A case of TSH-secreting pituitary adenoma with cyclic fluctuations in serum TSH levels

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Abstract. A 29-year-old man was referred to our department due to adrenal insufficiency with the inappropriate secretion of TSH (SITSH). Magnetic resonance imaging revealed a pituitary tumor. A weak TSH response in the TRH test, elevated sex hormone binding globulin (SHBG) levels, and the absence of a family medical history of SITSH or TRβ gene mutations supported the diagnosis of TSH-secreting pituitary adenoma (TSHoma). However, complete TSH suppression and a blunted cholesterol response in the T3 suppression test as well as normal glycoprotein α-subunit (α-GSU) levels were not compatible with TSHoma. Since TSH, FT3, and FT4 spontaneously returned to normal ranges after admission, he was discharged. One month after his discharge, thyrotoxicosis with elevated serum TSH levels relapsed. After admission, his serum TSH levels returned to within the normal range. After his discharge from the second admission, his serum TSH levels fluctuated in accordance with serum FT3 and FT4 levels and symptoms, such as palpitations. Ten months after his discharge, he was admitted to our department again due to adrenal insufficiency and thyrotoxicosis with elevated serum TSH levels, suggesting cyclic SITSH. Although resistance to thyroid hormone (RTH) was not completely excluded, the pituitary tumor was removed by transsphenoidal surgery (TSS). A pathological diagnosis confirmed TSHoma. We herein report a case of TSHoma in which serum TSH, FT3, and FT4 levels fluctuated periodically. To the best of our knowledge, this is the first case report of “cyclic TSHoma”, which needs to be considered when making a differential diagnosis of SITSH.

Key words: TSH-secreting pituitary adenoma, Cyclic fluctuation of serum TSH levels

IN THE CASE of syndrome of inappropriate secretion of TSH (SITSH), it is important and sometimes difficult to differentiate TSH-secreting pituitary adenoma (TSHoma) and resistance to thyroid hormone (RTH). SITSH with persistently high TSH levels is a hallmark of TSHoma, whereas TSH levels may fluctuate in mild RTHβ [1]. Plasma ACTH levels occasionally fluctuate in cyclic Cushing’s disease; however, there have been no reports of TSHoma with cyclic fluctuations in serum TSH levels. We herein report the first case of TSHoma with cyclic fluctuations in serum TSH levels, which was difficult to differentiate from RTH.

Case report

A 29-year-old man was diagnosed with influenza type A and exhibited unusual behavior and diarrhea upon the administration of oseltamivir phosphate. He was admitted to a local hospital and blood tests revealed hypona-
tremia (Na 125 mEq/L) and hypokalemia (K 2.8 mEq/L). Brain computed tomography (CT) revealed an enlarged pituitary. Endocrinological tests showed the inappropriate secretion of TSH with serum TSH 1.69 μU/mL, free T3 (FT3) 5.41 pg/mL, and free T4 (FT4) 1.86 ng/dL as well as panhypopituitarism with plasma ACTH 21.8 pg/mL, serum cortisol 4.2 μg/dL, GH 0.48 ng/mL, and IGF-1 9.0 ng/mL. Three weeks after his admission, SITSH developed (TSH 11.29 μU/mL, FT3 14.94 pg/mL, and FT4 4.02 ng/dL) and after the administration of 5 mg hydrocortisone, he was referred to our department for an intensive examination and treatment. He was 156 cm in height, 42.3 kg in weight, and had a body temperature of 36.4°C. His heart rate (HR) was 100 beats/minute as a regular/frequent pulse, blood pressure was 132/90 mmHg, his consciousness level on the Glasgow Coma Scale was E4V5M6, and he exhibited diffuse thyroid gland enlargement without hircus or pubic hair. He had an infant-like penis and testicles without the recognition of ejaculation. The Goldmann visual field test revealed bitemporal hemianopsia.

Since his plasma ACTH and serum cortisol levels returned to within normal ranges (ACTH 48.6 pg/mL and cortisol 8.1 μg/dL) (Table 1) following his admission to our department, the administration of 5 mg hydrocortisone was discontinued. The CRH test revealed hyperreactivity in ACTH increases (Fig. 1A), the insulin tolerance test showed an attenuated response in ACTH and cortisol increases (Fig. 1B), and the rapid ACTH test revealed a normal response in cortisol increases (Fig. 1C), indicating hypothalamic adrenal insufficiency, which transiently deteriorated due to influenza infection. Serum testosterone, LH, and FSH levels were below the normal ranges and the LHRH test revealed attenuated responses in LH and FSH levels (Fig. 2A), indicating hypogonadotropic hypogonadism. Thus, the administration of testosterone (250 mg of testosterone enanthate, every 4 weeks) was initiated. The GRH test revealed attenuated responses in GH (Fig. 2B) and the insulin tolerance test revealed a weak response in GH increases (Fig. 2C), indicating adult GH deficiency. The growth chart from birth to 20 years old is shown in Fig. 3 [2]. Although height and weight had both been within the range from 0 to –1 SD for Japanese boys until 12 years old, growth gradually attenuated thereafter and stopped at a height of 156 cm (–1 SD) at the age of 14 years (Fig. 3).

