

## Thyrotropin-Secreting Pituitary Microadenoma

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We present a 45-yr-old male with clinical signs and symptoms of mild hyperthyroidism, high serum levels of  $T_3$ ,  $T_4$ , and  $FT_4$ , as well as serum TSH concentration. The elevated  $\alpha$ -subunit level and  $\alpha$ -subunit/TSH molar ratio were also observed. These findings indicated the presence of hyperthyroidism due to inappropriate secretion of TSH, whose neoplastic origin was documented by nuclear magnetic resonance scan showing a 0.6 cm pituitary adenoma. Selective pituitary adenomectomy was completely successful;  $\alpha$ -subunit, TSH,  $T_3$ ,  $T_4$ , and  $FT_4$  normalized, and euthyroidism was restored. Light microscopic immunohistochemistry showed that the adenoma was composed of TSH-secreting cells.

**Key Words:** TSH-secreting pituitary microadenoma,  $\alpha$ -subunit

TSH-secreting pituitary adenomas first described in 1970 (Hamilton *et al.*) are uncommon tumors with about 100 cases reported in the medical literature (Gesundheit 1991). Patients with TSH-secreting pituitary adenomas are often misdiagnosed initially, resulting in inappropriate therapy. Hence, most of these tumors usually become large and are invasive at the time of the diagnosis (Lee *et al.* 1990; Becker *et al.* 1991). Microadenoma producing TSH is very rare and only 5 cases were reported (Kellelt *et al.* 1983; Mashiter *et al.* 1983; Gesundheit 1991). Un-suppressed TSH levels in spite of elevated serum thyroid hormone concentrations are characteristic features. Accordingly simultaneous assay of TSH and thyroid hormone in patients with hyperthyroidism is necessary to diagnose TSH-secreting

pituitary adenomas (Tolis *et al.* 1978).

In the present study we report a TSH-secreting pituitary microadenoma in a patient with long standing hyperthyroidism. We examined the effects of hypothalamic releasing hormones and thyroid hormone on hormone release from adenoma *in vivo*. Light microscopic immunohistochemistry of removed adenoma showed that the adenoma was composed of thyrotropes.

### SUBJECT AND METHODS

#### Case

In September 1991, a 45-yr-old man was admitted to Yongdong Severance Hospital for evaluation and management of hyperthyroidism. He had been in good health until 1981, when he noted increasing malaise and periodic paralysis. In 1985, weakness of the lower extremity was noted and prophylthiouracil was administered for 6 months. In September 1989, the symptoms of hyperthyroidism were developed,  $T_4$  was 270.3 nmol/L (normal values, 64.4~148.0);  $T_3$  6.9 nmol/L (normal, 1.23-2.46); TSH 7.6 mU/L (normal, 0.25-3.1), and prophylthiouracil was readministered until admission.

Physical examination revealed a somewhat hyperactive man with a blood pressure of 140/70

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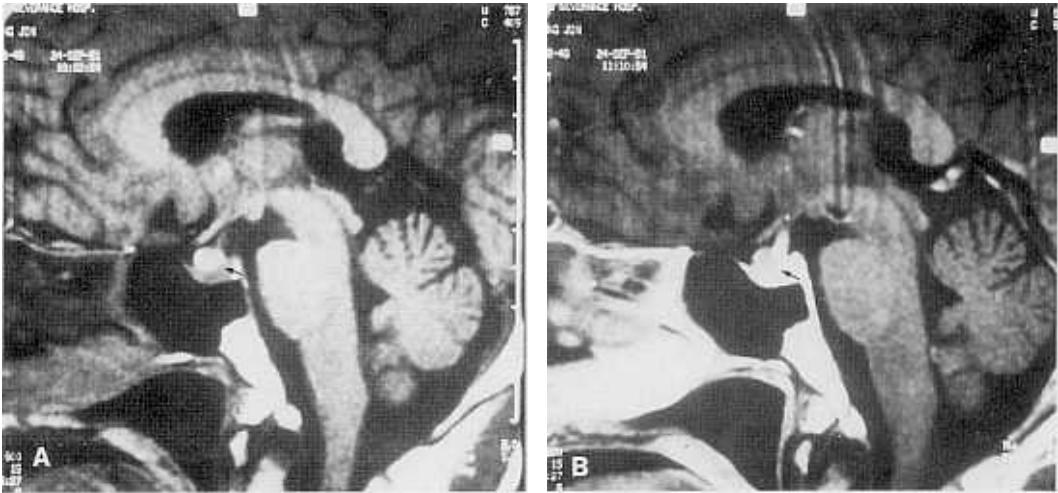
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**Fig. 1.** (A) Sagittal section of T1-weighted image by MRI. A well-circumscribed mass of slightly high signal intensity is noted at the left superior aspect of pituitary gland. The lesion is about 0.6 cm in diameter. The superior projection of tumor into the suprasellar cistern is showed. (B) Sagittal section of post-gadolinium enhanced, T2-weighted image by MRI. The tumor mass showed an area of relative hypointensity comparing to normal pituitary gland due to the enhancement of normal glandular tissue. Relationship of the mass to pituitary stalk and optic chiasm are well demonstrated.

