



Case Report

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A Rare Case of Thyrotoxic Periodic Paralysis Caused by TSH-Secreting Pituitary Adenoma: Case Report and Review of the Literature

Monami Koga¹, Takashi Fukuda¹, Kunitaka Murase¹, Ryoko Motonaga¹, Makito Tanabe¹, Takashi Nomiya¹, Toshirou Katsuta², Tooru Inoue², Hiroyuki Hayashi³, Kazuki Nabeshima³ and Toshihiko Yanase^{1*}

¹Department of Endocrinology and Diabetes Mellitus, Fukuoka University, Japan

²Department of Neurosurgery, Fukuoka University, Japan

³Department of Pathology, Fukuoka University, Japan

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***Corresponding author:** Toshihiko Yanase, Department of Endocrinology and Diabetes Mellitus, School of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan, Tel: +81-92-801-1011; Fax: +81-92-865-5163; Email: tyanase@fukuoka-u.ac.jp

Abstract

A 28-year-old man manifested thyrotoxicosis and periodic quadriplegia with hypokalemia. Further examination showed that he had inappropriate TSH secretion and a pituitary tumor. He was suspected as having thyrotoxic periodic paralysis (TPP) due to TSH-secreting pituitary adenoma. Therefore, transsphenoidal surgery was performed. The adenoma only stained positive for TSH. TPP is mostly associated with Basedow's disease. Our case is rare and the 6th reported TPP case caused by TSH-secreting pituitary adenoma. Our results suggest that TPP is not caused by an autoimmune mechanism, but thyroid hormones instead. We review five other rare cases of TPP caused by TSH-secreting pituitary adenoma.

Keywords: Thyrotoxic periodic paralysis; Inappropriate TSH secretion; TSH-secreting pituitary adenoma

Abbreviations: TPP: Thyrotoxic Periodic Paralysis; BMI: Body Mass Index; IRI: Immunoreactive Insulin; OGTT: Oral Glucose Tolerance test; IGT: Impaired Glucose Tolerance; T1WI: T1 Weighted Image; T2WI: T2 Weighted Image; HLA: Human Leukocyte Antigen

Introduction

Periodic quadriplegia presents with a transient quadriplegia attack, which lasts for several hours or for a few days. Periodic quadriplegia is generally categorized into three types of low, normal, or high potassium. Low potassium (hypokalemia) is the consequence of a rapid and massive shift of potassium from the extracellular into the intracellular compartment, mainly into the muscles. The low potassium type of periodic quadriplegia is frequently found as a type of familial periodic quadriplegia in Western countries. However, the low potassium type of periodic quadriplegia is frequently observed as thyrotoxic periodic paralysis (TPP) in Asian countries, including Japan [1,2], and is rare in Western countries [3,4]. The overall incidence of TPP in Japanese thyrotoxic patients is 1.9% and 8%, respectively [1,2]. In North America, the incidence rate of TPP is approximately 0.1–0.2% in thyrotoxic patients [4,5]. In addition, despite a much higher incidence of thyrotoxicosis in women, TPP predominantly

affects men [1-5]. TPP comprises approximately 50% of the total causes of periodic quadriplegia in Asia [2].

The biggest cause of thyrotoxicosis causing TPP is Basedow's disease, which accounts for 83% of the total cases [3]. Thyrotropin (TSH)-producing pituitary tumor is a rare pituitary tumor. This tumor only comprises 0.5–3% of functioning pituitary adenoma, and is the cause of Thyrotoxicosis at a rate of less than 1% [6,7]. We experienced an extremely a rare case of TPP in association with a TSH-producing pituitary tumor. To the best of our knowledge, only five other cases similar to our case have been reported worldwide [8-12]. We present our rare case in this report and review a total of six (including our case) case reports of TPP in association with a TSH-producing pituitary tumor.

