A Case of Thyrotropin (TSH)-Secreting Tumor Complicated by Periodic Paralysis


A 27-year-old man had symptoms of hyperthyroidism and periodic paralysis. While hyperthyroid, his serum thyrotropin (TSH) level was inappropriately elevated at 6.4 μU/ml. The serum alpha subunit level was also elevated. MR imaging revealed a pituitary tumor and transsphenoidal adenomectomy was performed. Immunocytochemistry with an antibody directed against the beta-subunit of TSH revealed a TSH-secreting tumor.

This is the first case of hyperthyroidism due to a TSH-secreting pituitary tumor complicated by periodic paralysis. This association indicates that thyrotoxicosis may induce paralysis in susceptible persons by a mechanism which is not autoimmune.

Key words: Thyrotoxic periodic paralysis, HLA typing

Thyrotoxic periodic paralysis (TPP) is an uncommon disease characterized by episodes of flaccid paralysis, usually accompanied by hypokalemia. The disorder occurs most frequently in Oriental men (1, 2) in their second and third decades (3, 4). Most reported cases are associated with Graves’ disease (5). Only a few cases have been described in patients with hyperthyroidism due to other diseases (6–8). It is thought that pituitary tumors rarely secrete TSH, but this phenomenon has been increasingly recognized as a cause of hyperthyroidism (9). We report here the first case of hyperthyroidism due to a TSH-secreting pituitary tumor associated with periodic paralysis.

MATERIALS AND METHODS

Hormone assays

Serum thyroxine ($T_4$), 3, 5, 3'-triiodothyronine ($T_3$), free $T_4$ and thyroxine binding globulin (TBG) concentrations were measured by radioimmunoassay (RIA). Serum TSH was measured with a highly sensitive immunoradiometric assay. The antithyro-globulin and antimicrosomal antibodies (TGHA and MCHA) were measured by a haemagglutination method using artificial gelatin particle carriers. Anti-TSH receptor antibody (TRAb) was measured by radioreceptor assay (10). Serum concentration of the alpha-subunit of TSH ($TSH-\alpha$) was measured by RIA (11) using reagents kindly provided by the National Institutes of Diabetes, Digestive and Kidney Diseases (NIDDKD). The achilles reflex time was determined by kinemometry. The assay results as well as the normal ranges are shown in Table 1. Serum growth hormone (GH), luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL) and adrenocorticotropic hormone (ACTH) were measured by RIA.
Endocrine stimulation and suppression tests

The thyrotropin releasing hormone (TRH) stimulation test was performed by intravenous injection of 500 μg TRH, and collection of serial blood samples for measurement of TSH and PRL. Other pituitary function tests were performed by subcutaneous injection of 50 μg sulpiride, intravenous injection of 0.5 μg/kg arginine, oral administration of 500 μg L-dopa or intravenous injection of 0.1 mg luteinizing hormone releasing hormone (LH-RH).

For the T3 suppression test, l-T3 (75 μg daily for four days and 150 μg for the succeeding four days) was given orally and serum TSH, 24-h uptake of 131I by the thyroid (RAIU), basal metabolic rate (BMR), and mean pulse rate – indices of the peripheral tissue effects of thyroid hormone – were measured.

After transsphenoidal adenomectomy, a bromocriptine test was done using a single oral dose of 2.5 mg bromocriptine, and TSH was measured.

HLA typing

Typing for the HLA-A,B,C and DR antigens was performed at the Special Reference Laboratories using the Terasaki-NIH standard method.

Immunohistochemical staining

The tumor tissues were fixed promptly after the operation in 10% formalin and embedded in paraffin. Deparaffinized sections were incubated with antisera overnight at 4°C. Antisera against ACTH, GH, PRL, FSH, LH and beta-subunit of TSH (a gift from Dainabot Radioisotope Lab.) were used. After washing, the sections were stained by the standard avidin-biotin peroxidase complex method.

CLINICAL HISTORY

A 27-year-old Japanese man experienced episodes of lower extremity weakness since 1981. He experienced these episodes two to three times a year, yet functioned normally between episodes. In 1982 he lost 15 kg over six months. He experienced excessive diaphoresis and fatigue in 1986. In August, 1987, he noted numbness in the extremities at midnight, progressing to complete paralysis by morning. He was admitted to a hospital, where doctors found he had intact sensation, normal cranial nerve function with flaccid paralysis of all four extremities and diffuse hyporeflexia. The electrocardiogram revealed inverted T waves with ST segment depression. The serum potassium level was 1.3 mEq/l, thus a diagnosis of hypokalemic periodic paralysis was made. With potassium replacement, the symptoms resolved within 12 hours. Thyroid function tests revealed that the serum TSH level was inappropriately elevated at 4.5 μU/ml in the presence of an elevated T4 (21.6 μg/dl) and T3 (270 ng/dl). After being diagnosed with a syndrome of inappropriate TSH secretion associated with periodic paralysis, he was referred to our hospital for further evaluation.

