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Endocrinology 111D, 11301 Wilshire Blvd.  
Los Angeles, CA 90073  
Email: jhershmn@ucla.edu

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Email: wendysacks@cshs.org

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6066 Leesburg Pike, Suite 550  
Falls Church, VA 22041  
Telephone: 703-998-8890  
Fax: 703-998-8893  
Email: thyroid@thyroid.org

**Designed By**  
**Karen Durland (kdurland@gmail.com)**

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# Clinical THYROIDOLOGY



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## Opinions Vary on How to Evaluate and Treat Possible Cases of TSH-Producing Pituitary Tumors

Stephen W. Spaulding

van Varsseveld NC, Bisschop PH, Biermasz NR, Pereira AM, Fliers E, Drent ML. A long-term follow-up study of eighteen patients with thyrotropin-secreting pituitary adenomas. Clin Endocrinol (Oxf). July 15, 2013 [Epub ahead of print]. doi:10.1111/cen.12290

### SUMMARY

#### Background

The rising incidence of TSH-producing pituitary tumors (TSHomas) probably reflects the increased reliability and sensitivity of TSH assays and improvements in pituitary imaging. Cases are being uncovered in patients originally diagnosed as having Graves' disease or toxic nodular goiter after they display recalcitrance to medical treatment. If a case has only subtle symptoms of hyperthyroidism, it may be diagnosed only after signs or symptoms of pituitary tumor develop. Doctors treating patients with hyperprolactinemia or acromegaly—which are present in about 25% of cases of TSHoma—may overlook thyroid problems. The key diagnostic laboratory feature of a TSHoma is a persistently inappropriate level of TSH in the face of elevated thyroid hormone levels, but this combination is also found in patients with reduced sensitivity to the actions of thyroid hormone, with minor mutations in the TSH receptor that reduce its sensitivity to TSH, or with defects in associated pathways. Surgical treatment of TSHomas is frequently unsuccessful, particularly in macroadenomas, which tend to be fibrotic. The authors of the current paper previously reported on a patient with a macroadenoma who was apparently cured after 4 years of treatment with a somatostatin analog (SSA). In the current report, they review the outcomes of 18 patients given various treatments for TSHomas; almost all had been given SSAs, and 3 have been treated only with SSAs. The authors findings are compared with some recent guidelines published by the European Thyroid Association (ETA) (1).

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### Methods

Between 1989 and 2011, a total of 18 cases with at least biochemical hyperthyroidism along with inappropriate TSH levels were studied in one of three academic centers in the Netherlands. Any patient who had been taking octreotide was not tested until the drug had been discontinued for 4 weeks. Records were reviewed to document each patient's initial clinical signs and symptoms and their initial biochemical and CT or MRI data. Data on mutational analysis of thyroid hormone receptor (TR)  $\beta$ ; dynamic testing with  $T_3$ , octreotide, or TRH; as well as histologic and immunohistochemical findings were checked. Tests on other pituitary/target organs and the use of hormones or endocrine antagonists were also recorded. Student's t-test was used for analysis of continuous variables, while Fisher's exact test was used for categorical variables.

### Results

Twelve of the 18 patients were men. The mean age at diagnosis was 48 years, and the median period of follow-up was 7 years (range, 1 to 21). Three had undergone partial thyroidectomy, while 2 had previously undergone block-and-replace therapy. Symptoms had generally had been present for more than 6 months: 16 had at least one symptom of thyrotoxicosis, 6 had headache, and 4 had visual-field defects. The basal TSH was above the upper limit in 8 patients and was inappropriately normal in the remaining 10. Five patients had microadenomas, whereas 13 had macroadenomas (9 had suprasellar extension [5 involving the optic chiasm], 10 had parasellar extension, and 10 had infrasellar extension). Pretreatment free  $T_4$  was high in all 14 cases tested, total  $T_4$  was high in 6 of 8 tested, total  $T_3$  in 10 of 12, and free  $T_3$  in 2 of 2. The rise in TSH after the administration of TRH was blunted in 10 of 13. In the one case tested, L- $T_3$  (200  $\mu$ g) suppressed the TSH by slightly more than 50%. Short-term administration of octreotide (subcutaneously or intravenously) suppressed the TSH by more than 50% in 5 of 5 cases. The level of glycoprotein hormone  $\alpha$ -subunit was above normal in 7 of 11 (after correcting for sex and

for age of females). The level of sex-hormone-binding globulin (SHBG) was high in 5 of 12. Two patients with macroadenomas oversecreted prolactin (PRL), and another 2 patients with macroadenomas oversecreted growth hormone (GH), while an additional patient with a macroadenoma oversecreted both PRL and GH (2 of the 3 patients with GH oversecretion had frank symptoms of acromegaly).

The therapy chosen was based on the characteristics of each individual case and on the treatments available at the time of diagnosis. Three patients were treated only with SSA, based on their initial responses to SSA and on patient preference. Of these 3, 1 patient (previously reported) was apparently cured, 1 had partial shrinkage of a macroadenoma and remains euthyroid on SSA, and 1 needed RAI for a concurrent toxic nodular goiter, but now is euthyroid on SSA. One of these patients also required a cholecystectomy after being on SSA for 3 years.

