CHAPTER 8

THYROID STIMULATING HORMONE SECRETING PITUITARY ADENOMA

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Thyroid-stimulating hormone (TSH) secreting pituitary adenoma (TSHoma) is one of the rare causes of hyperthyroidism (1). TSHoma account for less than 1% of all pituitary adenomas and 0.5 to 3% of functional pituitary adenomas (2,3). In this disease, TSH secretion is autonomous and resistant to negative feedback from thyroid hormones. TSH itself causes overstimulation of the thyroid gland and, as a result, oversecretion of free thyroxine (fT4) and triiodothyronine (fT3) (4). Therefore, this entity can be appropriately classified as a form of "central hyperthyroidism."

In 1970, Hamilton et al reported the first case of TSH-oma (5). Its incidence is 0.15-2.8/million/year and it is reported that it has increased five times over the years (1,6). It is thought that this increase may be related to both the use of more sensitive immunometric TSH measurements and more frequent pituitary imaging (6). Although TSHomas can be seen at any age, they often occur in the the fifth-sixth decade of life (2). Although the prevalence of the tumor does not differ between the gender, it has been reported more frequently in women in some studies (6).

PATHOLOGICAL ASPECTS

TSHoma secrete biologically active TSH autonomously. Therefore, TSH secretion usually does not increase much in response to thyrotropin-releasing hormone (TRH) and does not decrease much in response to exogenous thyroid hormone administration. The biological activity of secreted TSH is highly variable. Serum immunoreactive TSH concentrations range from normal to markedly elevated (>500 mU/L) (4). The molecular basis of TSH-secreting adenomas has not been fully elucidated. Somatic mutations or abnormal oncogene expression may contribute to these tumors, as with other pituitary tumors. It has been reported that the defect in this negative regulation of TSH secretion may be due to pitui-

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tary-specific transcription factor-1 (Pit-1) overexpression, somatic mutations of the thyroid hormone receptor beta (THRB) gene, and aberrant expression of TR-beta (7–9).

The vast majority (70-85%) of TSHomas secrete only TSH, and this is often accompanied by hypersecretion of the alpha subunit of glycoprotein hormones (alpha-GSU). Classic mixed adenomas, characterized by simultaneous hypersecretion of other anterior pituitary hormones, are found in approximately 20-25% of patients (2,3). Growth hormone or prolactin hypersecretion are the most common associations (3). This is because somatotroph and lactotroph cells share common transcription factors with thyrotropes such as Pit-1 and Prop-1 (3,10). While TSH and growth hormone-secreting adenomas are seen with equal frequency in men and women, co-secretion of TSH and prolactin is approximately five times more common in women than in men. In some patients hyperprolactinemia results from compression of the pituitary stalk. Mixed TSH/gonadotropin adenoma formation is rarely, but to date no reported coxistence with adrenocorticotropic hormone possibly due to the distant origin of thyrotrophic and corticotropic lineages (2).

CLINICAL PRESENTATION

The diagnosis of TSHoma can usually be made during the investigation of inappropriate TSH elevation or the investigation of pituitary incidentaloma. In many patients, typical signs and symptoms of hyperthyroidism such as palpitations, tremor, heat intolerance are observed due to high fT3 and fT4 (11). These clinical signs are often mild or moderate (11). Diffuse or nodular goiter may develop in patients due to prolonged TSH stimulation (12). Many of these patients may have been mistakenly diagnosed with Graves' disease because of their long-term history of hyperthyroidism and may have been inappropriately treated with thyroidectomy or radioactive iodine therapy (2). The characteristic signs of Graves' disease, such as ophthalmopathy and dermopathy, are absent unless there is concomitant Graves' disease (13). Graves' disease and TSH-oma has been reported in only a few cases (13,14). Thyroid cancer and toxic nodular goiter have also been developed rarely in these cases (6,15,16).

In addition to the symptoms of hyperthyroidism, visual field defects, headache or hypopituitarism may occur due to pressure effects of the pituitary adenomas. In cases of mixed TSH/growth hormone-secreting tumors, symptoms of acromegaly may occur, including acral enlargement, macroglossia and hyperhidrosis. If there is prolactin secretion, menstrual irregularity and galactorrhea can be seen (6,17).

