Endocrine Journal 2004, **51** (3), 287–293

A Case of Acquired Deficiency of Pituitary GH, PRL and TSH, Associated with Type 1 Diabetes Mellitus

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Abstract. A 75-year-old male showed combined anterior pituitary hormone deficiency (CPHD). Basal and TRH-stimulated PRL levels were undetectable. Basal and GRH-stimulated GH levels were very low, and could barely be measured by means of an ultrasensitive enzyme immunoassay. In addition, basal TSH levels were under the normal limit, and TRH-stimulated TSH secretions were impaired. On the other hand, the secretions of ACTH, LH and FSH remained intact. There was no mutation of *Pit-1* gene in this patient, and immunohistochemical studies using human pituitary and the patient's serum showed no positive staining. The HLA types frequently detected in lymphocytic hypophysitis were recognized, supporting the view that the CPHD in this case may be caused by lymphocytic hypophysitis, although magnetic resonance imaging of the pituitary gland showed no specific findings. Interestingly, a high titer of anti-glutamic acid decarboxylase antibody, suggested that the patient suffered from type 1 diabetes mellitus (DM). Five years ago, his thyroid function was normal and the treatment of DM with oral hypoglycemic agent was effective, indicating that the onset of both diseases at least occurred within the last half decade. We report here a rare case of SPIDDM with CPHD which might be caused by lymphocytic hypophysitis.

Key words: SPIDDM, Autoimmune, Adult onset, Lymphocytic hypophysitis

(*Endocrine Journal* **51**: 287–293, 2004)

ADULT onset of pituitary hormone deficiency usually results from tumors in the hypothalamic or pituitary region and/or surgery, and irradiation for their treatment. Traumatic brain injury, circulatory disorders such as pituitary apoplexy or Sheehan's syndrome, and mental disorders such as anorexia nervosa could also elicit pituitary hormone deficiency [1, 2]. The impaired secretion of pituitary hormones is commonly single, double or total, and the impairment of more than three hormones is very rare.

Lymphocytic hypophysitis, a definite clinical entity first documented by Goudie and Pinkerton in 1962, is associated with autoimmune inflammatory disease of the pituitary gland [3]. This disease is characterized to frequently complicate other autoimmune diseases such as chronic thyroiditis, pernicious anemia, idiopathic adrenalitis and type 1 diabetes mellitus [4]. Most patients with lymphocytic hypophysitis showed symptoms of either isolated or multiple anterior pituitary hormone deficiency. Especially, ACTH secretion is most frequently impaired, while PRL secretion is least disturbed. In addition, several types of human leukocyte antigen (HLA) are considered to be involved in this disease [4].

Slowly progressive insulin-dependent diabetes mel-

Received: August 20, 2003
Accepted: February 9, 2004
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litus (SPIDDM) is the clinical subtype of type 1 diabetes mellitus (DM) [5]. It has distinct characteristic findings including late-onset, high prevalence of islet cell antibodies or anti-glutamic acid decarboxylase (GAD) antibodies, and preserved β-cell function [6]. SPIDDM is also known to be frequently complicated by other autoimmune diseases.

We report here a case of CPHD, which might be presumably caused by hypophysitis. The pattern of CPHD is just like typical *Pit-1* deficiency which has rarely been reported. In addition, the present case suffered from SPIDDM with high anti-GAD and anti-islet cell antibody levels.

Case Report

A 75-year-old male was admitted to our hospital for control of diabetes mellitus (DM). He has suffered from DM for 10 years. On admission, his consciousness was clear. His body temperature was 35.4°C, the pulse rate was 64/min, regular, and blood pressure was 140/86 mmHg. His height was 176 cm and weight was 76 kg. The thyroid gland was not palpable. Systolic murmur was audible. Neither hepatomegaly nor splenomegaly could be detected. There was no peripheral edema or decreased skin turgor. Neurological tests suggested sensory and autonomic nerve disorders, indicating progressive diabetic neuropathy. Urinalysis showed no albuminuria and normal levels of N-acetyl-D-glucosamidase and β2-microglobulin, whereas creatinine clearance was decreased to 48 ml/min. Hematological tests showed a slight normocytic normochromic anemia. Blood chemistries were as follows: aspartate aminotransferase 24 IU/l (normal range: 10–40); alanine aminotransferase 10 IU/l (5–40); cholinesterase 2792 IU/l (3200–6800); alkaline phosphatase 236 IU/l (96–300); lactate dehydrogenase 328 U/l (130–235); total bilirubin 1.0 g/dl (0.2–1.3); total protein 7.7 g/dl (6.3–8.8); albumin 4.6 g/dl (3.5–5.2); creatine kinase (CK) 322 U/ml (55–160); amylase 104 IU/l (30–130); blood urea nitrogen 27 mg/dl (8–20); creatinine 1.4 mg/dl (0.6–1.1); fasting plasma glucose 256 mg/dl (70–130); serum Na 142 mmol/l (135–145); Cl 103 mmol/l (98–108); K 4.5 mmol/l (3.2–4.4); Ca 2.3 mmol/l (2.00–2.50); P 2.6 mg/dl (2.6–4.6); total cholesterol 292 mg/dl (120–219); triglyceride 114 mg/dl (30–149); LDL-cholesterol 179 mg/dl (70–139); C-reactive protein 0.06 mg/dl (0.3>).