His maternal aunt had thyroid disease, but there was no family history of periodic paralysis. On physical examination his height was 188 cm and weight, 85 kg. The pulse rate was 79/min, regular, and the blood pressure was 138/70 mmHg. A soft, diffuse but slightly enlarged thyroid gland was palpable. Exophthalmos and lid lag were absent. Fundus and visual fields were normal. He had moist skin and hyperreflexia, but no finger tremor. The liver was palpable at 1.5 finger-breathths below the costal margin, and was of normal consistency. The rest of the physical examination was normal. Chest x-ray and electrocardiogram showed nothing abnormal. Hematological findings, urinalysis and serum electrolytes were also normal. Liver function test revealed mild hepatic impairment. Total cholesterol and fasting blood sugar levels were normal, but serum creatine kinase was low.

PREOPERATIVE COURSE

The results of the thyroid function studies at the time of admission are shown in Table 1. Serum total T4, T3 and free T4 concentrations were all elevated with an inappropriately elevated TSH level of 6.4 μU/ml. T uptake and serum TBG concentration were normal. The serum TSH-α level was elevated and TSH-+/TSH molar ratio (6.3) was higher than 1.0. The basal metabolic rate (+10%) was in the high normal range and the achilles reflex time of 200 msec was in the hyperthyroid range. TGHA, MCHA and TRAb were negative. The thyroid 123I scan showed a slightly enlarged gland with diffuse increased uptake and an elevated RAIU of 53.3%.

The results of the TRH stimulation test are shown in Fig. 1. Administration of 500 μg TRH caused no rise in TSH. Serum PRL levels showed a small response. The results of the endocrine studies of
other hormones were as follows. The basal level of GH and its responses to both arginine and L-dopa stimulation were normal. The basal level of serum PRL was normal and its response to sulpiride administration was slightly low (29.4 ng/ml, peak value). Both basal and LH-RH stimulated gonadotropin (LH and FSH) levels were normal. The basal level of ACTH was normal.

The effect of exogenous L-T3 is shown in Table 2. After 150 μg/day of L-T3 administration, serum T3 increased from 256 to 492 ng/dl. Serum TSH and RAIU decreased from 6.4 to 3.1 μU/ml and from 53 to 26%, respectively, but complete suppression of neither TSH nor RAIU was achieved. The BMR value increased slightly from +10% to +12%. The mean pulse rate increased from 70 to 89 bpm.

HLA typing showed the following antigens: A2, A11, Bw46, Bw48, DRw8 and DRw9. A C locus was not found. Roentgenograms of the skull demonstrated enlargement of the sella turcica with a double floor. Magnetic resonance imaging (MRI) of the brain revealed a pituitary tumor of 15 x 20 mm in the sellar region with no destruction of the floor (Fig. 2). The presumptive diagnosis of a TSH-secreting pituitary tumor was made and the patient underwent surgery.

PATHOLOGICAL FINDINGS AND POSTOPERATIVE COURSE

In December 1988, transsphenoidal resection of the tumor was performed. Immunocytochemistry with an anti-beta-subunit of TSH antibody indicated that TSH immunoreactivity was present in the cytoplasm of adenoma cells (Fig. 3). Incubation with anti-ACTH, anti-GH, anti-PRL, anti-FSH and anti-
LH antibodies gave negative results.

After the operation, therapy with dexamethasone, 0.5 mg daily, and propranolol, 30 mg daily, was started. Four weeks after the operation the serum T<sub>4</sub> was 21.6 μg/dl and T<sub>3</sub> was 252 ng/dl. TSH remained inappropriately elevated at 2.76 μU/ml. A repeat MRI of the brain two months after the operation showed the suspected adenoma remnant with the pituitary stalk shifted leftward. After a single oral dose of 2.5 mg bromocriptine, TSH levels were effectively decreased (Fig. 4). Therefore, the patient was given bromocriptine 7.5 mg daily. Two weeks later, thyroid function tests revealed T<sub>4</sub> of 17.2 μg/dl and T<sub>3</sub> of 190 ng/dl. TSH was decreased to 1.72 μU/ml. After 6 months of follow-up he remains clinically euthyroid without any recurrence of paralysis, and gained 10-kg. Biochemically he remains mildly hyperthyroid (T<sub>4</sub> 13.1 μg/dl, T<sub>3</sub> 217 ng/dl, TSH 2.32 μU/ml).

