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## Manifestation of Primary Hyperthyroidism after Pituitary Adenomectomy: A Case Report

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**Abstract.** We report a 47-year-old Japanese man who presented with visual disturbance due to a pituitary tumor with suprasellar extension. The patient had mild secondary hypothyroidism preoperatively, and was started on administration of levothyroxine sodium immediately before transsphenoidal surgery. After the operation, levothyroxine sodium was continued for several months. Pathological examination of the surgical specimen, together with endocrinological investigation revealed that the suprasellar tumor was a FSH-producing pituitary adenoma. Since 3 months after the operation, he has developed muscle weakness and finger tremor. He was found to be thyrotoxicosis, and levothyroxine sodium was discontinued. Seven weeks after levothyroxine sodium was discontinued, thyrotoxicosis continued, with a positive thyrotropin binding inhibitory immunoglobulin (TBII) and a high diffuse  $^{123}\text{I}$ -uptake by the thyroid. He was started on thiamazole 30 mg/day. Although his thyroid dysfunction improved within 2 months, hyperthyroidism worsened repeatedly on attempts to discontinue thiamazole, and he required continuous treatment at 2.5 mg/day. Patients with occult autoimmune thyroiditis rarely progress to thyrotoxicosis after operations on other endocrine organs such as the adrenal or parathyroid gland. In patients with pituitary adenoma, thyroid function and thyroid-associated autoantibodies should be investigated pre- and post-operatively.

**Key words:** Pituitary adenoma, FSH, Hyperthyroidism, Thyrotropin binding inhibitory immunoglobulin (TBII), Thiamazole

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PREVIOUS reports have noted thyroid dysfunction attributable to autoimmune thyroiditis arising after surgery on other endocrine organs, such as adrenal or parathyroid [1–3]. No case of thyroiditis associated with pituitary adenoma surgery has been reported to date. We present a patient who, after initial secondary hypothyroidism, came to manifest hyperthyroidism 3 to 6 months after an operation for a pituitary adenoma producing FSH.

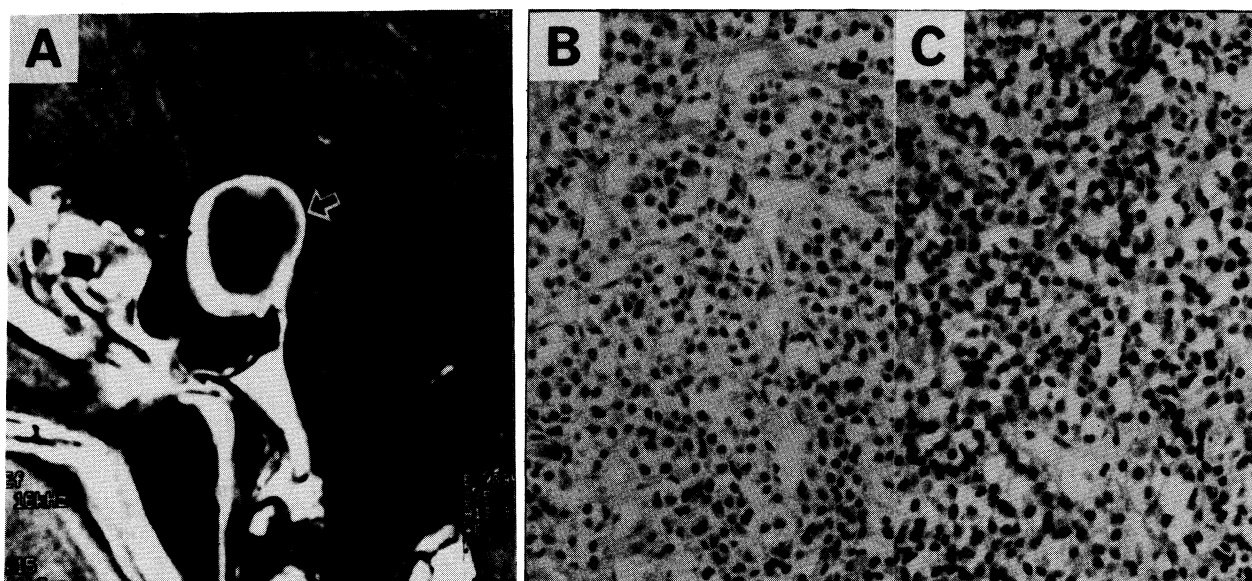
### Case Report

A 47-year-old Japanese man noted visual disturbance in April, 1995. Cranial magnetic resonance imaging (MRI) disclosed a cystic suprasellar tumor (Fig. 1A). He had no remarkable past or family history, and specifically no history of thyroid or gonadal dysfunction. On admission, the patient's visual field was severely restricted. Preoperative endocrinological data are shown in Table 1. Thyroid stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4) were 0.15  $\mu\text{U}/\text{mL}$ , 5.61 pg/mL and 0.90 ng/dL, respectively, consistent with mild secondary