Case Report

A 28 year-old man first noted fatigue of the limbs and muscle weakness of both femoral regions, especially when he got up in

the morning. He also noticed loss of pectoral muscle strength, palpitation, slight dyspnea, diarrhea, and excessive sweating at approximately one month. One morning, he experienced an attack of quadriplegia when he tried to get out of bed, and then he was urgently transferred to a nearby doctor. A blood test showed that the serum level of TSH was 2.5 μ IU/mL, FT4 was 2.7 ng/dL, and K was 2.5 mEq/L. Because of the severe hypokalemia and thyrotoxicosis, he was suspected as having the low potassium type of TPP. He was then immediately administered 10 mEq of KCL. His symptoms improved several hours after treatment. To improve thyrotoxicosis, medication of 15 mg/day of thiamazole was started the next day. However, because of the appearance of skin eruption, treatment with thiamazole was stopped and replaced with propylthiouracil at a dose of 150 mg/day. However, thyrotoxicosis was not improved. He visited our department for further examinations. He had no important past medical history. In his family history, his aunt was affected by Basedow's disease.

The patient's physical examination showed a height of 183.2cm, body weight of 73.6 kg body mass index (BMI) of 22.19 kg/m², blood pressure of 117/65 mmHg, pulse of 74 beats/min, no exophthalmoses, no abnormality of eye movement, and no visual field disturbance. In the neck, a diffusely enlarged and elastic hard thyroid gland was palpable, but showed no tenderness. No abnormalities of the head, chest abdomen, muscle strength, and nervous system were observed. The patient showed no Cushingoid or acromegalic features. General laboratory data of a peripheral blood cell count and serum chemistry showed no specific abnormalities, including serum potassium levels (4.4 mEq/L). A thyroid function test showed the following: TSH, 6.98 μ IU/mL (reference range 0.5-5.0); FT4, 2.56 ng/dL (0.9-1.7) and FT3, 7.95 pg/mL (2.3-4.0). These findings suggested the presence of the syndrome of inappropriate secretion of TSH, as also demonstrated by previous data that were measured by the first doctor. All of the thyroidal autoantibodies were negative as follows: anti-TPO antibody, 9IU/mL; anti-thyroglobulin antibody, <10 IU/mL, TRAb <1.0 IU/mL and TSAb, 102%. Importantly, the α subunit/TSH ratio, which was measured by an immunochem. iluminometric assay (Mayo Clinic, USA), was greater than the usual cut-off value of 1, namely 1.7. This finding also suggested the presence of a TSH-secreting pituitary tumor [7]. The basal

values of other pituitary, adrenal, and gonadal hormones were as follows: GH, 0.08 ng/ml (reference range \leq 2.47); ACTH, 20.6pg/ml (7.2-63.3); prolactin, 15.6 ng/mL (3.5-19.4), LH, 2.6mIU/ml (0.6-12.1); FSH, 3.1mIU/ml (1.0-12.0); IGF-1, 202 ng/mL (114-315); cortisol, 18.8 μ g/dL (6.2-19.4); and testosterone, 815.2 ng/mL (225.0-1039.0). All of these values were within the normal range. Table 1A-1C shows the hormonal responses of TSH and prolactin (PRL) to a thyrotropin-releasing hormone (TRH) loading test, responses of ACTH and cortisol to a CRH test, responses of LH and FSH to a LH-RH test, and the response of GH to a GHRP-2 test.