Hypothyroidism was suspected because of increased serum CK and cholesterol levels. Low concentrations of free T3 and free T4, associated with low TSH level suggested central hypothyroidism. In order to investigate the cause of hypothyroidism, endocrinological tests were performed (Tables 1 and 2). Moreover, immunological data were evaluated because we speculated that these abnormalities could be based on autoimmune disorders (Table 3). As shown in Tables 1 and 2, secretions of GH, PRL and TSH were impaired, indicating that CPHD existed. Although insulin tolerance test is considered as the golden standard to diagnose adult GH deficiency, we did not implement it, since it was expected that sensitivity to the test would fall off in this patient who was used to hypoglycemic attack due to DM. Low concentration of serum free testosterone (free T), associated with increased FSH and LH levels suggested primary hypogonadism. Additionally, poor responses of free T to human chorionic gonadotropin (HCG) also supported the diagnosis. Magnetic resonance imaging (MRI) of the pituitary gland showed no specific finding (Fig. 1). Furthermore, high titers of serum anti-GAD antibody and anti-islet cell antibody, late onset of DM, and very low urinary excretion of c-peptide strongly suggested that this patient suffered from SPIDDM, a subtype of type 1 DM.

It is generally accepted that SPIDDM is frequently complicated by other autoimmune diseases and that a certain type of HLA is involved in progression of SPIDDM [6, 7]. As shown in Table 3, other antibodies except anti-GAD and anti-islet cell antibodies, and HLA molecules associated with SPIDDM were not detectable, but the HLA types of this patient were the same as those frequently detected in lymphocytic hypophysitis [4]. Although we investigated several series of serum anti-pituitary antibodies using human and rat pituitaries, and human GH which were recently considered to cause lymphocytic hypophysitis [8], none could be detected. To detect other autoantibodies, we performed western blot analysis using patient's serum and porcine organs. However, we could detect only a single band at 65 kD, which was considered to be anti-GAD antibody (data not shown). We further performed immunohistochemical studies with patient's serum and human pituitary preparation obtained from surgical specimen, but no specific staining was detected.

The pattern of pituitary hormone deficiency in this patient mimics congenital CPHD due to *Pit-1* gene

Table 1. Endocrinological Data on Admission

	Patient's data	normal range		Patient's data	normal range
GH (ng/ml)	0.05	0.42>	5α-DHT (ng/ml)	0.47	0.2–1.0
Prolactin (ng/ml)	1.0>	1.5–9.7	Free T (pg/ml)	7.3	14–40
LH (mIU/ml)	15	1.8–5.2	DHEA-S (ng/ml)	352	140–2240
FSH (mIU/ml)	68	2.9–8.2	Cortisol (μg/dl)	12.5	4.0–18.3
ACTH (pg/ml)	9.0	9–52	Renin (activated; pg/ml)	17.0	2.49–21.4
TSH (μU/ml)	0.32	0.34–3.5	Aldosterone (pg/ml)	63	29.9–159
ADH (pg/ml)	0.7	0.3–3.5	<Urine>		
IGF-1 (ng/ml)	18	75–218	CPR (μg/day)	1.7	20.9–198
Somatostatin (pg/ml)	6.8	1.0–12	17-KS (mg/day)	3.8	4.6–18.0
Free T3 (pg/ml)	1.00	2.47–4.34	17-OHCS (mg/day)	5.4	3.4–12.0
Free T4 (ng/dl)	0.28	0.97–1.79	Cortisol (μg/day)	19.3	11.2–80.3

IGF-1; insulin-like growth factor
DHT; dehydrotestosterone
DHEA-S; dehydroepiandrosterone sulfate
CPR; C-peptide
T; testosterone

Table 2. Endocrinological Provocation Tests

GRH, GnRH, TRH, CRH stimulation test (GRH 0.1 mg, GnRH 0.1 mg, TRH 0.5 mg, CRH 0.1 mg i.v.)

	0	15	30	60	90	120	(min)	normal range
GH (ng/ml)	0.05>	0.05>	0.05>	0.05>	0.05>	0.05>		(0.42>)
FSH (mIU/ml)	79	82	85	95	98	110		(2.9–8.2)
LH (mIU/ml)	12	22	27	30	34	37		(1.8–5.2)
TSH (μU/ml)	0.32	0.40	0.42	0.36	0.35	0.34		(0.5–3.5)
PRL (ng/ml)	0.05>	0.05>	0.05>	0.05>	0.05>	0.05>		(1.5–9.7)
ACTH (pg/ml)	9.0	52.2	55.7	44.6	52.3	55.9		(9–52)
Cortisol (μg/dl)	12.5	15.3	16.4	19.1	17.5	17.5		(4.0–18.3)

Arginine stimulation test (arginine HCl 30 g d.i.v.)