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**Fig. 1.** Suprasellar tumor. On cranial magnetic resonance imaging (MRI), there was an iso-intense cystic tumor on T1-weighted images, and the cyst wall with gadolinium enhancement (arrow; A). Pathological findings of the resected tumor specimen were those of a pituitary adenoma consisting of trabecular arrangements of polymorphic cells with round nuclei (HE stain,  $\times 338$ ; B). Immunohistochemical study of  $\beta$ -FSH showed FSH in the surgical specimen ( $\beta$ -FSH staining,  $\times 338$ ; C).

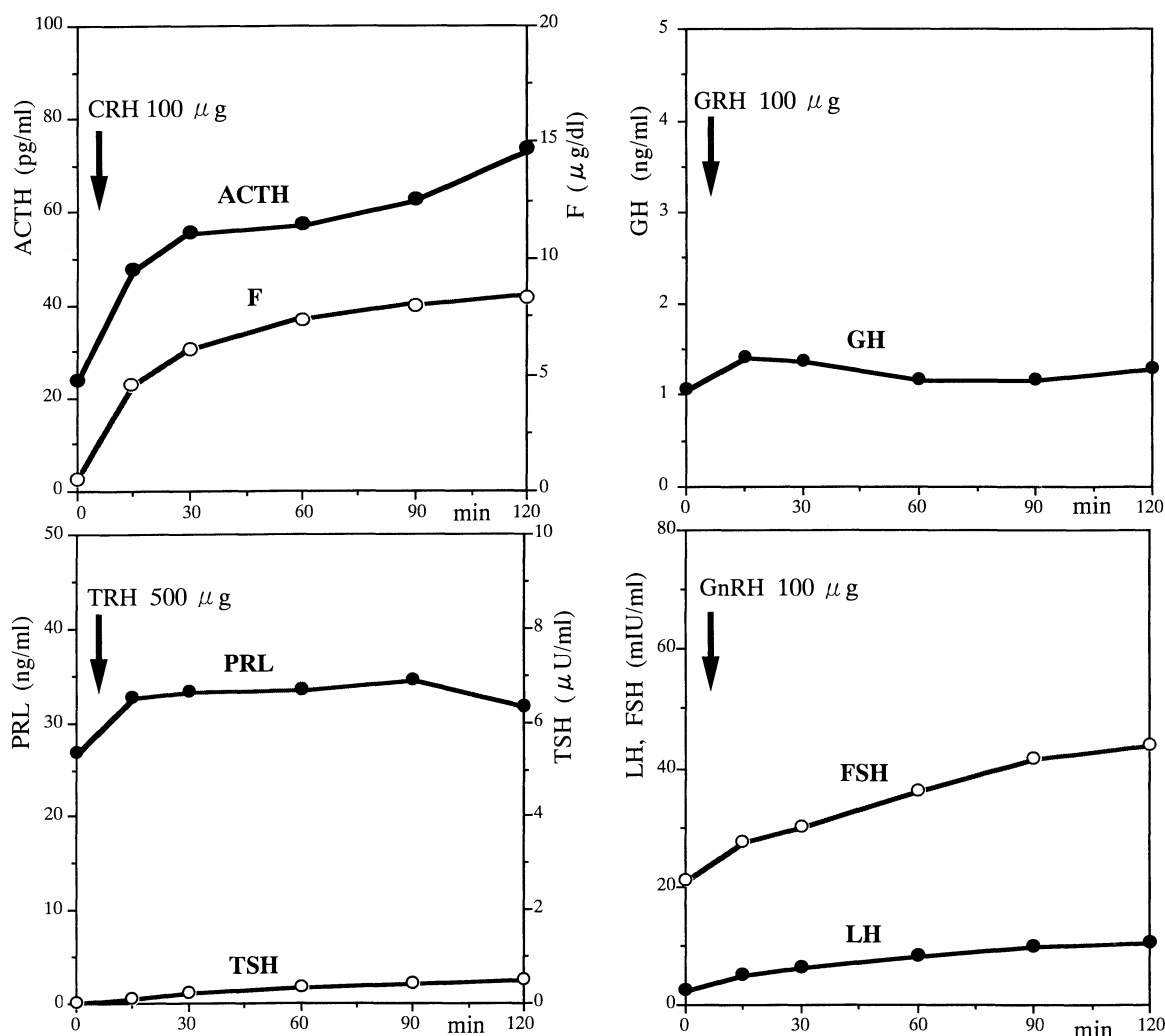
**Table 1.** Preoperative endocrine laboratory data

