Turkish Journal of Endocrinology and Metabolism, (2002) 4 : 159-162 **CASE REPORT**

A Case of Thyrotropin-Secreting Pituitary Adenoma (TSH-oma)

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Thyrotropin-secreting pituitary adenomas are rare tumors, and prevalence is about one case per million. Normal or elevated thyrotropin levels in hyperthyroid patients are characteristic of TSH-secreting pituitary adenoma. Because TSH-secreting pituitary tumors are uncommon, subjects with TSH-omas are often misdiagnosed as having Graves' disease, and misdiagnosis may leads to enlargement of tumor size. We present a patient with thyrotropin-secreting pituitary adenoma misdiagnosed as Graves' disease. The patient has high T3, FT3, FT4 and TSH, and she has a pituitary microadenoma (9 mm). Once the inappropriate secretion of TSH is established, the differential diagnosis between TSH-secreting tumor and resistance to thyroid hormone must be made.

Key words: TSH-oma, Thyrotropin, alpha subunit of TSH and Graves' disease

Introduction

Thyrotropin-secreting pituitary adenomas (TSH-omas) are rare tumors and represent about 1-2% of all pituitary adenomas (prevalence is about one case per million) and cause secondary or central hyperthyroidism. The number of reported cases of TSH-omas tripled in the last decade. The increased number of reported cases resulted principally from the introduction of ultrasensitive immunometric assay for TSH as a first-line test for the evaluation of thyroid function (1). TSH-secreting adenomas are part of the syndrome of inappropriate secretion of TSH (SITSH). The hormonal profile is characterized by nonsuppressed TSH in the presence of high levels of free thyroid hormones (FT3 and FT4). Normal or elevated thyrotropin levels in hyperthyroid patients are characteristic findings of TSH-secreting pituitary adenoma, which is easily detectable by computed tomographic (CT) scan or magnetic resonance imaging (MRI). Other diagnostic tools are an absent/impaired TSH response to TRH, high sex hormone-binding globulin, high alpha-subunit and high alpha-subunit/TSH molar ratio.

The presence of a pituitary tumor in a patient with inappropriate secretion of TSH, although strongly suggestive, is not diagnostic of TSH-secreting tumor, as pituitary incidentalomas have been found on MRI in up to 10% of normal subjects (2). Cosecretion of α-subunit is the rule. Absolute values of α-subunit have excellent sensitivity and specificity; however, if used alone it could be misleading in menopausal women, for whom determination of LH and FSH levels is mandatory. The α-subunit/TSH molar ratio also has excellent sensitivity, but less specificity, in patients with intact thyroid (3). TSH secreting tumors are characterized by an absent or inappropriate negative feedback of thyroid hormone on TSH secretion. The majority of TSH-omas (about 75%) secrete TSH alone, cosecretion of other anterior pituitary hormones occur in about 25% of TSH-omas (Hypersecretion of growth hormone

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or prolactin is the most frequent) (1). Surgical removal of TSH-oma leads to clinical and biochemical remission in most patients. However, some type of adenomas have clinical heterogeneity, and subsequently cannot be cured by surgery alone (4). In surgical failures, radiotherapy and octreotide treatment have a high success rate.

Case Report

GC, a 19-year old girl, was admitted to Dicle University, Department of endocrinology and metabolism for nodular goiter. (file number: 517790, protocol number: 2002044875), She was complaining from tachycardia, emotional instability, extreme sweating and heat intolerance. Pulse rate was 112 beats/min. Blood pressure was 120/75 mmHg. Hormonal evaluation showed increased thyroid hormone concentrations in the presence of inappropriately elevated levels of serum TSH (Table 1). Antithyroperoxidase and antithyroglobulin antibodies were absent. Thyroid scintigram by ^{99}TC showed moderate enlargement of the thyroid gland and a macro hypoactive nodule at the right lobe and multiple hypo and hyperactive nodules in the thyroid gland. Multinodular goiter was also found by ultrasonography. Benign cytology was defined with fine needle aspiration biopsy from the dominant hypoactive nodule. She had been mistakenly treated with propylthiouracil due to misdiagnosis as Graves' disease for one year before being admitted to our department. TRH injection (500 µ, iv, TRH ferring, Er-Kim) showed a mild effect on TSH the maximal TSH response being 9.28 mU/L from a baseline 8.82 mU/L 20 minute after stimulation. The ratio of α-subunit to TSH was calculated using the following formula (α-subunit in micrograms per L divided by TSH in milliunits per L) x 10. After administration of ocreotide (50 µ, sc) TSH concentration decreased significantly at 3h, maximal inhibition (40%) was at 5th h, and serum TSH suppression continued for the next 3h. After 24-h sc injection of octerotide three times daily (300µ/day), serum TSH decreased dramatically (65%). Sex-hormone binding globulin concentration was normal. Basal prolactin, LH, FSH, and growth hormone levels were normal. MRI revealed a pituitary adenoma with a diameter of 9 mm (Figure 1A and Figure 1B). Visual fields of the patient were normal. There was no sign of ophthalmopathy or acropachy. The patient was sent to the neurosurgery department for transsphenoidal microsurgery. In the histopathological specimens of the adenoma; strongly positivity for TSH was seen by immunohistochemical staining, postoperatively.