mmHg. The pulse was regular, with a rate of 88 per minute; the skin was moist, and a fine tremor was noted. The thyroid gland was not enlarged on palpation, and there was no exophthalmos and pretibial pitting edema.

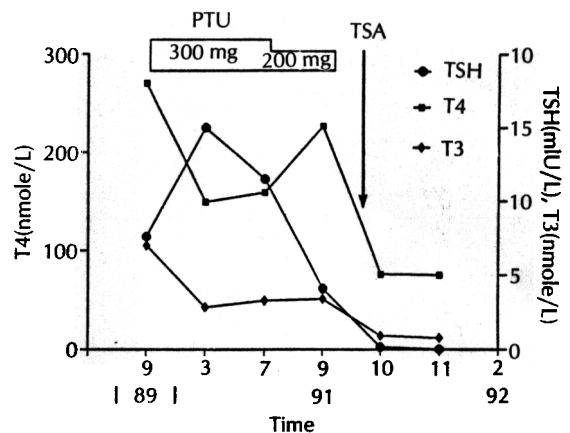
The visual field perimetry revealed no visual field defect. Thyroid function test on admission revealed:  $T_4$  was 226.5 nmol/L;  $T_3$  3.6 nmol/L; TSH 4.1 mU/L,  $FT_4$  32 pmol/L (normal, 10.3-25.8),  $\alpha$ -subunit 0.96 mIU/ml (normal, 0-0.8).

Radiological study with a nuclear magnetic resonance scanning of the sellar turcica, revealed a pituitary microadenoma measuring about 0.6 cm in diameter on the left superior aspect of the pituitary gland (Fig. 1).

In October 1991, The patient underwent selective transsphenoidal adenomectomy. After surgery, serum basal TSH,  $T_3$ ,  $T_4$ , and  $FT_4$  were in the normal range, indicating a complete removal of the tumor (Fig. 2).

### Clinical studies

The following endocrine tests were performed before surgery: 1) TRH (400  $\mu$ g, iv); 2) Combined pituitary stimulation with simultaneous injection of LHRH (100  $\mu$ g, iv), TRH (400  $\mu$ g, iv), regular insulin



**Fig. 2.** Clinical courses of the patient.

(0.15 U/kg, iv); 3) somatostatin (octreotide 50  $\mu$ g, iv); 4) bromocriptine (5 mg, po); 5)  $T_3$  suppression test (cytomel 75  $\mu$ g, p.o. daily for 7 days).

### Hormonal assay

Serum LH, FSH, PRL, GH, ACTH,  $FT_3$ , cortisol were measured by specific RIA. Serum  $T_3$ ,  $T_4$ ,  $FT_4$ ,

and TSH were measured by ELISA (Boehringer Mannheim GmbH, Mannheim, Germany). Serum  $\alpha$ -subunit was measured by immunoradiometric assay (Biocode, Sclessin, Belgium). The detection limit of the assay was 0.02 mIU/ml. The cross-reactivity of free  $\alpha$ -subunit in the LH and FSH assays are less than 0.1%. The  $\alpha$ -subunit/TSH molar ratio was calculated on the basis of the following mol wt values: TSH, 28,000; and  $\alpha$ -subunit, 14,700 (1  $\mu$ g TSH corresponds to 5 mU).

### Morphological techniques

A portion of surgically removed pituitary adenoma was fixed immediately after removal. Light microscopic immunohistochemistry was performed using 0.5  $\mu$ m semithin sections and according to the peroxidase-antiperoxidase method. The antisera used were rabbit antihuman sera for TSH $\beta$ , GH, PRL, FSH, LH, and ACTH, which were supplied by the DAKO (Kyoto, Japan).

