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Case Report

Persistent Pituitary Hyperplasia in Primary Hypothyroidism Despite Levothyroxine Therapy

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ABSTRACT

A 49-year-old woman was referred to our hospital with complaints of general fatigue and muscle weakness. Laboratory findings revealed hypothyroidism with thyroid autoantibodies. Primary hypothyroidism attributable to chronic thyroiditis was diagnosed, and replacement therapy with levothyroxine was started. However, the general fatigue remained unchanged after 4 months of treatment. Pituitary function was then evaluated. Laboratory findings showed hyperprolactinemia, low basal morning ACTH, and low cortisol levels. Magnetic resonance imaging showed enlargement of the pituitary gland. Pituitary provocation testing showed exaggerated responses of thyroid-stimulating hormone and prolactin and intact responses of growth hormone, luteinizing hormone, and ACTH. Goldman visual field examination revealed bitemporal quadrantanopia. On the basis of these findings, the enlarged pituitary gland was diagnosed as pituitary hyperplasia secondary to primary hypothyroidism, and replacement therapy was continued. After 10 months of the levothyroxine therapy, symptoms and endocrinological abnormalities were improved, but after 4 years of replacement therapy the pituitary gland has remained enlarged. This case is extremely unusual and suggests that careful management is needed to avoid unnecessary surgery, as pituitary hyperplasia secondary to primary hypothyroidism might easily be confused with pituitary adenoma. Also, the possibility of a pituitary tumor developing necessitates long-term follow-up. (Jikeikai Med J 2009 ; 56 : 63-8)

Key words : hypothyroidism, pituitary hyperplasia, pituitary adenoma

INTRODUCTION

After the first autopsy case report by Niepce of an enlarged sella turcica in a patient with cretinism[1], pituitary hyperplasia secondary to primary hypothyroidism has been well described[1-13]. It results from the negative feedback mechanism in the hypothalamic-pituitary-thyroid axis, i.e., the lack of thyroxine feedback leads to elevated levels of thyrotropin-releasing hormone (TRH), which cause both pituitary thyrotroph and lactotroph hypertrophy, leading to the hypersecretion of both thyroid-stimulating hormone (TSH) and prolactin[3]. Pituitary hyperplasia is difficult to distinguish from pituitary adenoma by means of magnetic resonance imaging (MRI). However, pituitary hyperplasia, in contrast to adenoma, generally decreases in size after thyroid hormone replacement therapy. Therefore, verifying

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whether pituitary hyperplasia regresses after therapy becomes extremely important. We report a case of pituitary hyperplasia due to primary hypothyroidism in which the pituitary gland remained enlarged despite 4 years of replacement therapy with levothyroxine.

CASE REPORT

A 49-year-old woman was referred to our hospital with complaints of general fatigue and muscle weakness. She had undergone appendectomy at age 18 years, and chronic type C hepatitis and iron-deficiency anemia had been diagnosed at age 30 years. In July 2001, at age 48 years, as she complained of general fatigue, she was examined at another hospital, and treatments for chronic type C hepatitis and iron-deficiency anemia were started. In June 2002, the patient's condition and anemia worsened (hemoglobin : 6.0 g/dL), and muscle weakness developed. After intravenous iron supplementation, the severe anemia improved slightly (hemoglobin : 8.0 g/dL), but muscle weakness and abnormal levels of myogenic enzymes persisted. On July 19, 2002, the patient was referred to our neurology clinic because muscle biopsy suggested progressive muscular dystrophy.