A differential diagnosis of SITSH was made. He had no remarkable previous or family medical history; however, tachycardia (HR: 100–120 bpm) was identified when he was 14 years old and he had palpitations, shortness of breath, and mild headaches without exacerbation from the age of 20 years. Endocrinological tests upon admission showed the inappropriate secretion of TSH, with serum TSH 9.57 μU/mL, FT3 14.7 pg/mL, and FT4 4.69 ng/dL (Table 1). Glycoprotein α-subunit (α-GSU) was within the normal range, while sex hormone binding globulin (SHBG) was elevated. Magnetic resonance imaging (MRI) revealed an irregularly shaped/lobulated tumor (Φ26 × 13 × 27 mm) in the suprasellar region (Fig. 4). There was no exclusion for a hypothyseal stalk and optic chiasma, although the tumor extended to the bottom of the sella turcica. Thyroid ultrasonography revealed diffuse goiter with a rough internal echogram and increased blood flow, while 99mTcO4-scintigraphy indicated that the uptake rate was 3.2%, which was within the normal range (Fig. 5). Since the TRH test upon admission to our department revealed that the increase in TSH levels was attenuated (Fig. 2D, TSH first), TSHoma was the most probable clinical diagnosis. However, 9 days after admission, serum TSH and RTH levels returned to almost within normal ranges (TSH 1.38 μU/mL, FT3 4.21 pg/mL, FT4 1.94 ng/dL). On the same day, TSH suppression was detected in the octreotide test (100 μg of octreotide was injected subcutaneously) (Fig. 6). Sixteen days after admission, serum TSH and RTH levels returned to within normal ranges (TSH 2.64 μU/mL, FT3 3.76 pg/mL, FT4 1.25 ng/dL) and the TRH test showed a weak response in TSH increases with a peak value of 7.39 μU/mL (Fig. 2D, TSH second). Thus, we concluded that SITSH was transient, its cause remained unclear, and he was discharged.

One month after his discharge, thyrotoxicosis with elevated serum TSH levels relapsed (TSH 16.57 μU/mL, FT3 24.30 pg/mL, FT4 6.03 ng/dL) and he was admitted to our department again for a further examination of SITSH. However, his plasma ACTH and serum cortisol levels were within normal ranges (ACTH 38.4 pg/mL and cortisol 9.3 μg/dL). We performed the T3 suppression test, in which 50, 100, and 200 μg/day of liothyronine (LT3) was administered every three days (total of nine days) and the TRH test was performed one day prior to the administration of LT3 and under its administration at each dose [3]. We noted TSH suppression in a LT3 dose-dependent manner (Fig. 7). We also found no mutations in the TRβ gene. Based on these results, RTHβ did not appear to be likely, even though attenuated responses to LT3 in body weight, total cholesterol, and creatine
kinase (CK) were found in the T3 suppression test (Table 2). After the T3 suppression test, his serum TSH levels returned to within the normal range and tachycardia resolved. After his discharge from the second admission, serum TSH levels fluctuated in accordance with serum FT3 and FT4 levels and symptoms, such as palpitations and malaise, were accompanied by thyrotoxicosis (Fig. 8).

Ten months after the second discharge, he was febrile with a body temperature of 40°C and abdominal pain, watery diarrhea, and general fatigue, suggesting relative adrenal insufficiency due to acute gastroenteritis. He was administered 30 mg of hydrocortisone orally without success and was admitted to our department. In his third admission, thyrotoxicosis with elevated serum TSH levels (TSH 11.21 μU/mL, FT3 12.77 pg/mL, FT4 3.79 ng/dL) were noted; however, his plasma ACTH and serum cortisol levels were within normal ranges (ACTH 133 ng/mL, LH 1 mIU/mL, α-GSU 0.22 ng/mL). His symptoms, including fever, abdominal pain with watery diarrhea, and general fatigue, quickly resolved with the intravenous administration of hydrocortisone. His thyrotoxicosis with SITSH improved since his admission and his thyroid function was normal (TSH 1.75 μU/mL, FT3 2.89 pg/mL, FT4 1.48 ng/dL) by day 10 of admission.