The TRH loading test indicated a poor response of TSH and PRL. This result suggested the presence of a TSH-secreting pituitary tumor because TSH secretion from a TSH-secreting pituitary tumor does not usually increase much in response to TRH [7]. In the CRH loading test, ACTH showed a poor response, but normal cortisol response. In the LH-RH loading test, FSH showed a normal response, but LH showed a poor response. In the GHRP-2 loading test, GH showed a normal response. While fasting blood glucose (96 mg/dL) and HbA1c (5.5%) were within the normal range, the IRI level (11.4 μ IU/mL) was slightly high. The 75-g OGTT showed 172 mg/dL of blood sugar level at 120 min, corresponding to IGT type. The insulin response was enhanced considering that he was not obese (BMI 22.2 kg/m²) (Table 1D). Magnetic resonance imaging of the pituitary showed a macroadenoma (31.4 \times 18.3 mm), which was a low signal in T1WI (Figure 1A) and a low-high signal in T2WI (Figure 1B). There was relatively uniform enhancement by a contrast agent, gadolinium, in T1WI (Figure 1C). Progression of the pituitary tumor to the spheroidal sinus and the left cavernous sinus, and compression to the upper part of both sides of the optic nerve and the optic chiasm were suspected. However, Goldman's test, which is used to examine the visual field, showed no abnormalities. Thyroid echography demonstrated a diffuse swelling of the thyroid gland with a small amount of increased blood flow in the total gland. We did not observe a thyroid tumor or lymph node swelling (data not shown). Based on these findings, the patient was highly suspected to have thyrotoxicosis by a TSH-secreting pituitary tumor.

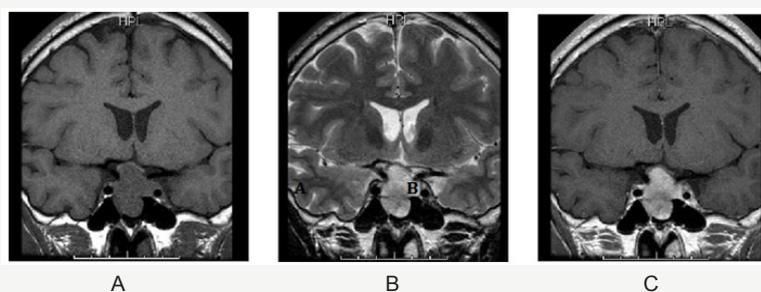


Figure 1: Magnetic resonance imaging of the pituitary.

Figure 1A:T1WI

Figure 1B:T2WI

Figure 1C:T1WI with gadolinium.

Table 1: Hormonal response to TRH, CRH, LH-RH, GHRP-2 and glucose loading.

Table 1A: TRH loading test.

	0 min	15min	30min	60min	90min
TSH (μU/ml)	6.96	8.36	8.69	8.6	8.35
PRL (ng/ml)	15.2	23.7	19.8	15.5	13.9

Table 1B: Combined loading test with CRH and LH-RH.

	0min	15min	30min	45min	60min
GH (ng/ml)	0.08	17.5	20.1	16.9	13.2

Table 1C: GHRP-2 loading test.

	0min	30min	60min	120min
blood sugar (mg/dl)	88	145	118	172
insulin (μU/ml)	9.6	56.5	31.8	119.4

Table 1D: Oral glucose (75 g) tolerance test.

	0min	30min	60min	120min
blood sugar (mg/dl)	88	145	118	172
insulin (μU/ml)	9.6	56.5	31.8	119.4

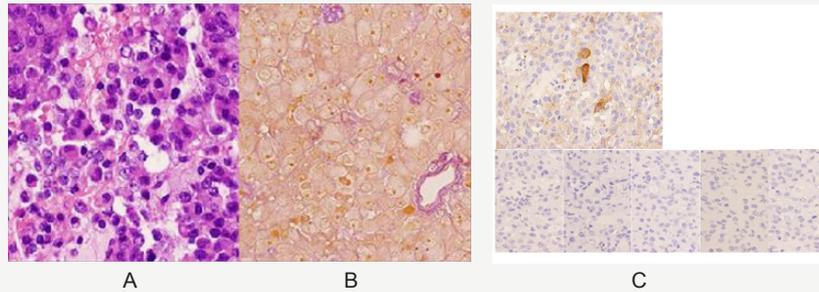


Figure 2: Histological findings of pituitary adenoma.

Figure 2A: H&E staining.