## RESULTS

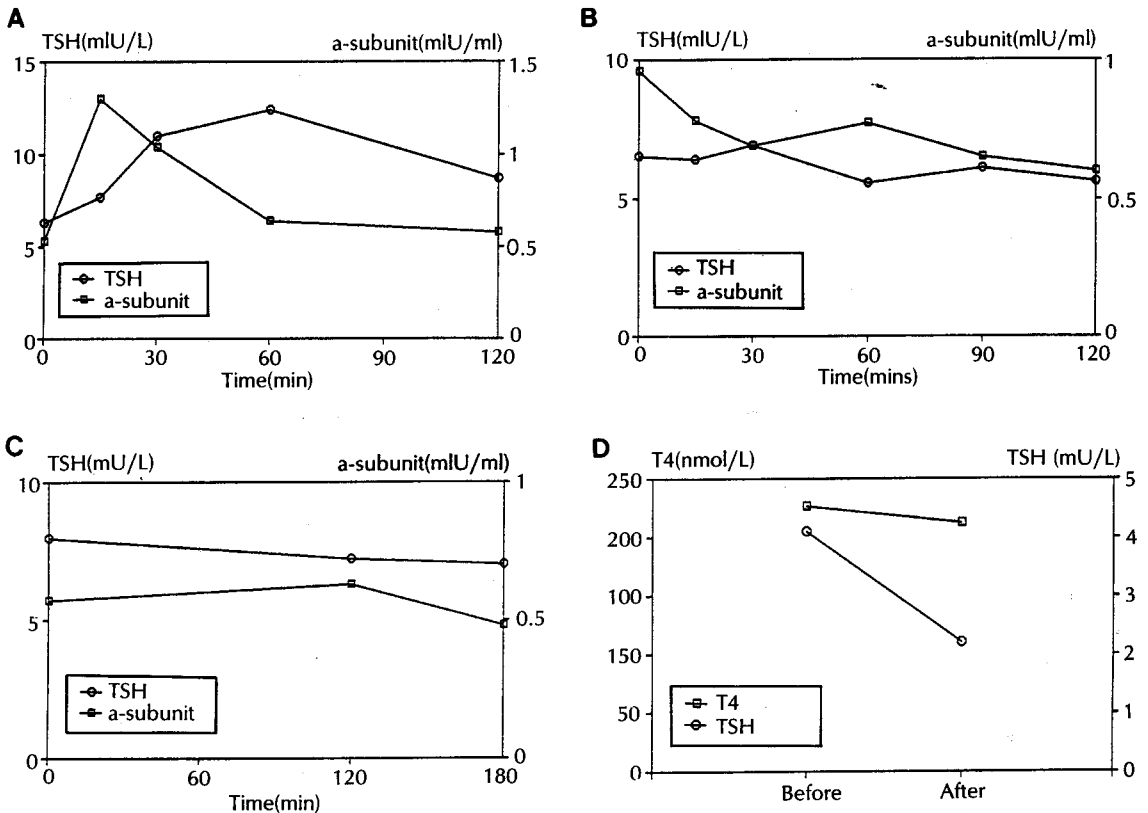
### Clinical studies

TRH injection induced moderate increase in serum TSH (from 6.3 to 12.4 mU/L) and  $\alpha$ -subunit (from 0.53 to 1.3 mIU/ml; Fig. 3A). Pituitary hormonal response to combined stimulation gave normal results (PRL, from 7.0 to 18.5  $\mu$ g/L; LH, from 5.0 to 28.2 U/L; FSH, from 7.7 to 13.9 U/L; GH, from 0.6 to 6.2  $\mu$ g/L) except in ACTH (41.5 to 6.6 pg/ml) and cortisol (6.3 to 10.2  $\mu$ g/dl; Table 1).

Somatostatin injection failed to suppress TSH (from 6.5 to 5.6 mU/L) and  $\alpha$ -subunit (from 0.96 to 0.60 mIU/ml; Fig. 3B).

Bromocriptine ingestion did not suppress TSH (from 7.9 to 7.0 mU/L) and  $\alpha$ -subunit (from 0.57 to 0.48 mIU/ml; Fig. 3C).

T<sub>3</sub> administration failed to suppress <sup>131</sup>I thyroid uptake at 24 h (from 64 to 64%), but suppressed TSH

