can be explained by differences in the biological activity of TSH due to altered glycosylation of the TSH molecule [1,3]. This condition, known as central hyperthyroidism, can result from two different conditions: TSHoma or pituitary resistance to thyroid hormone action. Failure to recognize a TSHoma could lead to inappropriate treatment and dramatic consequences for the patient, including aggressive tumor growth, causing visual disturbances. Most are macroadenomas, and the diagnosis may be delayed up to 9.5 years [4,5].

TSH-secreting pituitary adenomas present with hyperthyroidism of varying degrees, ranging from mild thyrotoxicosis to clinically severe, or even asymptomatic, often with diffuse goiter but no exophthalmos [6,7].

In addition to TSH, they usually secrete the common alpha subunit of glycoprotein hormones (α-SU) [8,9]. Immunohistochemistry is performed for diagnosis, evaluating TSH expression or co-expression of TSH in pituitary tumors. In most cases, TSH is co-expressed with growth hormone (GH) in patients with acromegaly and is not accompanied by hyperthyroidism [10,11].

Case 1

A 21-year-old male presented with a six-month history of progressive stabbing headaches, anxiety, psychomotor restlessness, muscle tension, irritability, decreased appetite, and a weight loss

of 4 kilograms. He also reported difficulty falling asleep and a sense of non-restorative sleep, followed by a subsequent decrease in visual acuity. Treatment was initiated with 70 mg of thiamazole and 120 mg of propranolol, resulting in initial improvement. Physical examination revealed tachycardia, palmar diaphoresis, and hyperactive reflexes. Neuro-ophthalmological evaluation with perimetry showed a peripheral deficit of 10 degrees. The right eye had a visual acuity of 20/60, the left eye 20/20, and normal ocular movements.

A simple T1 MRI scan of the sellar region revealed an isointense image enlarging the sella turcica, extending dorsally deforming the floor of the third ventricle and laterally without encircling adjacent vessels. Heterogeneous enhancement with contrast medium application showed a formation in the anterior subcallosal region. Isointensity in T2 and dorsal compression of the optic chiasm were observed, measuring 22x14x20 mm.

Thyroid profile results were as follows: Thyroxine 201.9 nmol/L (normal range: 58-154), ITL (Iodothyronine) 17.8 (normal range: 5-12), Free T4 38.1 pmol/L (normal range: 9.1-23.8), T3 3.3 nmol/L (normal range: 2.8-8.2), Free T3 9.8 pmol/L (normal range: 2.8-8.2), Thyrotropin (TSH) 9.6 IU/L (normal range: 0.32-5).

Transsphenoidal endoscopic surgery (TSEM) was performed without complications. The lesion, described as neoplastic with a white-yellowish color, firm consistency, vascularity, and mucoid appearance, was completely resected. Immunohistochemistry revealed prolactin 0, growth hormone (GH) +, FSH (follicle-stimulating hormone) 0, LH (luteinizing hormone) 0, TSH 0, ACTH (adrenocorticotropic hormone) 0.

Postoperative pituitary profile: GH 1 mUI/L, FSH 1.9 mUI/mL, Prolactin 3.7 ng/mL, cortisol 10.3 ug/dL, Testosterone 1.1 ng/mL.

Despite treatment, the patient did not achieve remission at three months, with a TSH level of 6.6 mIU/L. A thyrotropin-releasing hormone (TRH) stimulation test showed no response, elevated alpha subunit, and a high molar ratio of alpha subunit to TSH. An MRI revealed residual tumor, and a thyroid scan showed diffuse goiter. Thiamazole was resumed at 15 mg/day. Remission was not achieved until radiotherapy was performed at the five-year postoperative mark with 18 Gy for 4.56 cc. Thiamazole was discontinued three years later, with MRI showing a sellar arachnoidocele and chiasmatic retraction. Secondary hypopituitarism was diagnosed, and replacement therapy was initiated.