ACTH	13.5 pg/mL (4.4–48)	FT3	5.61 pg/mL (4–5.8)
GH	0.86 ng/mL (<1.46)	FT4	0.90 $\mu$ g/dL (1.03–2.21)
LH	1.91 mIU/mL (1.8–5.2)	F	1.0 $\mu$ g/dL (5–21)
FSH	19.99 mIU/mL (2.9–8.2)		
PRL	25.0 ng/mL (<30)	U-17OHCS	4.8 mg/day (2.1–11.5)
TSH	0.15 $\mu$ U/mL (0.55–4.8)	U-17KS	3.6 mg/day (3–9)

TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; F, cortisol; U-17OHCS, urine 17-hydroxycorticoids; U-17KS, urine 17-ketosteroids. Parentheses include the normal ranges.

hypothyroidism due to compression by the suprasellar mass. Although serum cortisol was low, urine 17-hydroxycorticoids (17-OHCS) were within normal limits. The concentration of FSH was significantly high in comparison with LH. Endocrinological stimulation tests revealed an impaired response of TSH and mildly blunted responses of ACTH and GH (Fig. 2). FSH response to gonadotropin releasing hormone (GnRH) was excessive compared with the LH response, suggesting that the suprasellar tumor produced FSH. After hormonal replacement with levothyroxine sodium 50  $\mu$ g/day and hydrocortisone 10 mg/day, he underwent transsphenoidal surgery on June 6, 1995. The

pathological diagnosis from the surgical specimen (Fig. 1B) was pituitary adenoma. The surgical specimen was positively stained by immunohistochemical staining of  $\beta$ -FSH (Fig. 1C). Postoperatively, under the thyroidal replacement therapy, serum FT3 (4.05 pg/mL) and FT4 (1.45 ng/dL) concentrations were normalized, but the serum TSH (0.01  $\mu$ U/mL) concentration was decreased. Despite a favorable course and normalized visual field following the operation, the patient has developed muscle weakness, general fatigue and finger tremor since August, 1995. Thyroid function tests in September, 1995 revealed total T3, 4.5 ng/mL (normal, 0.8–1.8); total T4, 22.7  $\mu$ g/dL (4.6–12.6); and TSH, not detectable, and



**Fig. 2.** Preoperative endocrinological stimulation tests. ACTH and F showed a delayed response to CRH administration, and GH release to GRH was also blunted. TSH release to TRH was impaired, but PRL and FSH responses were excessive.