On day 11 of admission, he was discharged from our department and prescribed 10 mg of hydrocortisone orally on a daily basis. Even though fluctuations in serum TSH levels were not characteristic of TSHoma, based on his clinical course and the findings obtained, we selected removal of the pituitary tumor by transphenoidal surgery (TSS) in order to eradicate cyclical thyrotoxicosis with SITSH.

Three months after his third admission, the patient underwent TSS and the intrasellar pituitary tumor was completely removed. Under the administration of 10 mg of hydrocortisone, his plasma ACTH and serum cortisol levels remained within normal ranges in the perioperative period (Fig. 8).

Histopathological and immunohistochemical analyses of the pituitary tumor showed pituitary adenoma with positive immunostaining for TSH-β and PRL, which had a MIB-1 proliferation index of <3%. We found positive

Table 1  Laboratory data on the first admission

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Biochemistry</th>
<th>Endocrine</th>
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<tbody>
<tr>
<td>WBC 3,400 /μL</td>
<td>TP 8.6 g/dL</td>
<td>TSH 9.57 μIU/mL (0.50–5.00)</td>
</tr>
<tr>
<td>Neutro 68.3%</td>
<td>Alb 4.1 g/dL</td>
<td>FT3 14.7 pg/mL (2.30–4.30)</td>
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<tr>
<td>eosino 1.2%</td>
<td>Cr 0.26 mg/dL</td>
<td>FT4 4.69 ng/dL (0.90–1.70)</td>
</tr>
<tr>
<td>Hb 12 g/dL</td>
<td>BUN 14 mg/dL</td>
<td>Tg 101 ng/mL (0–32.7)</td>
</tr>
<tr>
<td>RBC 502 × 10^11 /μL</td>
<td>Na 135 mEq/L</td>
<td>Tg-Ab 0.7 U/mL (0–0.2)</td>
</tr>
<tr>
<td>Hct 36.6%</td>
<td>K 3.5 mEq/L</td>
<td>TPO-Ab 86.8 U/mL (0–0.2)</td>
</tr>
<tr>
<td>Plt 15.0 × 10^4 /μL</td>
<td>Cl 99 mEq/L</td>
<td>TRAb 0.4 IU/L (0–0.9)</td>
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<tr>
<td></td>
<td>AST 23 IU/L</td>
<td>ACTH 48.6 pg/mL (7.0–56.0)</td>
</tr>
<tr>
<td></td>
<td>ALT 13 IU/L</td>
<td>Cortisol 8.1 μg/dL (6.4–21.0)</td>
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<td></td>
<td>T-Chol 202 mg/dL</td>
<td>GH 0.352 ng/mL (0.11–3.90)</td>
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<tr>
<td></td>
<td>TG 64 mg/dL</td>
<td>IGF-1 11.4 ng/mL (111–309)</td>
</tr>
<tr>
<td></td>
<td>HbA1c 4.6%</td>
<td>PRL 2.2 ng/mL (4.1–28.9)</td>
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<tr>
<td></td>
<td>BS 133 mg/dL</td>
<td>LH 1 mIU/mL (1.8–5.2)</td>
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<tr>
<td></td>
<td>α-GSU 0.22 ng/mL (0.16–0.36)</td>
<td>FSH 3.1 mIU/mL (2.9–8.2)</td>
</tr>
<tr>
<td>SHBG 111 nmol/L (10–55)</td>
<td>Testosterone 0.37 ng/mL (2.00–7.60)</td>
<td></td>
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</table>

WBC, white blood cell; Neutro, neutrophil; eosino, eosinophil; Hb, hemoglobin; RBC, red blood cell; Hct, hematocrit; Plt, platelets; TP, total protein; Alb, albumin; Cr, creatinine; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-Chol, total cholesterol; TG, triglyceride; HbA1c, hemoglobin A1c; BS, blood sugar; α-GSU, Glycoprotein α-subunit; SHBG, sex hormone binding globulin; Tg, thyroglobulin; Tg-Ab, anti-thyroglobulin antibody; TPO-Ab, anti-thyroid gland peroxisome antibody; TRAb, thyrotropin receptor antibody; IGF-1, insulin-like growth factor-1.