Case 2

A 38-year-old male presented with progressive headaches, bilateral visual acuity loss predominantly on the right side, and a weight loss of 10 kg over 6 months. Visual field examination revealed a classic chiasmal pattern with bitemporal heteronymous hemianopsia OD 20/200, OI PL. Bilateral optic atrophy was more pronounced on the left side, attributed to compressive optic neuropathy. OD: nasal visual island, III4e stimulus, 22/20.7 deg. OI: superior nasal visual island, V4e stimulus, 378.7 deg. The patient exhibited jaundice with normal liver function tests, LH 1.7 mIU/mL, testosterone 3.4 nmol/L, prolactin 4.2 ng/ml, cortisol 6.5 ug/dL, T4L 39 pmol/L, TSH 5.5 mIU/L.

MRI revealed a sellar lesion measuring 29x37x25mm (See Figure 1), and thyroid ultrasound showed diffuse homogeneous goiter with the right lobe measuring 38x20x18mm and the left lobe measuring 39x18x20mm. Treatment commenced with thiamazole at a dose of 20 mg and beta-blockers until euthyroidism was achieved. Transsphenoidal endoscopic surgery (TEE) was performed. The patient developed secondary panhypopituitarism and received replacement therapy.

Table 1: Biochemical Evolution of the Patient in Case 1

	Pre-surgery		Surgery	Post-surgery							Stereotactic radiosurgery (SRS)	Post-SRS		
Follow-up	-5 m	-1 m		3 d	1 m	3 m	1 y	2 y	3 y	4 y		5y	12 y	15 y
Methimazole dosage, mg	70	70		0	20	5	5	15	15	15		15	0	0
T4, nmol/L (58-154)	201.9	197.4		178	63.8	222.9	244	232.9	101.1	264		166	140	134
FTI (5-12)	17.8	17.8		14.5	4.4	20.3	23.4	22.3	10.2	25		16	130	138
T4 Free, pmol/L (9.1-23.8)	38.1	38.1		29.8	8	45.2	54.2	51	19.7	59.6		33.3	15.7	14.7
T3, nmol/L (2.8-8.2)	3.3	3.8		2.5	1	4.1	4.3	3.8	1.7	5.4		2.4	2.8	2.5
T3 Free, pmol/L (2.8-8.2)	9.8	11.5		6.5	1.9	13.1	15	13.1	5.2	19.2		7.5	6.7	6
TSH (0.32-5)	9.6	8.9		20.1	63.3	6.2	5.2	3.7	26.4	3.6		11.9	2.1	2.5

m = months, y = years, mg = milligrams, nmol/L = nanomoles/liter, FTI = thyroxine binding globulin, pmol/L = picomoles/liter, TSH = thyroid stimulating hormone.

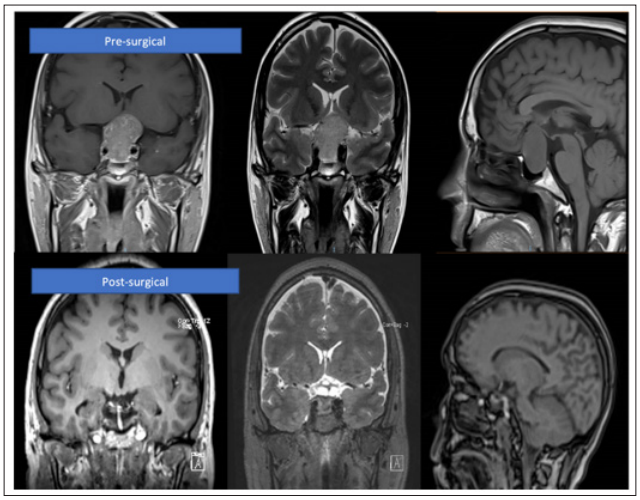

Figure 1: Representative MRI of Patient Case 2 with TSHoma

Follow-up laboratory results: Triiodothyronine 1.55 nmol/L, Free T4 2.83 pmol/L, thyroxine 58.4 nmol/L, thyrotropin 0.053 uIU/mL, prolactin 1.4 ng/ml, cortisol 0.2 ug/dl, IGF1 63 ng/ml, with normal electrolyte levels.