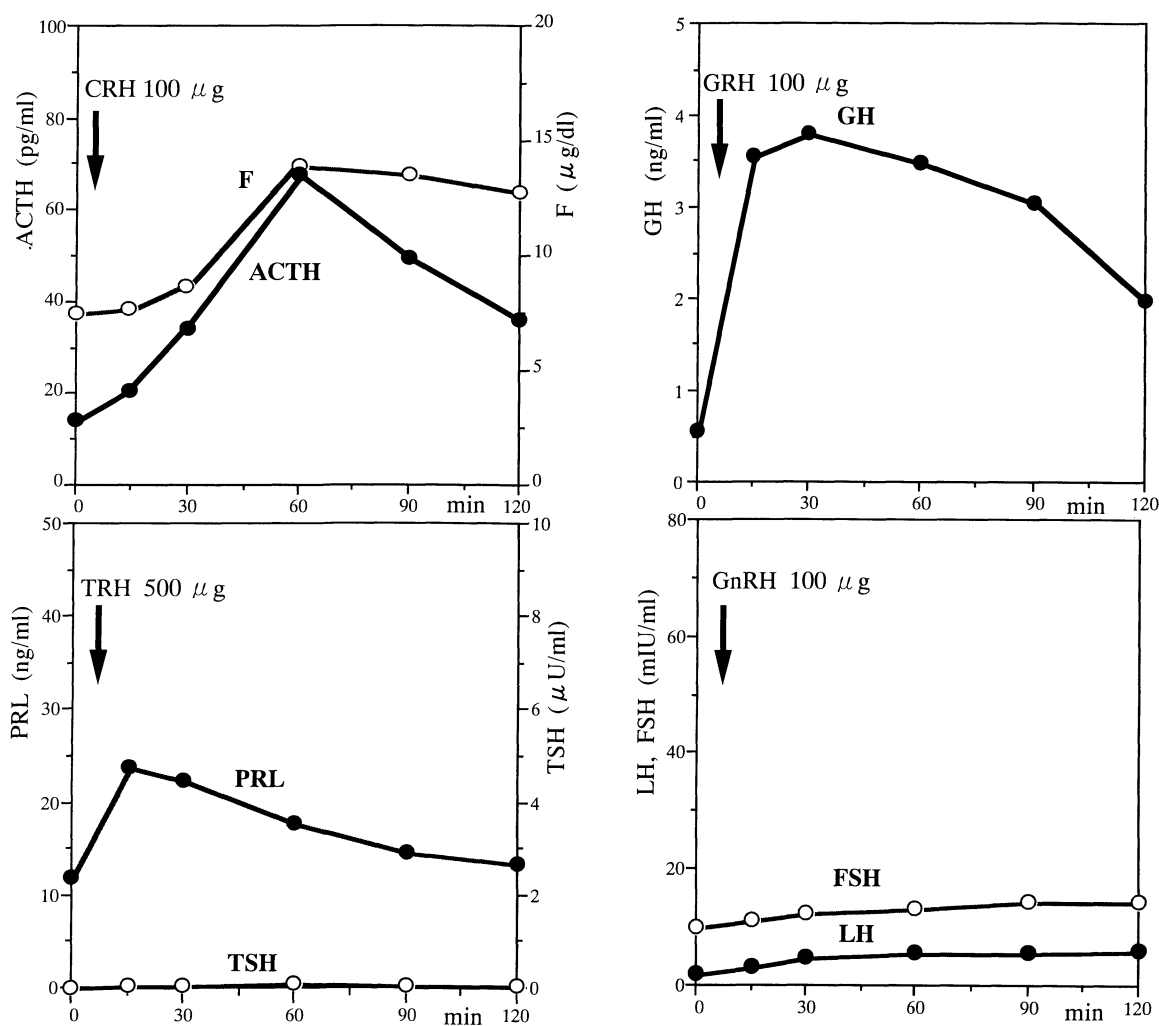
then, the dose of levothyroxine sodium was reduced by degrees. Because the thyrotoxicosis has remained (total T3, 3.2 ng/mL; total T4, 15.2 µg/dL; TSH, not detectable) in October, levothyroxine sodium was discontinued on November 1, 1995. The patient was referred to our department for endocrine reevaluation in December, 1995. Physical examination revealed that he had no goiter or exophthalmos, but had tachycardia and finger tremor. His endocrinologic data at that time are shown in Table 2. TSH, FT3 and FT4 were 0.01 µU/mL, 13.8 pg/mL and 4.48 ng/dL, respectively. FSH was slightly increased,

suggesting that the remaining tumor which was not detected by postoperative MRI might exist even after the operation. The serum testosterone concentration was normal. Stimulation tests showed normal pituitary response of ACTH and GH, but TSH was completely suppressed (Fig. 3). FSH response to GnRH was remarkably decreased, and PRL response to TRH was moderately impaired in comparison to the preoperative state. In the thyroidal autoimmune antibodies, thyrotropin binding inhibitory immunoglobulin (TBII) was positive (23.2%, normal: -15-15) but both anti-thyroglobulin (TG) and anti-thyroid peroxidase