Normal ranges are shown in parentheses.
and negative immunostaining for Pit-1 and GH, respectively (Fig. 9). Based on the 2004 World Health Organization classification [4], we pathologically diagnosed the pituitary tumor as TSH-PRL-producing plurihormonal pituitary adenoma without invasiveness. We also did not detect any necrosis or hemosiderosis in the pituitary tumor.

After TSS, SITSH disappeared and LT4 replacement was initiated against hypothyroidism. However, this replacement was stopped four years after TSS because his thyroid function, including serum TSH levels, completely normalized. Thus, based on the pathological findings of the tumor and improvement in thyrotoxicosis with SITSH after surgery, we conclusively made a definite diagnosis of SITSH due to TSHoma.

Discussion

We encountered a case of TSHoma with cyclic fluctuations in serum TSH levels. Since SITSH was confirmed, it is important and sometimes difficult to differentiate TSHoma from RTHβ. When SITSH is found in family medical histories, RTHβ is highly likely. However, 28% of RTHβ cases are de novo, with TRβ gene mutations being newly detected with no family history of SITSH [5]. Moreover, a patient with TSHoma accompanied by RTH (P453T) has been reported [6]. The TRH test, T3 suppression test, and TRβ genetic analysis are commonly performed to reach a differential diagnosis of SITSH [7, 8]. In the TRH test, serum TSH levels generally show a normal or strong response in RTHβ, but no or a weak response in TSHoma [9]. In 10–20% cases of TSHoma, serum TSH levels may show some responses to TRH [8], although the magnitude of the response is still less than that of RTHβ [9]. Previous studies proposed that the T3 suppression test is the most sensitive and specific test to assess the presence of TSHoma [8] and reported that the complete inhibition of TSH secretion by the administration of T3 was not found in patients with TSHoma, in contrast to patients with RTH [10]. On the other hand, the T3 suppression test is only useful for differentiating RTH from normal subjects [11], and the inhibition of TSH secretion by the administration of T3 has also been reported in 17% of patients with TSHoma [12]. Furthermore, approximately 15% of RTH cases are non-TR-RTH, in which no TRβ gene mutations are found [13].
Although an elevated α-GSU/TSH molar ratio was previously reported in more than 80% of patients with TSHoma [9], normal α-GSU levels have also been found in patients with TSHoma [14], similar to the present case. Even though TSHoma is a rare disease, occurring in 0.15 out of 1 million people [7], in the present case, TSHoma was considered as the primary diagnosis, particularly with the presence of the pituitary tumor on MRI, a weak TSH response to TRH, elevated SHBG levels, and the absence of a family medical history of SITSH or TRβ gene mutations. However, complete TSH suppression and a blunted cholesterol response in the T3 suppression test and normal α-GSU levels in the present case were not compatible with the diagnosis of typical TSHoma.

In the present case, cyclic fluctuations in serum TSH levels were noted in the clinical course. A previous study reported the potential of fluctuations between SITSH and the euthyroid status in a case of mild RTH [1]. Since no cases of TSHoma with periodically fluctuating serum TSH levels have ever been reported in the literature, difficulties were associated with distinguishing RTH from TSHoma. Nevertheless, we selected removal of the pituitary tumor by TSS in order to eradicate the risk of cyclical thyrotoxicosis with SITSH and relative adrenal insufficiency, and, thus, the present case was conclusively diagnosed as TSHoma because SITSH disappeared after surgery and TSH-β immunopositivity was demonstrated in immunohistochemical staining.

Although the diurnal pattern of serum TSH levels in patients with TSHoma differs from that in healthy subjects in terms of the presence of increased TSH pulse numbers with normal pulsing variability, increased basal (non-pulsatile) TSH release, decreased secretory pattern regularity, increased spikiness, and a significant phase delay in the diurnal TSH rhythm [15], the molecular mechanisms responsible for the cyclic fluctuations in serum TSH levels observed in the present case have not yet been elucidated.

Macro-TSH, a rare macromolecule composed of a bond between TSH and anti-TSH IgG molecules, leads to falsely elevated levels of TSH. Macro-TSH exhibits reduced biological activity and similar binding efficiency to immunoassay antibodies. Patients with macro-TSH...
show normal FT4 levels and no symptoms of thyroid dysfunction despite elevated serum TSH levels, suggesting SITSH [16]. However, in the present case, we noted that serum TSH, FT3, and FT4 levels concurrently fluctuated with the clinical symptoms of thyrotoxicosis, and, thus, this was not a case of macro-TSH.