Figure 2B: Pearse's PAS staining.

Figure 2C: Immunohistochemical staining with antibodies against TSH, ACTH, GH, PRL, FSH, and LH. Antibodies used in the immunohistochemical studies were monoclonal or polyclonal antibodies against TSH, GH, GH, ACTH, FSH, and LH, and were purchased from DAKO (Tokyo, Japan).

As a result, endoscopic transsphenoidal surgery to remove the pituitary tumor was performed. The pathological finding of the resected tumor was pituitary adenoma (Figure 2A), which consisted of chromophobic cells as shown by Pearse's PAS staining (Figure 2B). A PAS-stained small body was also partly seen. Immunohistochemically, the adenoma was positive for TSH and negative for GH, PRL, ACTH, FSH, and LH (Figure 2C). Pathologically, there was no progression to the spheroidal sinus, but invasion to the cavernous sinus was observed. Based on these findings, TSH-secreting pituitary adenoma was finally diagnosed. After the surgery, he had no episode of periodic paralysis so far (Figure 3).

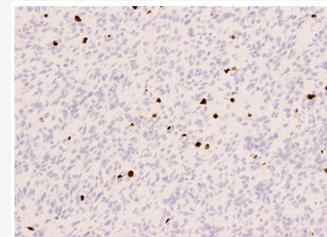


Figure 3: MIB-1 staining by immunohistochemistry using an antibody against MIB-1.

The MIB-1 index was determined as 2.8% because there were 20 MIB-1-positive cells among a total of 716 counted cells.

Table 2: Summary of previously reported TPP caused by TSH-secreting pituitary adenoma, including this case.

	Case 1 [8]	Case 2 [9]	Case 3 [10]	Case 4 [11]	Case 5 [12]	Case 6 [this case]
country	Japan	Indonesia	China	Syria	India	Japan
gender	Male	Male	Male	Male	Male	Male
Age (y.o)	27	43	44	31	40	28
FH of quadriplegia	(-)	(-)	(-)	(-)	(-)	(-)
FH of thyroid disease	(+)	(-)	(+)	undescribed	undescribed	(+)
BMI	25.9	22.9	unknown	25.4	undescribed	22.1
Heart Rate (beats/min)	79	92	100	102	117	74
Thyrotoxicosis	(+)	(-)	(-)	(-)	(-)	(-)
Headache	(-)	(-)	(-)	(-)	(+)	(-)
visual field defect	(-)	(-)	(-)	(-)	(+)	(-)

K (mmol/l)	1.3	1.2	1.8	3.3	2.8	2.5
TSH (μU/ml)	4.5	4.3	2.1	5.55	56.8	6.98
FT4 (ng/dl)	4.13	3.76		2.12	4.87	2.56
T4 (μg/dl)	undescribed	undescribed	14.4	undescribed	undescribed	not determined
FT3 (pg/ml)	undescribed	undescribed	undescribed	undescribed	19.9	7.95
T3 (ng/ml)	270	428	227	190	undescribed	230
Anti-thyroid antibodies	undescribed	(-)	undescribed	(-)	(-)	(-)
thyroid enlargement	(+)	(+)	Normal	(+)	Normal	(+)
pituitary tumor	macro	macro	macro	micro	macro	macro
αSU	undescribed	3	undescribed	0.62	undescribed	not determined
αSU/TSH ratio	6.3	undescribed	undescribed	undescribed	undescribed	1.7

Discussion

TPP is mostly observed in patients with Basedow's disease [1-5]. Our case is rare in that TPP was not caused by Basedow's disease, but by TSH-secreting pituitary adenoma instead. Only five cases of a TSH-secreting tumor that manifested as TPP have been reported to date. The characteristics of all of the six cases, including our case, are shown in Table 2. All of the patients were men from Asia to the East Asian region, and their age ranged from the twenties to the forties. Sex, area, and age of our case were similar to those of usual TPP cases [1-5]. No family history of quadriplegia was noted. BMI of these patients was 22-25 kg/m², suggesting that no excessive thyrotoxicosis causing emaciation was present. All of the six patients had mildly elevated serum thyroid hormone levels and manifested few symptoms, except for case 1. These findings are also compatible with a previous report on TPP, which described that because of a mild elevation in thyroid hormones, only 10% of patients showed mild thyrotoxic symptoms [13].