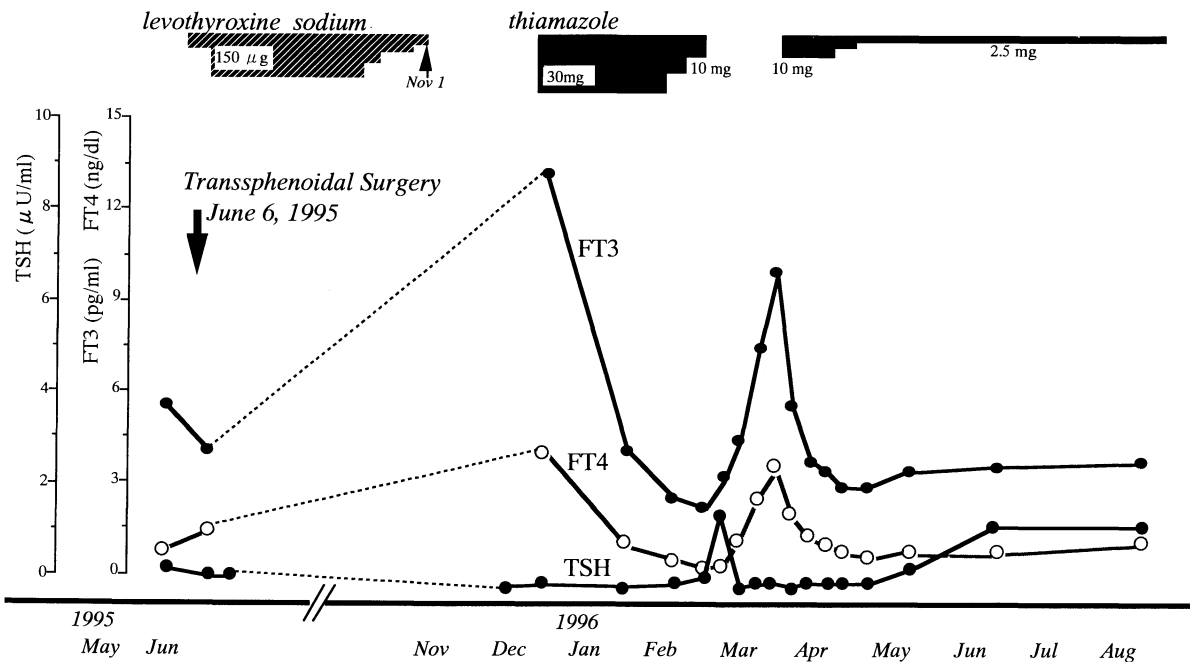
**Table 2.** Endocrine laboratory data 5 months after surgery

ACTH	24.4 pg/mL (4.4–48)	FT3	13.8 pg/mL (4–5.8)
GH	0.17 ng/mL (<1.46)	FT4	4.48 ng/dL (1.03–2.21)
LH	2.62 mIU/mL (1.8–5.2)	F	8.2 $\mu$ g/dL (5–21)
FSH	9.34 mIU/mL (2.9–8.2)	PRA	0.4 ng/mL/h (0.3–2.9)
PRL	10.4 ng/mL (<30)	T	3.6 ng/mL (2.9–10.7)
TSH	0.01 $\mu$ U/mL (0.55–4.8)	U-17OHCS	9.2 mg/day (2.1–11.5)
		U-17KS	3.9 mg/day (3–9)

TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; F, cortisol; PRA, plasma renin activity; T, testosterone; U-17OHCS, urine 17-hydroxycorticoids; U-17KS, urine 17-ketosteroids. Parentheses include the normal ranges.



**Fig. 3.** Postoperative endocrinological stimulation tests on manifestation of hyperthyroidism. ACTH and F responses to CRH were quite improved. Both GH response to GRH and PRL response to TRH were adequately normalized. The FSH response to GnRH was remarkably decreased in comparison to the preoperative state. The TSH response to TRH was completely suppressed.



**Fig. 4.** The clinical course. Immediately before the operation, the patient was given levothyroxine sodium for mild hypothyroidism. Transsphenoidal surgery was performed on June 6, 1995. Three months after the operation, he developed muscle weakness, general fatigue and finger tremor. He was found to be thyrotoxic, and therefore, levothyroxine sodium was gradually reduced and discontinued on November 1. Seven weeks after discontinuation, hyperthyroidism continued with positive TBII and high diffuse  $^{123}\text{I}$ -uptake in the thyroid gland, and then he was started on thiamazole. Although the hyperthyroidism improved gradually, cessation of thiamazole caused relapse. The serum TBII level altered in parallel with the thyroid function as follows: 23.2% in December, 1995; 19.8% in February, 1996; 24.7% in March, 1996; 13.6% in May, 1996; 5.8% in July, 1996. Resumption of thiamazole maintained euthyroidism.