At that time, the patient was 151.1 cm tall and weighed 65 kg (body mass index : 28.3 kg/m^2). Blood pressure was 121/68 mmHg, body temperature was 36.8°C, and the heart rate was 49 beats per minute (bradycardia). The patient appeared somnolent and showed facial and periorbital edema, glossomegaly, and hoarseness. Her skin was dry, rough, and cold ; her hair was somewhat dry ; and the palpebral conjunctiva was pale. No indication of an enlarged thyroid gland, goiter, or galactopoiesis was present. The respiratory and heart sounds were normal. Pretibial nonpitting edema was present. Neurological examinations revealed bradylalia, muscle mounding, muscle weakness in the extremities, and a slow Achilles' tendon reflex relaxation but no muscular atrophy. Laboratory findings at our neurology clinic indicated mild anemia ; an elevated erythrocyte sedimentation rate ; slightly elevated values on the thymol turbidity test and zinc sulfate turbidity test ; and slightly elevated levels of asparatate aminotransferase and alanine aminotransferase, lactate dehydrogenase, creatinine phosphokinase, total cholesterol, and triglyceride (Table 1). A muscle biopsy performed at the previous hospital showed atrophy and degeneration of muscle fibers with proliferation of nuclei. Neurophysiological examinations showed normal nerve conduction velocity, no "waning and waxing" patterns on evoked electromyography, and negative findings on the Tensilon test. Thus, neurological examination revealed no specific abnormalities, but the physical findings and laboratory findings suggested hypoth-

Table 1. Laboratory findings

Peripheral Blood		Na	142 mmol/L
WBC	3,600/μL	K	3.8 mmol/L
RBC	302×10^4/μL	Cl	100 mmol/L
Hb	9.4 g/dL	TC	284 mg/dL
Ht	29.2%	TG	153 mg/dL
PLT	30.5×10^4/μL	CRP	0.1 mg/dL
ESR	73 mm	Serological Test	
Blood Chemistry		ANA	60.5 IU/mL
TTT	22.6 K.U	IgG	3,087 mg/dL
ZTT	10.5 K.U	Endocrinological Data	
AST	91 IU/L	TSH	318.24 μIU/mL
ALT	36 IU/L	free T3	0.95 pg/mL
LDH	497 IU/L	free T4	0.10> ng/dL
TP	9.2 g/dL	TGAb	100.0< U/mL
BUN	8.6 mg/dL	TPOAb	14.0 U/mL
Cr	0.8 mg/dL	TRAb	87.3%
CK	2,820 IU/L	TSAb	121%

WBC ; white blood cell
RBC ; red blood cell
Hb ; hemoglobin
Ht ; hematocrit
PLT ; platelet
ESR ; erythrocyte sedimentation rate
TTT ; thymol turbidity test
ZTT ; zinc sulfate turbidity test
AST ; asparatate aminotransferase
ALT ; alanine aminotransferase
LDH ; lactate dehydrogenase
TP ; total protein
BUN ; blood urea nitrogen
Cr ; creatine
CK ; creatinine phosphokinase
TC ; total cholesterol
TG ; triglyceride
CRP ; C-reactive protein
ANA ; antinuclear antibody
TGAb ; thyroglobulin antibody
TPOAb ; thyroperoxidase antibody
TRAb ; TSH receptor antibody
TSAb ; thyroid stimulating antibody

