Thyroid stimulating hormone microadenoma as a rare cause of thyrotoxicosis amenable to surgical cure

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A B S T R A C T

Hyperthyroidism due to a thyroid stimulating hormone (TSH) pituitary adenoma is rare. We report a 29-year-old woman with thyrotoxicosis and elevated serum 3,5,3',5'-tetraiodothyronine and TSH levels that resolved after a transsphenoidal excision of the detected TSH pituitary adenoma. The diagnosis and management options in such patients are reviewed.

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1. Introduction

Thyrotrope (TSH) adenomas are the rarest type of functional tumours accounting for 1% of all pituitary adenomas, 70%–80% of these tumours being macroadenomas.1,2 These adenomas are part of the “syndrome of inappropriate secretion of thyroid stimulating hormone (TSH)” characterized by non-suppressed TSH in the presence of high levels of the free thyroid hormones triiodothyronine (3,3',5-triiodothyronine, FT3) and tetraiodothyronine (3,5,3',5'-tetraiodothyronine, FT4). Inappropriately normal or elevated TSH levels in an individual with thyrotoxicosis should alert the physician to the possibility of this condition. Pituitary resistance to thyroid hormones is an important differential diagnosis to be considered.2

In this report we describe a 29-year-old woman who presented with clinical features of thyrotoxicosis and was cured by surgical excision of the TSH-secreting pituitary adenoma. We review the current literature on clinical features, diagnosis and treatment.

2. Case report

A 29-year-old woman presented with a 9-month history of hand tremors and intermittent palpitations and had a diffuse, firm thyroid swelling. There was no ophthalmopathy. Biochemical investigations confirmed thyrotoxicosis: total T4–17.2 μg/dL (normal: 4.5–12.5 μg/dL) and free T4–2.73 ng/dL (normal: 0.8–2 ng/dL); in addition her TSH was also elevated at 8.4 μIU/mL (normal: 0.3–4.5 μIU/mL). Serum cortisol, prolactin and follicle stimulating hormone (FSH) levels were normal. The serum sex hormone binding globulin (SHBG) concentration was 53.63 nmol/L (normal: 26.1–110.0 nmol/L), and serum angiotensin converting enzyme (ACE) concentration was 42.9 U/L (normal: 8–52 U/L). A brain MRI showed an 8 mm by 8 mm, moderately enhancing with contrast, hypointense lesion on the left side of the pituitary gland (Fig. 1a).

After controlling her heart rate with propranolol, the patient underwent an endoscopic transsphenoidal excision of the pituitary microadenoma, which was removed as a single nodule (Fig. 2) Histopathology confirmed the diagnosis of pituitary adenoma, which was immunopositive for TSH, FSH and the alpha subunit. Postoperatively the patient's thyrotoxic symptoms subsided and her serum TSH concentration was reduced to 0.01 μIU/mL, her total T4 to 10.4 μg/dL, and free T4 to 1.22 ng/dL. A 3-month follow-up MRI showed no tumour (Fig. 1b) and her thyroid function remained normal.

3. Discussion

The low incidence of TSH adenoma (around 1%) results from thyrotroph cells accounting for fewer than 5% of all pituitary cells. However, with the advent of ultrasensitive TSH diagnostic methods and modern pituitary MRI, these tumours are diagnosed earlier and more frequently.1 Most instances are diagnosed in the third to fifth decade of life with a long history of hyperthyroidism, often mistakenly diagnosed as Graves’ disease, which can lead to an inappropriate thyroidectomy and/or radioiodine thyroid ablation. The clinical features of hyperthyroidism are usually present with a detectable goitre, but ophthalmopathy, pretibial myxedema, and acropachy are usually absent. Graves’ disease, autoimmune and Hashimoto’s thyroiditis can coexist in patients with TSH adenomas, but this is rare. One-third of patients report menstrual irregularities or galactorrhea while hypersecretion of growth hormone and/or prolactin is observed in about 40% to 50% of patients, and 10% to 15% of patients are asymptomatic.1,2 Other rarer forms of presentation are with hypokalemic periodic paralysis, osteoporosis, weight loss and cardio-embolic stroke due to atrial fibrillation.

The classical diagnostic criteria of TSH-secreting adenomas are inappropriate secretion of TSH despite increased free thyroid hormone concentrations, and evidence on MRI of a pituitary tumour. Elevated sex hormone binding globulin (SHBG), elevated ACE levels, loss of normal diurnal rhythm of TSH, less than 2-fold or no elevation of serum TSH levels with thyroid releasing hormone (TRH) stimulation, and non-suppression of TSH concentrations following administration of T3 favour a diagnosis of thyrotropinoma. It must be kept in mind that 10% of the population can have an incidental pituitary adenoma.

In a patient with true inappropriate secretion of TSH, a TSH adenoma needs to be distinguished from resistance to thyroid hor-
mone (RTH). These patients should undergo investigations according to the algorithm suggested by Beck-Peccoz et al. to avoid a misdiagnosis. Measurement of the alpha subunit/TSH molar ratio may be helpful in differentiating TSH adenoma from RTH.

About seven out of 25 patients (33%) in Clarke et al.’s study had clinically silent tumours, and did not present with clinical or biochemical evidence of elevated TSH, but demonstrated strong immunopositivity for TSH. The reason for this is not well understood but is possibly due to variable levels of various TSH isoforms, or that TSH secretion in some tumours is too low to induce biological or clinical signs of hyperthyroidism.

3.1. Treatment

The goal of endoscopic transsphenoidal surgery for TSH adenoma is meticulous tumour resection, elimination of mass effect, and normalization of TSH while maintaining pituitary function. Thus, the success of surgery depends on tumour size and invasiveness, duration of symptoms, and severity of hyperthyroidism. Since many of these tumours are invasive macroadenomas, an initial biochemical stabilization eventually leads to a relapse in hyperthyroidism due to residual tumour remnants. A postoperative thyroid storm after surgery for a TSH adenoma may be prevented by preoperative propanolol treatment. The medical treatment of TSH adenomas mainly rests on the administration of somatostatin analogs, such as octreotide and lanreotide. More recently octreotide has been found to reduce TSH secretion in 91% of patients and normalize thyroid hormone levels in 73% of patients, supporting the role of primary octreotide therapy in those who are unfit or decline surgery, or to achieve a euthyroid state prior to surgical resection. Due to its high cost and limited availability, the use of octreotide is limited to a select population.

In conclusion, TSH adenomas are uncommon, although probably not as rare as previously reported. An inappropriately high serum TSH level in a patient with clinical and biochemical evidence of thyrotoxicosis should raise the suspicion of a TSH adenoma from RTH. Although cure rates with surgery for macroadenomas are still not satisfactory, microadenomas have a favorable outcome. Radiation therapy and octreotide serve as useful adjuvant therapy.

References