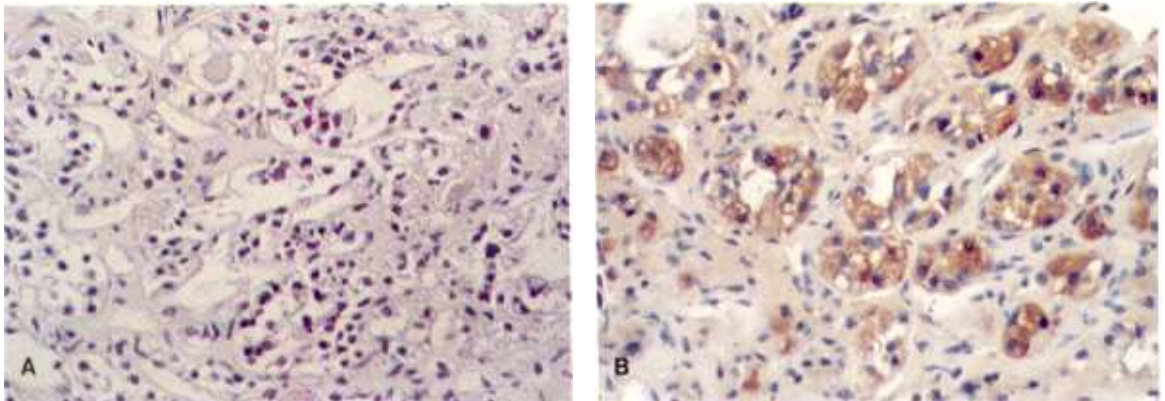


**Fig. 3.** TSH and  $\alpha$ -subunit release after TRH (A), somatostatin injection (B), bromocriptine ingestion (C), and T<sub>4</sub> and TSH change after a 7-day treatment with T<sub>3</sub> (D).

**Table 1.** The results of combined stimulation test with TRH (400 µg), Regular insulin (8.0 U), and LH-RH (100 µg)

Hormone	Before	30 min	60 min	120 min	180 min
TSH (mU/L)	6.3	7.7	11.0	12.4	
α-subunit (mIU/ml)	0.53	1.30	1.04	0.64	
Prolactin (ng/ml)	7.0	15.7	18.5	6.8	
LH (mIU/ml)	5.0	28.2	26.6	18.5	14.5
FSH (mIU/ml)	7.7	12.8	13.4	11.1	13.9
GH (ng/ml)	0.6	0.6	6.2	0.7	0.4
Cortisol (µg/dl)	6.3	9.9	10.2	4.8	2.7
ACTH (pg/ml)	41.5	20.3	26.9	6.6	22.9
Sugar (mg/dl)	70	30	68	75	79

Normal ranges for hormonal values are as follows: TSH, 0.25-3.1 mU/L; α-subunit, 0-0.8 mIU/ml; Prolactin, 4.6-23.0 ng/ml; LH, 5-20 mIU/ml; FSH, 5-20 mIU/ml; GH, <5 ng/ml; Cortisol, 5-25 µg/dl; ACTH <80 pg/ml



**Fig. 4.** (A) Regular thin fibrous septa surrounding and separating tumor cell nests, some of which showing tubular structure with eosinophilic secretion in the lumen (H-E, ×200). (B) Diffuse positivity for TSH in the cytoplasm of tumor cells (peroxidase antiperoxidase technique, ×200).

moderately (from 4.1 to 2.2 mU/L; Fig. 3D).

### Morphological studies

The light microscopic immunohistochemical staining of the adenoma tissue showed that most of the adenoma cells contained TSH β in their cytoplasm (Fig. 4).

### DISCUSSION

TSH secreting pituitary adenomas are rarely encountered and represent about 1% of all pituitary adenomas. Most of them reported in the literature were macroadenomas. The microadenomas pro-

ducing TSH are very rare and only 5 cases have been reported (Kellett et al. 1983; Mashiter et al. 1983; Gesundheit 1991).

For the diagnosis of TSH secreting pituitary adenoma, four criteria should be fulfilled (Tolis et al. 1978). (1) Measurement of a supranormal serum concentration of TSH despite increased concentrations of thyroid hormones. (2) Presence of pituitary tumor. (3) Identification of thyrotropes in the tumor. (4) Disappearance of hyperthyroidism with removal of the pituitary tumor. The finding in our patient of elevated levels of T<sub>3</sub>, T<sub>4</sub>, and FT<sub>4</sub> and unsuppressed TSH indicated that the negative feedback mechanism was not operative and suggested autonomous TSH overproduction. Nuclear magnetic resonance scan demonstrated a pituitary microadenoma and

after the transsphenoidal surgery, serum basal TSH,  $T_3$ ,  $T_4$ , and  $FT_4$  were in the normal range. Immunostaining of the removed tumor tissue revealed thyrotrope adenoma.