Ando et al. demonstrated that a somatic mutation in TRβ occurred in TSHoma and appeared to be responsible for the defect in the negative regulation of TSH by RTH in the tumor [17]. They reported a somatic mutation in the ligand-binding domain of TRβ1 in TSHoma [17]. Furthermore, Tagami et al. identified a new TR isoform (referred to as TRβ4) in TSHoma, which may contribute to a defect in the negative regulation of TSH, and indicated that the aberrant expression of TRβ4 partly contributes to the inappropriate secretion of TSH in TSHoma [18]. These findings suggest that somatic TRβ mutations in TSHoma characterize a clinical feature. Thus, further studies are warranted in order to investigate somatic TRβ mutations in TSHoma tissue in the present case, which may provide an insight into the mechanisms responsible for fluctuating serum TSH levels.

In the present case, we confirmed hypothalamic adrenal insufficiency, which was presumably due to the pituitary tumor. Adrenal insufficiency potentially influences serum TSH levels, but not entire thyroid function [19]. Thus, in the present case, adrenal insufficiency did not appear to be the main cause of fluctuations in thyroid function because his serum TSH levels had fluctuated in accordance with serum FT3 and FT4 levels (Fig. 8). In addition, his plasma ACTH and serum cortisol levels had been within normal ranges at several time points during thyrotoxicosis (Fig. 8). However, we cannot completely rule out the influence of a relative adrenal insufficiency.

Fig. 3 The patient’s growth chart from birth to 20 years old. The red closed circles show the patient’s height (top panel) and the red closed squares show weight (bottom panel).
on fluctuations in thyroid function in the present case. Conversely, the patient periodically exhibited the clinical symptoms of adrenal insufficiency in accordance with thyrotoxicosis caused by elevated TSH levels. Since
RTH is associated with an accelerated cortisol turnover, adrenal insufficiency appears to have developed at the time of thyrotoxicosis [20].

We preoperatively detected central hypogonadism and growth hormone deficiency in this case. Due to the absence of secondary sexual characteristics and the cessation of growth with a short stature at the age of 14 years, the pituitary tumor appeared to have already developed in early adolescence and central hypogonadism and growth hormone deficiency may have been attributed to the pituitary tumor. Furthermore, tachycardia from the age of 14 years suggested thyrotoxicosis with SITSH in early adolescence.

Cyclic Cushing’s disease is a rare disorder characterized by repeated episodes of a cortisol excess interspersed by periods of normal cortisol secretion, and accounts for 15% of adult cases of Cushing’s disease. Cycles of hypercortisolism may regularly or irregularly occur with intercyclic phases ranging between days and years. Generally accepted criteria to diagnose cyclic Cushing’s disease include three peaks and two troughs in cortisol production [21]. Based on these criteria, the present case was diagnosed as “cyclic TSHoma”. The pathophysiology of cyclic Cushing’s disease remains largely unknown; however, spontaneous, episodic hemorrhage, such as pituitary apoplexy in the tumor, resulting in temporary damage to actively secreting cells, or the synchronous growth and death of ACTH-secreting tumor cells have been proposed to lead to periodic hypercortisolism [22]. In our case, although the patient had headaches from the age of 20 years, no pathological findings of apoplexy, necrosis, or hemosiderosis were found in the tumor tissue.

In cyclic Cushing’s disease, cortisol stimulation or suppression tests may provide spurious results due to spontaneous decreases or increases in serum cortisol levels at the time of testing [22]. Therefore, in the present case, we speculate that suppressed serum TSH levels and a blunted cholesterol response in the T3 suppression test were attributed to cyclic TSH fluctuations.

In conclusion, we herein reported a case of TSHoma, in which serum TSH, FT3, and FT4 levels fluctuated...
Fig. 8  Clinical course of the current case and changes in serum TSH, FT3, and FT4 levels. The severity of clinical symptoms, such as palpitations and malaise, are indicated as triangles. Plasma ACTH and serum cortisol levels were also indicated below the graph.

Fig. 9  Histological findings. A: Hematoxylin and eosin staining revealed a solid growth tumor with stromal fibrosis, composed of pale acidophilic and short spindle-shaped cells with irregular nuclei. B: Immunostaining of TSH-β showed universal positivity in tumor cells. C: Approximately 20% of tumor cells were immunopositive for PRL. D: The MIB-1 labeling index was approximately 2%. E: Immunostaining for GH was negative. F: Immunostaining for Pit-1 showed universal positivity in tumor cells. Images were in high power fields at 400× magnification.
periodically. To the best of our knowledge, this is the first case report of “cyclic TSHoma”, which needs to be considered when making a differential diagnosis of SITSH.

**Disclosure**

None of the authors have any potential conflicts of interest associated with this manuscript.

**References**