Case 3

A 43-year-old male presented to a neurosurgeon with complaints of headache and visual deterioration. An MRI revealed a lesion measuring 18x13x3mm. Transsphenoidal endoscopic surgery (TSEM) was performed with partial resection. Immunohistochemistry indicated positivity for adrenocorticotropic hormone (ACTH), negativity for growth hormone (GH) and prolactin. He was referred to endocrinology, where a thyroid profile with TSH 7.71 and Free T4 1.34 was obtained. Ki67 was positive (5%), TSH was positive (10%), FSH was positive (5%), and LH was negative. The diagnosis at that point was classified as a TSHoma.

Despite treatment, hyperthyroidism persisted, and the patient continued antithyroid therapy with 10 mg of thiamazole daily. A follow-up MRI at 2 years revealed a sellar lesion measuring

20.6x24.4x21.6 with a volume of 6.7cc. Due to the patient's refusal of TSEM, radiosurgery was performed. He continued treatment with octreotide 20 mg per month, thiamazole 5 mg every 24 hours, prednisone 5 mg every 24 hours, and testosterone enanthate 250 mg every 3 weeks. Thyroid profile control showed Free T4 22 pmol/L and TSH 14.8 mIU/L.

A follow-up MRI at 1 year post-radiosurgery indicated a lesion of 21x22x19mm and 5.1cc.

Analysis

Thyroid-stimulating hormone (TSH)-secreting pituitary adenomas are a rare cause of hyperthyroidism. Diagnosing thyrotropinomas can be challenging, and the differential diagnosis includes laboratory analysis interference and resistance to thyroid hormones (RTH). Though these situations are rare, endocrinologists must be aware of interferences and closely collaborate with endocrine laboratories for additional studies when necessary [12]. Antibodies against TSH or thyroid hormones, along with abnormal forms of albumin or transthyretin, can lead to falsely elevated TSH or thyroid hormone levels.

Resistance to thyroid hormones (RTH) constitutes a group of genetically caused syndromes characterized by decreased tissue sensitivity to these hormones. Currently, three forms are distinguished, where hormonal action resistance is due to mutations in the gene encoding the T3 nuclear receptor TR, alterations in cellular transport of T4 and T3, and defects in T4 to T3 conversion mediated by deiodinases. In most cases, RTH is caused by a mutation in the beta receptor gene.

TSH-secreting adenomas release biologically active TSH somewhat autonomously. Therefore, TSH secretion usually does not increase significantly in response to thyrotropin-releasing hormone (TRH) and does not decrease significantly in response to exogenous thyroid hormone administration. The secreted TSH's biological activity varies considerably, leading to varying levels of immunoreactive TSH in the serum, ranging from normal (though inappropriately high in the presence of hyperthyroidism) to markedly elevated [13].

The course of thyrotropinomas, as in the presented cases, tends to be insidious, sometimes persisting for years after diagnosis. This may be due to delayed diagnosis or, in some cases, the therapeutic options offered. For example, patient 1 experienced a prolonged course due to delayed diagnosis, while patient 3 was initially categorized as a macroadenoma due to a lack of a biochemical profile, resulting in perioperative complications.

Some patients may not be surgical candidates, or others may prefer non-surgical treatments, as seen in patient 3. Most TSH-omas express somatostatin receptors. Somatostatin analogs (SSAs) are used in the preoperative treatment of TSH-oma patients to control TSH-dependent hyperthyroidism and in patients with residual tumor after pituitary surgery. SSAs could also be beneficial for patients with invasive TSH-omas at high risk of not being cured by surgery [14].

Clinical remission of hyperthyroidism, resolution of neurological symptoms, normalization of neuroimaging abnormalities, and thyroid hormone, TSH, or α-subunit/GSU to TSH molar ratio are considered for evaluating the efficacy of surgery or radiotherapy. In patients receiving prior thyroid ablation, some criteria may not be applicable [15].

Due to relatively poor surgical outcomes, many patients with macroadenomas require additional treatment. The choice between long-term somatostatin analogs and pituitary radiation is based on individual discussions with patients regarding the risks and benefits of each therapy. The advantage of radiotherapy is the potential suspension of long-term medical treatment. However, long-term adverse effects of pituitary radiation may include hypopituitarism, infertility, and, rarely, cognitive function impairment [16].