Several distinctive biochemical features are present in patients with TSH-secreting pituitary adenomas. TSH response to TRH was blunted or absent in 77% of these adenomas (Faglia et al. 1987, Samliridge et al. 1987), but opposite findings were also reported (Fesundheit et al. 1989). In our case, serum TSH increased normally in response to TRH. This responsiveness may be explained by two possible mechanisms. One is that the increased portion of serum TSH was originated not from the adenoma but from the normal functioning thyrotrope. The other is that TSH secretion is not completely independent from the regulatory mechanism in some thyrotrope adenomas. The unresponsiveness to exogenous administration of  $T_3$  was reported in 84% of TSH secreting adenomas (Kourides et al. 1977; Gesundheit et al. 1989). In our patient, exogenous administration of  $T_3$  failed to suppress  $^{131}I$  thyroid uptake and serum  $T_4$  but lowered serum TSH moderately. It is, however, unclear whether the decreased portion of serum TSH was secreted from the normal thyrotrope or whether the unresponsiveness of  $^{131}I$  thyroid uptake and  $T_4$  despite lowered TSH levels was due to a high bioactivity of secreted TSH from the adenomatous thyrope.

In addition, measurement of the free  $\alpha$ -subunit has proved to be a useful biochemical marker for the presence of a TSH secreting adenoma. TSH is a heterodimeric glycoprotein composed of an  $\alpha$ -subunit and a hormone-specific  $\beta$ -subunit; under normal physiologic conditions, the production of these subunits is coordinately regulated. As was shown by Kourides et al. (1977), TSH secreting pituitary adenomas are characterized by excessive production and secretion of  $\alpha$ -subunit. The molar ratio in serum of  $\alpha$ -subunit to TSH is a good discriminating factor for the diagnosis and the evaluation of treatment of TSH-secreting adenoma. In our patient, serum  $\alpha$ -subunit was elevated and the  $\alpha$ -subunit/TSH molar ratio was higher than 1.

The  $\alpha$ -subunit responsiveness to TRH is almost invariably absent or sluggish in TSH secreting adenoma (Weintraub et al. 1981). However, in our patients, the serum  $\alpha$ -subunit showed two fold increase after TRH injection.

In geneneral, serum TSH and  $\alpha$ -subunit do not change during manipulation of the dopaminergic tone in TSH secreting adenoma (Kellett et al. 1983),

although inhibition of either TSH or  $\alpha$ -subunit release by dopamine agonists has been described in some patients (Connel et al. 1982; Beck-Peccoz et al. 1986). The unresponsiveness of TSH to bromicriptine in this patient indicates that he had autonomous TSH release.

Octreotide acetate, the long acting analog of somatostatin (SMS 201-995), has proven to be promising in controlling basal and stimulated thyrotropin secretion from normal and tumorous thyrotropes (Gesundheit 1991; Allyn et al. 1992). Somatostatin infusion caused a slight decrease in basal serum TSH and  $\alpha$ -subunit concentration in this patient.

For the diagnosis of TSH secreting adenoma at the early stage, in addition to elevation of the  $\alpha$ -subunit tumor marker, high resolution nuclear magnetic resonance scanning with gadolinium may disclose the pituitary abnormality, or inferior petrosal venous sampling may disclose a gradient and lateralization consistent with tumor (Frank et al. 1989; Newton et al. 1989).

The pathogenesis of TSH secreting adenoma has not been elucidated. A hypothalamic basis with excessive TRH production has been suggested (Emerson and Utiger 1972; Kamoi et al. 1985), although the data supporting this view are not compelling. It is unlikely that hypothalamic peptides are directly involved in pituitary DNA mutagenesis and cell transformation. However, persistent hypothalamic stimulation may confer growth advantage to a clone of neoplastic pituitary cells, thus promoting tumor progression. An alternative explanation is that pituitary-specific growth and differentiation factors and protooncogenes may be activated by unknown environmental factors in patients with susceptible genetic background (Gesundheit 1991). Both explanations provide intriguing hypothesis for the pathogenesis of these and other pituitary tumors and are the subject of current investigation.

Surgery is the treatment of choice for TSH secreting pituitary adenomas. Early diagnosis and prompt surgery, preferably by transsphenoidal route, provide the best opportunity for cure. Several patients have been reported who were diagnosed and treated at the stage of a microadenoma (diameter < 1 cm), and these patients have had favorable outcomes (Kellett et al. 1983; Mashiter et al. 1983; Gesundheit 1991). In patients with macroadenomas, surgical therapy is recommended to debulk tumor and permit management by radiotherapy and pharmacotherapy. Although radiation therapy has been used to control further tumor growth, the effi-

cacy of this treatment has not been specifically documented with TSH secreting adenomas (Gesundheit 1991). Octreotide is an effective therapeutic modality for reducing TSH hypersecretion secondary to a pituitary adenoma. Additionally, it has been shown in four patients to shrink tumors (Gesundheit 1991; Allyn et al. 1992). In our patient, selective pituitary adenomectomy was completely successful;  $\alpha$ -subunit, TSH,  $T_3$ ,  $T_4$ , and FT $_4$  normalized, and euthyroidism was restored.

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