Cases of cardiotoxicosis with atrial fibrillation, heart failure, massive pleural and pericardial effusion have been reported, and typical episodes of periodic paralysis were described in two patients (18–21). Recently, there are studies showing an increased prevalence of vertebral fractures in patients with TSH-oma (22).

BIOCHEMICAL FINDINGS

The essential biochemical abnormalities in patients caused by TSHoma are elevated serum fT3 and fT4 levels and not suppressed TSH levels (normal or high). The α-GSU level is high, especially in macroadenomas (50–85%). A high α-subunit/TSH molar ratio is important for diagnosis since the increase in α-subunit is higher than the increase in serum TSH level (23). This ratio can be detected normally in microadenomas. The level of sex hormone binding globulin (SHBG) is usually elevated (6). Normal values should suggest thyroid hormone resistance or TSH interference. Anterior pituitary hormones should also be measured to detect the simultaneous secretion of another hormone. These measurements may also indicate possible hypopituitarism due to compression of the mass.

Dynamic tests are used in the differential diagnosis of TSHoma from other conditions with inappropriate TSH secretion, especially thyroid hormone resistance. TRH testing is widely used in the differential diagnosis of TSH-oma. Serum TSH concentrations do not increase in response to TRH administration in the majority of patients (2,4). The T3 suppression test has been used to assess the presence of a TSHoma (75-150 ug/day for 7-10 days). The absence of suppression in TSH following this procedure is in favor of TSHoma. Furthermore, that blood supply does not decrease in Doppler ultrasonography (USG) after T3 suppression may also help in the diagnosis of TSHoma (6,24). However, this test is contraindicated in elderly patients or individuals with coronary artery disease. T3 suppression test can be used in combination with the TRH test in the differential diagnosis of inappropriate TSH secretion. The differential diagnosis of TSHoma and thyroid hormone resistance are summarized in Table 1.

IMAGING STUDIES

In most patients, macroadenoma is detected on pituitary magnetic resonance imaging (MRI) (25). CT evaluation can be performed when MRI is contraindicated (2). It may be difficult to distinguish TSHoma from thyroid hormone resistance when the tumor is very small or empty sella (6).

Table 1: Differential diagnosis of TSHoma and thyroid hormone resistance (2)		
Parameters	**TSHoma**	**Thyroid Hormone Resistance**
Female/Male ratio	1.3	1.4
Familial	% 0	% 85
TSH	Normal/High	Normal/High
fT4	Normal/High	Normal/High
fT3	Normal/High	Normal/High
Lesions at MRI	% 99	% 23
Germline THRB mutation	% 0	% 84
High α-subunit levels	% 69	% 3
High α-subunit/TSH molar ratio	% 81	% 2
Elevated SHBG levels	% 90	% 8
Blunted TSH response to TRH test	% 87	% 2
Abnormal TSH response to T3 suppression	% 90	% 12-25
Long acting SSA response	% 92	%0

TSHoma: Thyroid-stimulating hormone secreting pituitary adenoma, TSH: thyroid-stimulating hormone, fT4: free thyroxine fT3: free triiodothyronine, MRI: magnetic resonance imaging, THRB: Thyroid hormone receptor β gene, SHBG: sex hormone binding globulin, SSA: somatostatin analogs

Although Indium-0111 octreotide scintigraphy is not a specific test, it can be used to localize TSHoma (26). Thyroid Doppler USG is important in terms of the presence of diffuse or nodular goiter and increased blood supply in TSHoma patients.

TREATMENT

Primary treatment in TSHoma patients is adenoma resection by the transnasal or transcranial surgery (3). Patients should be given medical treatment with somatostatin analogs (SSA) to restore euthyroidism before surgery. While most patients with microadenomas are treated with this approach, approximately half of patients with macroadenomas require additional treatment for residual disease (2). In general, the frequent cavernous sinus invasion, and dense fibrosis within the adenoma make surgical removal of these macroadenomas difficult (2). While surgical remission rates are approximately 100% in microadenomas, this rate decreases to 50-60% in macroadenomas (6). When the tumor is completely removed, TSH may decrease to undetectable levels, and temporary or permanent

levothyroxine treatment may be needed. The post-surgical cure criteria are not clearly known. However, improvement in hyperthyroidism symptoms, normalization of thyroid function tests, and absence of rest tumor tissue in MRI can be considered in the cure evaluation (2,6). Since hypopituitarism (50%) can be seen after surgery, patients should be evaluated in this regard.