Somatostatin analogs are administered after transsphenoidal surgery for long-term control of residual disease [2]. For example, in a series of 73 patients treated with octreotide (50 to 750 micrograms subcutaneously two or three times a day), most of whom had already undergone surgery, the following results were observed: TSH serum concentration decreased by over 50 percent in 92 percent of patients and normalized in 79 percent; Serum concentrations of T4 and T3 returned to normal in 95 percent of patients after one year; The tumor size decreased in 52 percent of patients after one year; Less than 10 percent of patients developed resistance to the action of octreotide. A slow-release formulation of a somatostatin analog, lanreotide, has proven effective in patients with TSH-secreting pituitary adenomas [17,18]. In 16 patients (most of whom had residual disease after transsphenoidal surgery), 30 mg of lanreotide administered intramuscularly two or three times a month for six months resulted in improved hyperthyroidism symptoms in all patients and normalization of TSH and thyroid hormone concentrations in 13 patients, but no change in tumor size was observed. Thyroid tests (TSH, Free T4, Total T3) should be monitored as somatostatin analogs can induce TSH deficiency, requiring a reduction in dosage frequency [1]. Adverse effects include nausea, abdominal discomfort, abdominal distension, diarrhea, glucose intolerance, and cholelithiasis. Treatment cost should be considered when choosing this option. Most thyrotropinomas are macroadenomas that invade parasellar structures, do not achieve remission post-surgery, and require adjuvant therapy [19].

Patients with TSH-secreting adenomas who seem cured require TSH, Free T4, and Free T3 monitoring two or three times in the first postoperative year and less frequently (annually) thereafter. Pituitary MRI should be performed one year after the operation and then less frequently (every two or three years, and even less frequently) if the MRI is normal and there is no clinical or biochemical evidence of recurrence. For patients with mixed tumors (i.e., TSH/Growth Hormone-secreting tumors), this does not include evidence of secretion of any tumor component. MRI should be repeated more frequently if there are indications of biochemical or clinical recurrence [20].

While most patients evolve reasonably well, in a series of 25 patients, there were three deaths, including one due to metastatic thyrotroph carcinoma. An additional case of metastatic pituitary adenoma secreting prolactin co-secretor has been reported [13-23].

Conclusion

In our series, TSHomas predominantly affect men with macroadenomas, emphasizing the importance of preoperative hormone assessment in patients with sellar lesions for achieving proper diagnosis, treatment, and reducing complications. Due to their low prevalence, there are few centers with expertise in the diagnosis, treatment, and follow-up of these cases. Given their complexity and potential complications, patients with TSHomas should be managed in centers of excellence specializing in pituitary pathology.

No specific funding was received for the study. The authors declare that they have no conflicts of interest. No additional disclosures to report. Terms and conditions are accepted.