(TPO) antibodies were negative. In addition, both thyroid stimulating antibody (TSAb) and thyroid stimulation blocking antibody (TSBAb) also were not detectable. Although the patient had no goiter and no remarkable echographic findings,  $^{123}\text{I}$  thyroid scintigraphy after 24 h showed diffuse uptake to be increased by 58.5%. He was diagnosed as hyperthyroid and administered thiamazole 30 mg/day. As thyroid function normalized, the dose of thiamazole was gradually decreased, but discontinuation of thiamazole caused immediate relapse into hyperthyroidism. He has required continuous administration of a small dose of thiamazole (2.5 mg/day; Fig. 4), which has maintained the euthyroid status, and the serum TBII level changed in parallel with the thyroid function. The patient's complaints were completely resolved in May, 1996, and he has been well since then.

## Discussion

Hyperthyroidism is rarely reported in association with another endocrinopathy. Thyrotoxicosis after adrenalectomy in a patient with Cushing's syndrome has been reported [1, 2], as well as after discontinuation of steroid therapy in a patient with rheumatoid arthritis [3]. In these reports, it was suggested that the acute reduction in glucocorticoid may have exacerbated a subclinical thyroiditis. Postparathyroidectomy thyrotoxicosis was also reported, and thyroid autoantigen release during surgery was suggested as a cause of this case [4]. In our case, the surgery was for an FSH-producing pituitary adenoma. Its response to GnRH stimulation and its histologic appearance confirm to earlier descriptions [5, 6]. Although thyrotoxic symptoms appeared about 3 months after the pituitary adenomectomy in the present case, the

definite diagnosis of hyperthyroidism was made later than 6 months after the surgery. The thyrotoxicosis is considered due to autoimmune primary hyperthyroidism because of a positive TBII and a high diffuse  $^{123}\text{I}$ -uptake by the thyroid gland. Unfortunately TBII was not examined preoperatively. On the basis of preoperative endocrinological data, mild secondary hypothyroidism was evident and was attributable to the compression of the normal pituitary by the pituitary adenoma. Preoperative ACTH showed a normal basal concentration but a delayed response to CRH stimulation. Postoperatively this response was quite improved, probably because of pituitary decompression. Unlike some previous cases, this patient's glucocorticoid level was relatively increased postoperatively, so that an exacerbation of subclinical thyroiditis rebounding to steroid reduction is difficult to postulate. This increased cortisol level, however, may rather reflect the patient's stressful state [7], which has continued since the surgery. Stressful life events, especially emotional stress [8] or negative life events [9], were reported to be related to significantly the pathogenesis of Graves' disease. Activation of the stress system affects the regulatory mechanisms of immune function in many ways [7], and therefore stressful life events are suggested to be one of the risk factors of Graves' disease. There still remains the possibility that some autoantigens were released from the pituitary during surgery. In this patient, hyperthyroidism required continuous

administration of low dose thiamazole. In previous cases, postparathyroidectomy thyrotoxicosis occurred in 2 weeks postoperatively, and resolved within 2 months in all reported 3 patients [4], compared with the possible onset of persistent hyperthyroidism 3 to 6 months postoperatively in our case. Interestingly, FSH, secreted by our patient's tumor, has a structural resemblance to TSH, a common  $\alpha$ -subunit [10]. Preoperatively the increased serum FSH in the present case might have interfered with TBII binding to the TSH receptor, taking into consideration the fact that FSH competed with monoclonal TSH-receptor antibodies on binding to the receptors on Chinese hamster ovary cultured cells [11]. In the present case, the postoperative decrease in the serum FSH concentration may have unmasked the effect of TBII, resulting in hyperthyroidism. But, because the competition between FSH and TSH-receptor antibody has not been proven on the thyroid gland [11] and the increase of FSH level in this case was relatively mild, this hypothesis cannot fully explain the pathogenesis of the present hyperthyroidism, despite the possibility that the aberrant FSH which had biologically high affinity for TSH-receptor was secreted from the pituitary tumor.

In retrospect, preoperative thyroid evaluation of pituitary adenoma patients should include thyroid autoantibodies and TSH-receptor antibodies, and regular endocrinological and immunological examinations should be performed postoperatively.

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