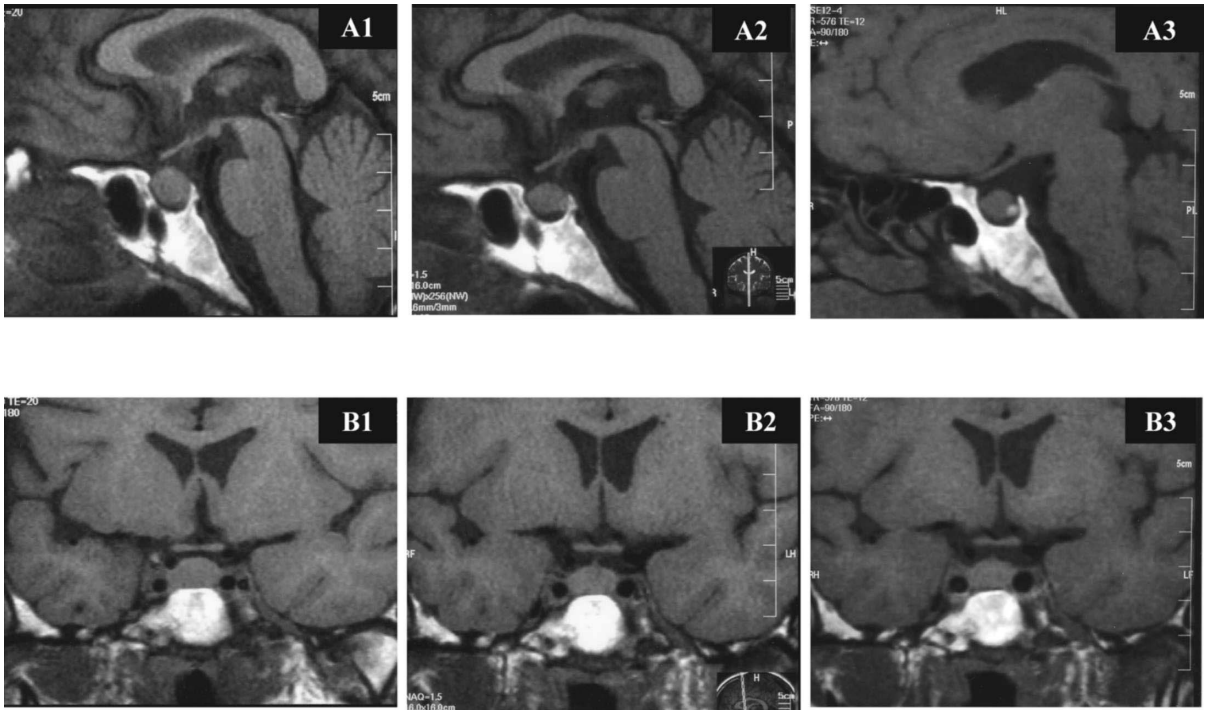

Fig. 1. Characteristics of the pituitary gland on T1-weighted MRI
Panels A, 1-3, show coronal views, and panels B, 1-3, midsagittal views.
A1/B1 : After 4 months of treatment with levothyoxine (December 2002)
A2/B2 : After 1 year of treatment with levothyoxine (July 2003)
A3/B3 : After 4 years of treatment with levothyoxine (July 2006)

roidism. Soon thereafter, thyroid function tests revealed severe hypothyroidism. The patient was given levothyroxine (50 μg/day) and was referred to our endocrinology clinic on July 31, 2002.

At our endocrinology clinic, further examined showed elevated levels of thyroglobulin antibody, thyroperoxidase antibody, and TSH receptor antibody (Table 1), which led to a diagnosis of chronic thyroiditis. Thyroid ultrasonography in August 2002 revealed a coarse internal echo and a depressed echo level but no apparent enlargement of the thyroid gland or increased blood flow in the gland. The patient had been treated with levothyroxine, 75 μg/day, since October 12, 2002. Although thyroid function gradually improved, the patient continued to complain of general fatigue. Therefore, pituitary function was evaluated on December 2, 2002, 4 months after the start of levothyroxine replacement therapy. The pituitary function testing showed low levels of ACTH (7.6 pg/mL) and cortisol (14 μg/dL) and high levels of prolactin (35.9 ng/mL) against a background of hypothyroidism (TSH, 29.34 μIU/mL ; serum free thyroxine [free T3], 1.91 pg/mL ; and serum free triiodothyronine [free T4], 0.99 ng/dL). Therefore, pituitary disease was suspected. MRI demonstrated a symmetrical 1-cm-diameter enlarged suprasellar pituitary gland on T1-weighted images (Fig. 1). At that time, the patient was suspected of having pituitary adenoma and was hospitalized for further evaluation in January 2003.

On December 13, 2002, the dose of levothyroxine was increased to 100 μg/day, and additional endocrinological examinations were performed. Thyroid function was found to have returned to the normal range (TSH, 2.27 μIU/mL ; free T3, 3.47 pg/mL ; and free T4, 1.41 ng/dL). Levels of both ACTH and cortisol had also returned to their normal ranges, and the diurnal cortisol variation showed a normal pattern. Pituitary provocation testing showed exaggerated responses of TSH and prolactin and intact responses of growth hormone (GH), luteinizing hormone, and ACTH (Table 2). An initial Goldman visual field

Table 2. Endocrinological Data

Diurnal variation of plasma ACTH, cortisol levels

Time (hr)	8 : 00	16 : 00	23 : 00
ACTH (pg/ml)	49.3	28.1	8.9
Cortisol (μg/dl)	14.2	6.4	2.0