Surgery was performed on 14 patients; 2 remain apparently cured, and 6 were initially in remission off medical treatment, but half of them had recurrences (as much as 2½ years later), although the residua of their tumors did not change in size. Seven of the patients were given SSA before surgery, 6 of them became euthyroid before surgery, including 2 who had tumor shrinkage and 1 who had tumor progression. The other 7 patients underwent tumor resection without SSA pretreatment; 1 was apparently cured, 1 is in remission off medical treatment, while the remaining 5 are continuing to take SSAs. Two patients are taking methimazole; 1 had mild hyperthyroidism with an empty sella, and psychological symptoms developed in 1 after only a single injection of SSA. Radiation was used in 2 patients with incompletely resected macroadenomas, but after more than 13 years of follow-up, their TSH levels remain elevated. One is euthyroid while taking cabergoline for high GH, and the other remains euthyroid while taking SSA. One patient refused any treatment; his TSH and thyroid hormone levels remain elevated, and he is being followed closely.

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## Conclusions

Patients with large TSH-secreting macroadenomas presenting with extrasellar extension can have an excellent response to treatment with SSAs. In view of the frequently disappointing results with surgery

and radiotherapy, the authors suggest that primary therapy with SSA might be considered for virtually all patients, except those with evidence of compression of the optic chiasm.

## ANALYSIS AND COMMENTARY ● ● ● ● ●

Upon finding that a patient's TSH level is inappropriate in the face of high thyroid hormone levels, one must rule out assay artifacts such those as can occur when nondialysis assays of free  $T_4$  and free  $T_3$  are used or antimouse antibodies or certain binding-protein abnormalities are present. One must also recognize that many physiological and pathological conditions can transiently alter the level of TSH until counter-regulatory pathways adjust (2).

The recent ETA guidelines (1) reviewed tests used in the differential diagnosis of TSHomas, and strongly recommended using both a suppression and a stimulation test, since neither test is very sensitive or specific. They stated that the TSH response to TRH stimulation is "blunted" in 90% of TSHomas, while the TSH response to  $T_3$  never shows "complete inhibition" in TSHomas. In the current study, blunted TSH responses to TRH were found in only 10 of the 13 (77%) cases tested. In comparison, in cases of resistance to thyroid hormone, which are some 30 times more common than TSHomas, one expects a normal or exaggerated TSH response to TRH. Alas, TRH is no longer available in the United States. One needs to use caution when contemplating a  $T_3$ -suppression test, particularly in the elderly or in those with possible cardiovascular disease. In the current study, the  $T_3$ -suppression test was used only once: 200  $\mu\text{g}$  suppressed the TSH level by more than 50%. Certainly, if one uses the formal three-step 9-day  $T_3$ -suppression test, it would seem to be important to assess more than the just the TSH response; perhaps serum markers like cholesterol, creatine kinase, SHBG, and ferritin should also be assessed. The responses in patients with TSHomas may be smaller than what is observed

in normal subjects who haven't been chronically exposed to above-normal thyroid hormone levels. In comparison, in cases of thyroid hormone resistance, responses to  $T_3$  are not generally observed.

Clinically, patients with TSHomas can have almost any of the symptoms of thyrotoxicosis. In comparison, in cases of resistance to thyroid hormone, about 50% of patients have an increased resting pulse, 40% will have a goiter, and 10% will be hyperactive. Sequencing the TR $\beta$  gene will uncover a mutation in about 85% of cases thyroid hormone resistance, although the same mutation may have different clinical manifestations in different patients, possibly reflecting genetic variability in other factors that interact with the receptor. Patients with thyroid hormone resistance have a positive family history about 75% of the time, whereas familial TSHomas are rare but have been observed, particularly in families with multiple endocrine neoplasia type 1. Another disease included in the differential diagnosis is a recessive mutation in SBP2, the gene required for synthesis of selenoproteins, including the deiodinases. These patients have a high serum  $T_4$ , low  $T_3$ , high  $rT_3$ , and normal or slightly elevated serum TSH. Finally, some patients with a mild loss-of-function mutation in the TSH receptor can have an elevated serum TSH level, but be euthyroid; these patients generally lack a goiter or signs of hyperthyroidism or hypothyroidism.

The recent ETA guidelines, in reviewing therapy for TSHomas, strongly recommend surgical adenectomy as the first-line treatment, with complete cure being expected for most microadenomas but being less likely in macroadenomas (1). Postsurgical complications, although not specifically addressed in the

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ETA guidelines, were observed in 3 of 14 patients in the current series, although no patient developed panhypopituitarism. The ETA guidelines, however, do state that SSAs reduce TSH levels in almost all cases, produce euthyroidism in 90%, goiter reduction in 30%, and reduce pituitary tumor mass in 40%, although in the current study only two tumors shrank after SSA treatment. The results of the current paper

provide some support for using SSAs as primary therapy for some patients with TSHomas, but it bears noting that tachyphylaxis and glucose intolerance can also be side effects of SSAs. In the future, chimeric drugs that selectively target cells that express specific combinations of somatostatin and dopamine receptor types may provide another avenue for treating TSHomas that become resistant to octreotide (3).

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