Medical treatment is recommended either in the preoperative period to make the patient euthyroid or in cases where surgery is insufficient. Since TSHomas express the somatostatin receptor, SSA can be used in primary treatment and cases that do not remission after surgery due to their hormonal control and tumor-reducing effects (27,28). Treatment with a short-acting SSA should first be initiated to determine whether patients can tolerate the drug and whether it is effective in lowering TSH. A short-acting SSA is administered 50 micrograms subcutaneously twice daily, increasing to three times daily and then in increments of 50 micrograms per injection as needed to 100 micrograms three times daily. Serum TSH and fT4 concentrations should be measured at intervals of two to three weeks. If the short-acting SSA is tolerated and appears adequate, it can be converted to a long-acting SSA administered intramuscularly every four weeks (29). The long-acting SSA are used every 28 days. The dose should be individualized, starting with the smallest doses of SSAs. Thyroid hormone measurements should be made at basal and on the 28th day, and the drug dose should be adjusted (6). Treatment with SSAs should be continued for an average of three to four months in order to achieve euthyroidism. Patients using SSA should be followed closely for gastrointestinal side effects, cholecystolithiasis, and hyperglycemia (2,6,30). In addition, if treatment-related central hypothyroidism develops, L-thyroxine replacement should be performed. Dopamine agonists can be used in patients who cannot tolerate SSAs. Dopamine agonists are more effective, especially in cases with prolactin secretion (31,32).

β-blocker therapy (propranolol 80–160 mg/day or atenolol 25 50 mg/day) can be used to control the signs and symptoms of hyperthyroidism. Antithyroid drug use is not recommended in the treatment of TSHoma. However, there is an opinion that it can be tried in some cases for a short time before pituitary surgery. On the other hand, antithyroid drugs can be used in cases where euthyroidism cannot be achieved before surgery with SSAs or dopamine agonists. Long-term use of antithyroid drugs is inconvenient as it may enlarge the pituitary tumor (29).

Radiotherapy may effectively reduce adenoma size and TSH, fT4, and fT3 concentrations in TSHoma patients (23,33). Radiotherapy can be recommended in cases where surgery is contraindicated, or the patient does not accept surgery,

in patients whose disease cannot be controlled with surgery and SSAs, and in cases with an aggressive and invasive course (6). Although there are no head-to-head comparative studies, no significant difference has been shown between the responses to radiotherapy and radiosurgical treatments. It is recommended that the treatment is not less than 10-25 Gy if given in a single dose or 45 Gy if given in divided doses (6).

OUTCOME AND FOLLOW-UP

The response rates of TSHomas to surgical and medical treatments are variable. The postoperative rest tumor rate is between 30–80%. Biochemical remission is between 70-90% (6,34). The discontinuation of antithyroid treatment, even for a while, can be considered as a biochemical response. Undetectable TSH levels one week after surgery are likely to indicate complete adenomectomy (2).

The recurrence rate varies between 0-31% in patients who achieved remission after surgery (35). Postoperative evaluation for pituitary hormone deficiencies should be done 4-6 weeks later. The patient should be evaluated clinically and biochemically 2 or 3 times in the first postoperative year and every year after that. Initial pituitary imaging should be performed 12 weeks after the operation, every 2-3 years in patients in remission, and more frequently in patients with rest tumors. Pituitary imaging should be performed promptly when an increase in TSH and thyroid hormone levels or clinical symptoms occur. In the case of a persistent macroadenoma, close visual field monitoring is necessary as visual function may be threatened (2,3,6).

Exposure of the thyroid gland to inappropriately high TSH levels in patients with TSHoma may lead to an increased risk of differentiated thyroid cancer. Therefore, periodic screening with high resolution ultrasonography is recommended for thyroid nodules and thyroid cancer risk (6).

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