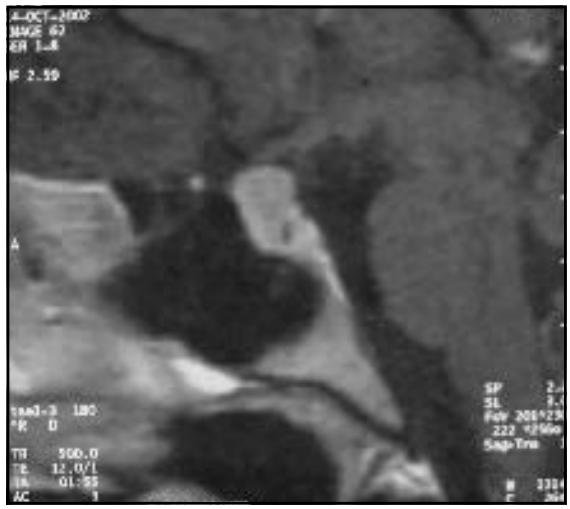

Figure 1A. Micro adenoma in MRI of pituitary of the patient in sagital view.

Table 1. Biochemical and hormonal results of the patient

	Patient	Normal range
TSH (mU/L)	8.82	0.270-4.2
T3 (ng/mL)	3.86	0.846-2.02
T4 (ug/L)	11.55	5.13-14.06
Free T3 (ng/dl)	1.03	0.182-0.462
Free T4 (ng/dl)	2.14	0.932-1.71
TRH test (basal, 20th, 60th, 90th, 120th minutes TSH (mU/L) levels, respectively)	8.83, 9.28, 8.89, 8.74, 8.92	
α-TSH (µg/L)	2.15	0.1-0.7
α-TSH / TSH ratio	2.4	
Prolactin (ng/mL)	7.82	3.4-24.1
FSH (mIU/mL), (follicular phase)	4.92	3.3-11.3
LH (mIU/mL), (follicular phase)	2.95	2.4-12.6
GH (ng/ml)	0.9	<2
SHBG (nmol/L)	280	24-230

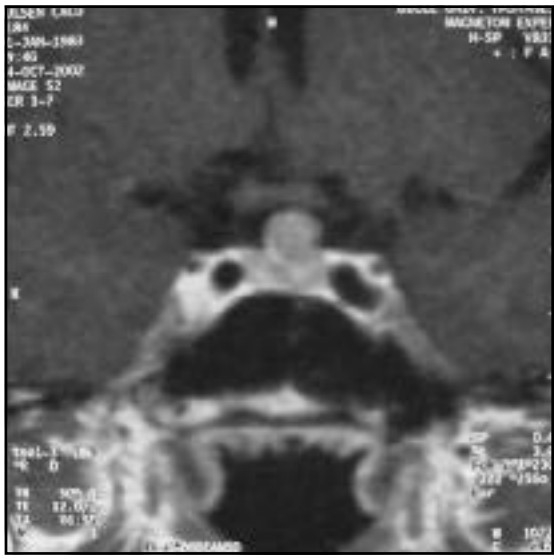

Figure 1B. Micro adenoma in MRI of pituitary of the patient in frontal view.