**DISCUSSION**

TSH-induced hyperthyroidism is a relatively uncommon type of hyperthyroidism. Some of these patients have selective pituitary resistance to thyroid hormones, whereas others have pituitary TSH-secreting tumors (12). In general, the secretion of TSH by pituitary tumors appears to be autonomous. TSH does not respond to intravenous TRH in most reported cases (12). However, in some cases TSH secretion varied inversely with serum thyroid hormone levels as shown by decreases in serum TSH level and RAIU after T<sub>3</sub> administration (13), or the increase in serum TSH after treatment with anti-thyroid drugs (14). In patients with pituitary tumors, the serum α subunit level was elevated and the molar ratio of α/TSH was more than 1.0 (12). Serum TSH levels ranged from 1.7 to 480 μU/ml (12) and about one fourth had normal levels (15). In contrast, in most patients with selective pituitary resistance to thyroid hormones, TRH administration resulted in rapid TSH secretion. In these patients, the serum α subunit level was not elevated and the molar ratio of α/TSH was less than 1.0 (12).

In the present case, the serum TSH level did not change with TRH, but was partially suppressed after T<sub>3</sub> administration. The serum α subunit level was elevated and the molar ratio of α/TSH was 6.3. These biochemical data strongly suggest that this patient has a TSH-secreting tumor. Furthermore, MR imaging revealed a pituitary tumor, and the final diagnosis of a TSH-secreting tumor was confirmed by immunohistochemistry.

Hyperthyroidism due to a pituitary TSH-secreting tumor has characteristic clinical features (9). The hyperthyroidism seen is usually mild. The thyroid gland, though variable, is often minimally enlarged. Graves’ ophthalmopathy is absent in most cases. There is usually poor correlation between the degree of TSH elevation and the increase in thyroid hormone levels. The present case had all these
characteristics.

The incidence of TPP among thyrotoxic patients is reported to be 1.8% (1), 1.9% (3) and 8.8% (2). Rarely, is the family history positive. In a few studies, patients with TPP have been typed for HLA. Yeo et al reported (16) that Singapore Chinese thyrotoxic patients with TPP had a higher frequency of HLA-Bw22 compared to patients without TPP and to controls. Tamai et al (17) reported that Japanese patients with TPP were more likely to have DRw8 compared to thyrotoxic patients without periodic paralysis.

This patient's HLA antigens were A2, A11, Bw46, Bw48, DRw8 and DRw9 (C locus HLA was not detected). The haplotypes of DRw8 corresponded to the antigens described above. HLA associations taken with the epidemiologic characteristics (a 27-year-old Japanese male) suggest that this patient may be genetically susceptible to TPP. As far as we know, a relationship between pituitary tumors and periodic paralysis has not been reported. The periodic paralysis in the present patient may have resulted from hyperthyroidism due to a TSH-secreting tumor.

The mechanism and pathophysiology of TPP have been described (18), but precise causes have been elusive. Episodes of periodic paralysis subside after restoration of euthyroidism and are reproducible by thyroid hormone administration (19). These facts indicate that thyrotoxicosis may elicit episodes of paralysis in susceptible persons. Most cases of TPP have been reported in association with Graves' disease. Only a few cases are associated with the transient thyrotoxicosis due to chronic thyroiditis (6–8). These associations implicate undefined immunogenetic factors in the pathophysiology of this disease (17). In this case, however, an association with autoimmune thyroid disease was not detected and thyrotoxicosis was caused by a TSH-secreting tumor. Our case suggests that elevated thyroid hormones may play an important role in the pathogenesis of TPP independent of an autoimmune mechanism.

A TSH-secreting pituitary adenoma is reported to be aggressive and invasive. Although selective pituitary adenomectomy and irradiation are recommended, recurrence is not rare. Dopamine agonists, such as bromocriptine, reduce TSH secretion from thyrotrophs (20, 21). It is reported that after bromocriptine administration, TSH secretion does not decrease in most patients with a TSH-secreting pituitary tumor. However, a decrease in TSH secretion and reduction of tumor size during bromocriptine treatment has been reported in some cases (22). In our patient, the TSH level did not decrease sufficiently after transsphenoidal adenomectomy. After a single oral dose of 2.5 mg bromocriptine, TSH levels decreased, therefore, therapy with 7.5 mg bromocriptine treatment was started. After the treatment, TSH and thyroid hormone levels were effectively lowered, but biochemically he remained mildly hyperthyroid.

In this paper, we describe the first case, to our knowledge, demonstrating the association between hyperthyroidism due to a TSH-secreting tumor and periodic paralysis. Our case illustrates that TPP can occur in susceptible persons even when hyperthyroidism is due to a TSH-secreting tumor.

REFERENCES