GRH, LHRH, TRH, CRH stimulation test (GRH 0.1 mg, LHRH 0.1 mg, TRH 0.5 mg, CRH 0.1 mg iv)

Time (min)	0	15	30	60	120	normal range
TSH (μIU/ml)	1.82	20.59	31.44	27.70	13.91	(0.34–4.04)
PRL (ng/ml)	16.7	83.4	113.6	88.8	46.2	(3.2–26.2)
GH (ng/ml)	0.06	2.40	3.76	4.48	1.51	(0.17>)
LH (mIU/ml)	18.0	35.1	56.3	72.4	57.1	(0.90–19.38)
ACTH (pg/ml)	43.1	122.0	152.0	33.0	65.0	(7.4–55.7)
Cortisol (μg/dl)	9.5	12.0	14.3	15.8	12.3	(4.0–18.3)

GRH ; growth hormone releasing hormone
LHRH ; luteinizing hormone releasing hormone
TRH ; thyroid stimulating hormone releasing hormone
CRH ; corticotropin releasing hormone
PRL ; prolactin
GH ; growth hormone
LH ; luteinizing hormone

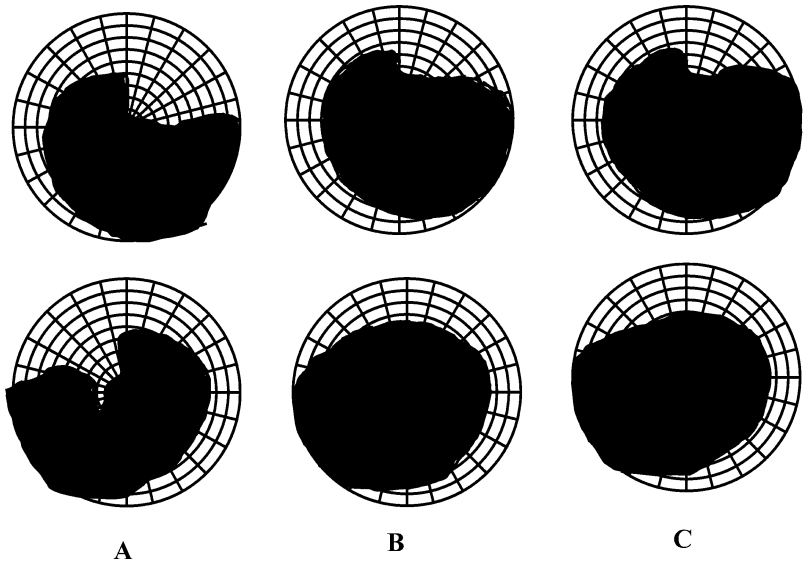

Fig. 2. Goldman visual field examination. Time course of visual field changes during levothyroxine replacement therapy. Above : right side. Below : left side.
A : After 5 months of treatment with levothyoxine (January 2003)
B : After 10 months of treatment with levothyoxine (June 2003)
C : After 17 months of treatment with levothyoxine (December 2003)

examination revealed bitemporal quadrantanopia (Fig. 2). The gadolinium-enhanced MRI after admission showed even enhancement without filling defects in the intrapituitary area or changes in the hypophyseal stalk. On the basis of these findings, the enlarged pituitary gland was diagnosed as pituitary hyperplasia secondary to primary hypothyroidism. As the visual field disturbance was not thought to be an indication for surgery, the patient was simply followed up and treated medically.

The levels of free T3 and free T4 had normalized with 100 μg/day of levothyroxine, and the TSH level was slightly suppressed to within the range of 0.06 to 0.25 μIU/mL. Goldman visual field examination showed that the visual field and all related symptoms had improved to near-normal levels after 10 months of replacement therapy (Fig. 2). However, MRI in July 2006 showed no regression of pituitary hyperplasia despite 4 years of levothyroxine replacement therapy (Fig. 1).

Discussion

We have described a case of severe hypothyroidism in a patient presenting with marked enlargement of the pituitary gland and bitemporal quadrantanopia. After 10 months of levothyroxine therapy, the symptoms and endocrinological abnormalities had improved. However, the pituitary gland remained enlarged even after 4 years of replacement therapy.