Discussion

TSH-secreting pituitary adenomas comprise less than 1% of pituitary tumors. In one neurosurgical series, only two TSH-producing tumors were found among 1000 hormonally active pituitary tumors (5). We also determined a patient with TSH-oma for the first time during almost 10 years of our clinical experience. The presence of a pituitary tumor in MRI of pituitary in a patient with inappropriate secretion of TSH is not diagnostic of TSH-secreting tumor, as pituitary incidentalomas have been found on MRI in up to 10% of normal subjects (2). Because TSH-secreting pituitary tumors are uncommon, subjects with TSH-omas are often misdiagnosed as having Graves' disease. Our patient has also been mistakenly treated with propylthiouracil due to misdiagnosis as Graves' disease for one year before being admitted to our clinic. Misdiagnosis may lead to enlargement of tumor size. Therefore possible occurrence of TSH-secreting tumors, although rare, underscores the need for mandatory TSH measurements to rule out secondary hyperthyroidism in thyrotoxic patients with goiter. Once the inappropriate secretion of TSH is established, the differential diagnosis between TSH-secreting tumor and resistance to thyroid hormone (6) must be made. Familial studies help rule out thyroid hormone resistance (RTH). Most patients have been diagnosed at the stage of macroadenoma and often after having been mistaken for having Graves' disease. The mean duration of symptoms before diagnosis is long (almost 9 yr). So, tumoral symptoms and signs, such as headaches and/or visual field defects, are frequent at diagnosis (7). But our patient has microadenoma and the visual field of the patient is normal. About two thirds of patients had thyroid nodules, probably due to sustained TSH stimulation over many years. The present case has multinodular goiter in both thyroid scintigram by ^{99}TC and ultrasonography of the thyroid.

Normal or elevated TSH levels in hyperthyroid patients are characteristic of TSH-secreting pituitary adenoma. The lack of response of TSH to TRH present in patients with TSH-oma, conversely, patients with resistance to thyroid hormone typically have a robust response of TSH to TRH (8). Other diagnostic findings are high sex hormone-binding globulin (SHBG) levels, high alpha-subunit levels, and a high alpha-subunit/TSH molar ratio. TRH injection showed only a mild effect on TSH from a baseline in our patient and the patient had high sex hormone-binding globulin levels, high alpha-subunit levels, and a high alpha-subunit/TSH molar ratio. Cosecretion of α-subunit is the rule. Absolute values of α-subunit have excellent sensitivity and specificity; however, if used alone it could be misleading in menopausal women, for whom determination of LH and FSH levels is mandatory. The α-subunit/TSH molar ratio had excellent sensitivity, but less specificity, in patients with intact thyroid. Our patient was 19 years old and she has regular menses.

Antithyroid drugs do not treat thyrotroph adenomas directly, and because thyrotroph adenomas respond to a decrease in the serum thyroxine concentration by increasing TSH secretion and perhaps by an increase in adenoma size, antithyroid drugs should be used only to make a patient euthyroid prior to surgery or as adjuvant therapy following radiation (5). Our patient had been misdiagnosed as Graves' disease before being admitted to our department, and propylthiouracil treatment had been used. The great majority of TSH-omas are macroadenomas and about 75% of TSH-omas secrete TSH alone, cosecretion of other anterior pituitary hormones occurs in about 25% of TSH-omas (1). Hypersecretion of growth hormone or prolactin is the most frequent association. We evaluated the patient in terms of growth hormone and prolactin, but we did not find any abnormality in these hormones. As a result our patient was accepted to be TSH-oma which secretes TSH alone. After administration of ocreotide, TSH concentration

decreased significantly at 3rd h, maximal inhibition was at 5th h, and serum TSH suppression continued for the next 3h. After 24-h sc injection of octerotide three times daily (300 μ/day), serum TSH concentration decreased dramatically (65%). The octreotide test is useful before surgery to predict whether the drug could be used as therapy if surgery alone was not curative. The different response is due to the high concentration of somatostatin receptors (9) on TSH-secreting tumors, which usually respond immediately to somastostatin with a marked decrease in TSH secretion. The test also had the advantage of preparing the patients for surgery, resulting in decreased TSH and thyroid hormone levels (6). Therefore we can say that the TSH-secreting tumor of our patient has a high concentration of somatostatin receptors. Surgical removal of TSH-oma leads to clinical and biochemical remission in most patients. Previous reports have described the surgical cure of TSH adenoma to be more difficult than other functional adenomas because of large and invasive features. However, with the current introduction of ultrasensitive immunometric assays, TSH-secreting adenomas are more often recognized. Early diagnosis of TSH-secreting adenomas leads to a high rate of remission of hyperthyroidism after surgery. However, some type of adenomas have clinical heterogeneity, and subsequently cannot be cured by surgery alone (4). Undetectable TSH concentration at the end of the first week after surgery, suggests a definitive cure, backed up by tests for cosecreted hormones from the adenoma and dynamic tests of TSH suppression.

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