The subtlety or silence of the features of hyperthyroidism [5] together with the rarity of TPP may make it difficult to diagnose this condition. All six patients showed hypokalemia, but the extent of hypokalemia was not correlated with the severity of hyperthyroidism (i.e., levels of serum FT4 and TSH). Thyroid antibodies were negative in patients in whom anti-thyroid antibodies were measured. The thyroidal gland varied from a normal size to diffuse swelling. The finding of negative anti-thyroid antibodies in the five previously reported cases suggests that an autoimmune mechanism is probably not important for the mechanism of TPP, even though TPP is mostly observed in Basedow's disease. With regard to the size of the pituitary tumor, macroadenoma was observed in five of six cases, which is also consistent with the fact that TSH-secreting pituitary adenomas are relatively large [7].

The pathogenesis of TPP remains unclear. Hypokalemia is thought to be related to increased sodium-potassium-adenosine triphosphatase (Na/K-ATPase) pump activity. Na/K-ATPase pump activity determined in peripheral tissues, such as red blood cells, leukocytes, and platelets, shows a higher activity

in patients with thyrotoxicosis and TPP than in thyrotoxic patients without TPP [14-16]. Importantly, when thyrotoxicosis is controlled, Na/K-ATPase activity returns to the level of healthy controls. Thyroid hormones can increase Na/K-ATPase activity in various tissues, including skeletal muscle, thus inducing an influx of potassium into the intracellular space [17-19]. These findings suggest that elevation of thyroid hormones appears to be a central mechanism of TPP, regardless of the cause (e.g. Basedow's disease or TSH-secreting pituitary adenoma). Catecholamines can also increase Na/K-ATPase activity in skeletal muscle [20]. Therefore, an enhanced β-adrenergic response in thyrotoxicosis may further increase Na/K-ATPase activity. In addition, patients with TPP have an exaggerated insulin response during an oral glucose challenge compared with thyrotoxic patients without TPP [21,22]. Insulin-response sequences are present in the upstream region of Na/K-ATPase genes, and insulin has been shown to stimulate Na/K-ATPase activity [23]. Therefore, insulin can play a permissive role in the potassium shift in patients with TPP [24]. A hyperinsulinemic response is reasonable to explain the association of TPP with carbohydrate-rich meals. While a high carbohydrate meal intake was not clear in our patient, he showed hyperinsulinemia in a 75-g OGTT, despite his normal BMI. Therefore, hyperinsulinemia could be a potential factor for the susceptibility to TPP in this patient. Exercise releases potassium from the skeletal muscles, whereas rest promotes influx of potassium. This explains why paralytic attacks occur only during recovery from exercise [4]. The reason for male predominance in TPP is unclear, but is suggested to be due to increased Na-K ATPase activity by hyper androgenism [25].

There is a relatively high prevalence of some types of human leukocyte antigens (HLAs) in Asian patients with TPP [26,27]. However, specificities of such HLA genes in TPP is not clear because these HLA associations are also observed in Basedow's disease. Further investigations are needed for clarifying the total mechanism of TPP. Overall, patients with TPP appear to have an underlying predisposition for activation of Na/K-ATPase activity, either directly by thyroid hormones, or indirectly via sex, unknown constitution, adrenergic stimulation, insulin or exercise.

Conclusion

In conclusion, we report a case of TPP by TSH-producing pituitary adenoma. The mechanism appears to be related to mild elevation of thyroid hormones and possibly hyper insulinemia after carbohydrate loading.

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