At first, we had believed that the enlarged pituitary gland was due to pituitary hyperplasia, because of an excessive response on the TRH test, which is typical of pituitary hyperplasia attributable to primary hypothyroidism[1,14], and the features of MRI[4,5,10]. However, we cannot easily diagnose the pituitary enlargement as pituitary hyperplasia due to primary hypothyroidism. Establishing the correct diagnosis is important because the treatment of pituitary hyperplasia is medical, whereas the treatment of pituitary adenoma is surgical.

Pituitary enlargement due to hypothyroidism normally resolves within 1 to 12 months after the start of treatment[3,4,6,10,13], with one study reporting that pituitary regression occurs in as early as 6 days[5]. Therefore, verifying the regression of pituitary hyperplasia after therapy is extremely important. Despite this assumption, a few reports have suggested that pituitary tumors may remain unchanged after thyroid hormone replacement[7,8,11]. A review by Beck-Peccoz et al. has found that after thyroid hormone replacement therapy lasting an average of 1 year, pituitary tumors completely disappeared in 62% of patients, partially regressed in 29% of patients, and remained unchanged in 4% of patients[1]. Another study has shown that of 26 patients, only 1 showed no change in pituitary size despite adequate thyroxine treatment[12]. These reports suggest that the present case is unusual, although thyroid function normalized within 5 months after the start of levothyroxine replacement therapy, and the pituitary hyperplasia remained unchanged throughout the 4 years of follow-up with MRI.

However, some evidence indicates reduction of the mass effect. The patient's visual disturbances showed improvement, indicating some reduction of the mass effect, despite MRI showing no regression of the pituitary gland. The normalized plasma levels of ACTH and cortisol with levothyroxine replacement therapy also suggested reduction of the mass effect. In the hypothyroid state, the half-life of plasma cortisol may be prolonged due to decreased metabolic clearance, leading to elevated cortisol levels[15]. However, another study has found that cortisol levels decrease in patients with pituitary hyperplasia associated with hypothyroidism and then recover after pituitary hyperplasia resolves with replacement therapy[1,6]. In the present case, the levels of ACTH and cortisol increased to their normal ranges during treatment, suggesting that the treatment had reduced the mass effect.

There are 2 possible reasons that hyperplasia remained unchanged over the 4 years of treatment. The first is the induction of hyperplasia and further progression to adenoma caused by hypothyroidism. Experiments in animals have shown that the chronic hypothyroid state induced by thyroidectomy or iodine 131 administration leads to nodular hyperplasia, followed by the formation of adenoma[1]. In a study of 64 patients with primary hypothyroidism examined at autopsy, diffuse and nodular thyrotroph hyperplasia and TSH-stained adenoma were present in 69%, 25%, and 8% of the patients, respectively[16]. In addition, Katz et al. have reported that a tumor that was believed to be a thyrotroph cell adenoma arose owing to protracted overstimulation secondary to chronic thyroid hormone deficiency[17], and Ghannam et al. have reported that thyrotroph adenoma/irreversible hyperplasia could result from long-standing primary hypothyroidism[9]. While the present case could be considered transformation of the pituitary through

chronic TRH stimulation, we concluded that long-term follow-up was required because of the possibility of a pituitary tumor developing.

The second possible reason the hyperplasia remained unchanged over the 4 years of treatment is insufficient supplementation with levothyroxine: Yamamoto et al. have reported on 2 patients in whom visual field defects progressed during thyroid hormone replacement. These cases indicate that the use of low doses of thyroid hormone inhibits the release of TSH but not its synthesis[2]. In the present case, thyroid hormone replacement with 100 μg/day of levothyroxine was believed to be adequate, as it resulted in modest inhibition of TSH with levels of 0.06 and 0.25 μIU/mL, but also returned free T3 and free T4 levels to their normal ranges.

We concluded that this case called for careful management to avoid unnecessary surgery, as pituitary hyperplasia secondary to primary hypothyroidism might easily be confused with pituitary adenoma. We also concluded long-term follow-up was needed, because of the possibility that a pituitary tumor might develop.

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