References

1. Amlashi FG, Tritos NA (2016) Thyrotropin-secreting pituitary adenomas: epidemiology, diagnosis, and management. Endocrine 52: 427-440.
2. Latrech H, Rousseau A, Le Marois E, Billaud L, Bertagna X, et al. (2010) Présentation et pronostic des adenomes thyreotropes: a propos de trois observations. Rev Med Interne 31: 858-862.
3. Koulouri O, Moran C, Halsall D, Chatterjee K, Gurnell M (2013) Pitfalls in the measurement and interpretation of thyroid function tests. Best Pract Res Clin Endocrinol Metab 27: 745-762.
4. Mazerkina N, Trunin Y, Gorelyshev S, Golanov A, Kadashev B, et al. (2016) Thyrotropin-secreting pituitary adenoma in an 11-year-old boy with type 1 autoimmune polyglandular syndrome. J Pediatr Endocrinol Metab 29: 237-240.
5. Glynn N, Agha A (2013) Unexpected clinical course during treatment of a TSH-secreting pituitary adenoma. Endocr Pract 19.
6. Perdomo CM, Arabe JA, Idoate M, Galofre JC (2017) Management of a pregnant woman with thyrotropinoma: a case report and review of the literature. Gynecol Endocrinol 33: 188-192.
7. Guijarro de Armas M aG, Vega Pinero B, Pavon de Paz I, Alameda Hernando C, Monereo Megías S (2012) Tirotoxicosis por tiroiditis subaguda en el postoperatorio de un tirotropinoma. Endocrinol y Nutr 59: 270-273.
8. Nazato DM, Abucham J (2018) Diagnosis and treatment of TSH-secreting adenomas: review of a longtime experience in a reference center. J Endocrinol Invest 41: 447-454.
9. Lleva RR, Inzucchi SE (2011) Diagnosis and management of pituitary adenomas. Curr Opin Oncol 23: 53-60.
10. Pawlikowski M, Pisarek H, Jaranowska M, Radek M, Winczyk K, et al. (2016) Silent thyrotropin (TSH) expression in acromegaly and clinically non-functioning pituitary adenomas. Endokrynol Pol 67: 515-518.
11. Vasilev V, Daly A, Naves L, Zacharieva S, Beckers A (2012) Clinical and genetic aspects of familial isolated pituitary adenomas. Clinics 67: 37-41.
12. Azzalin A, Appin CL, Schniederjan MJ, Constantin T, Ritchie JC, et al. (2016) Comprehensive evaluation of thyrotropinomas: single-center 20-year experience. Pituitary 19: 183-93.
13. Beck-peccoz P, Brucker-davis F, Persani L, Smallridge RC, Weintraub BD (2015) Thyrotropin-Secreting Pituitary Tumors 17.
14. Gruszka A, Zielinski GM, Kunert-Radek J (2014) Preoperative long-acting octreotide treatment for invasive thyrotropin-secreting pituitary macroadenoma after previous radioiodine thyroid ablation. J Clin Neurosci 21: 340-342.
15. Lania A, Beckers A, Chatterjee K (2013) European Thyroid Association Guidelines for the Diagnosis and Treatment of Thyrotropin-Secreting Pituitary Tumors 76-82.
16. Kuhn JM, Arlot S, Lefebvre H, Caron P, Archambaud F, et al. (2015) Evaluation of the Treatment of Thyrotropin-Secreting Pituitary Adenomas with a Slow-Release Formulation of the Somatostatin Analog Lanreotide 85.
17. Beck-Peccoz P, Brucker-Davis F, Persani L, Smallridge RC, Weintraub BD (1996) Tumores hipofisarios secretores de tirotropina. Endocr Rev.Diciembre de 17: 610-638.
18. Kuhn JM, Arlot S, Lefebvre H, Caron P, Cortet-Rudelli C, et al. (2000) Evaluation of the treatment of thyrotropin-secreting pituitary adenomas with a slow-release formulation of the somatostatin analog lanreotide. J Clin Endocrinol Metab 85: 1487-1491.
19. Illouz F, Chanson P, Sonnet E, Brue T, Ferriere A, et al. (2021) Somatostatin receptor ligands induce TSH deficiency in thyrotropin-secreting pituitary adenoma. Eur J Endocrinol 184: 1-8.
20. Beck-Peccoz P, Lania A, Beckers A, Chatterjee K, Wemeau J-L (2013) European Thyroid Association Guidelines for the Diagnosis and Treatment of Thyrotropin-Secreting Pituitary Tumors. Eur Thyroid J 2: 76-82.
21. Schindhelm RK, Heima NE, Schoor NM Van, Simsek S (2013) European Journal of Internal Medicine Thyroid hormones and erythrocyte indices in a cohort of euthyroid older subjects. Eur J Intern Med 24: 241-244.
22. Brucker-Davis F, Oldfield EH, Skarulis MC, Doppman JL, Weintraub BD (1999) Thyrotropin-secreting pituitary tumors: Diagnostic criteria, thyroid hormone sensitivity, and treatment outcome in 25 patients followed at the National Institutes of Health. J Clin Endocrinol Metab 84: 476-486.
23. Casanueva FF, Barkan AL, Buchfelder M, Klibanski A, Laws ER, et al. (2017) Criteria for the definition of Pituitary Tumor Centers of Excellence (PTCOE): A Pituitary Society Statement. Pituitary 20: 489-498.