	0	30	60	90	120	(min)	normal range
GH (ng/ml)	0.05>	0.05>	0.05>	0.05>	0.05>		(0.42>)

ACTH stimulation test (tetracosactide acetate 1.0 μg. i.v.)

	0	30	60	(min)	normal range
cortisol (μg/dl)	18.9	25.0	21.1		(4.0–18.3)
aldosterone (pg/ml)	62	94	61		(30–159 recumbency)

HCG stimulation test (chorionic gonadotropin 3000 unit/3 days. i.m.)

	1	2	3	4	5	6	(day)	normal range
HCG	○	○	○					
Free T (pg/ml)	3.3	4.2	3.8	3.4	2.6	3.0		(14–40)

i.v.; intravenous injection d.i.v.; drip intravenous injection i.m.; intramuscular injection

mutation. Hence we investigated his *Pit-1* gene sequence. In order to investigate the mutation of *Pit-1* gene, genomic DNA was isolated from leukocyte and analyzed directly with polymerase chain reaction method. Although all six exons were surveyed, there was no mutation of the *Pit-1* gene. In our preliminary data using ultrasensitive enzyme immunoassay of GH [9], basal GH levels were detectable, but GH responses to GRH were impaired in the patient with complete deficiency of *Pit-1* function. GH responses to GRH were measured again in this case using this GH assay system. As shown in Table 4, basal and stimulated

Table 3. Immunological Data on Admission

anti-GAD antibody	64,600 U/ml	A locus	A2
anti-islet cell antibody	163,840 U/ml	B locus	B54 (22) B35
anti-insulin antibody	(–)	C locus	Cw1 Cw3
anti-IA-2 antibody	(–)	DR locus	DR2 DR8
anti-TPO antibody	(–)	IgG (mg/dl)	1606
anti-thyroglobulin antibody	(–)	IgA (mg/dl)	271
anti-TSH-R antibody	(–)	IgM (mg/dl)	147
anti-pituitary antibody	(–)	C3 (mg/dl)	61.0
anti-nuclear antibody	(–)	C4 (mg/dl)	24.0
anti-DNA antibody	(–)	CH50 (U/ml)	35.5

GAD; Glutamic acid decarboxylase TSH-R; thyroid stimulating hormone-receptor
IA-2; insulinoma-associated antigen-2 TPO; thyroid peroxidase

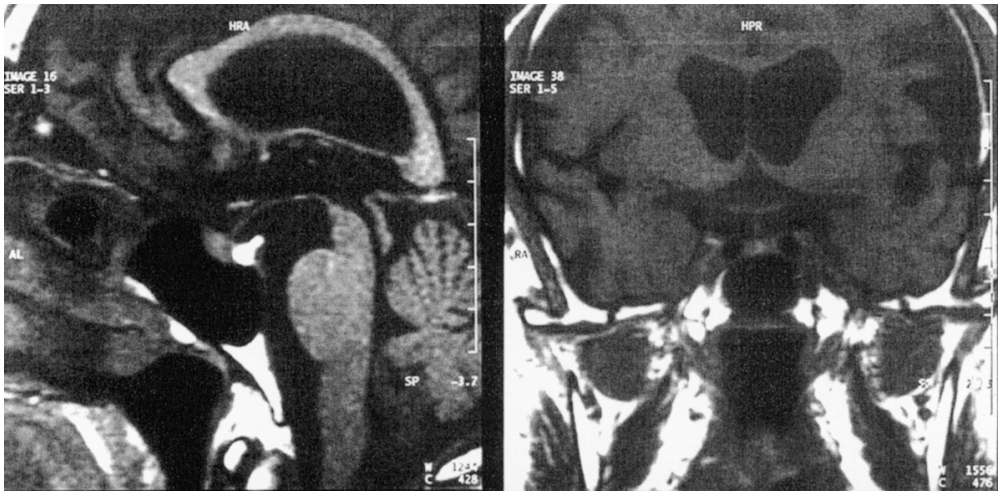

Fig. 1. Magnetic resonance imaging of the pituitary gland. Left, Sagital image. Right, Coronal image. A normal stalk and hypophysis are visible.

Table 4. Endocrinological Provocation Test

GRH stimulation test (GRH 0.1 mg i.v.)

	0	15	30	60	90	120	(min)
GH (pg/ml)	21.0	32.2	29.8	29.0	29.8	26.8	

These data were measured by means of ultrasensitive enzyme immunoassay.

GH levels could be measured, and significant GH responses to GRH could be observed, although their concentrations were very low. These data indicated that the present case did not have complete deficiency of *Pit-1* function.

After evaluation of adrenal function, the patient was treated with levothyroxine. He was finally discharged on a maintenance dose of levothyroxine (50 μg/day) after induction of basal bolus insulin therapy. One year after, serum free T3 and free T4 levels have increased up to normal range, while TSH level remains low.

Discussion

SPIDDM is defined as 1) late onset, 2) continuously positive anti-GAD antibody, anti-IA-2 antibody and/or anti-islet cell antibody, 3) slow progress of type 1 DM, and 4) possible to obtain good control of DM using diet therapy and oral hypoglycemic agents at the early stage of onset. The onset of DM in this patient was presumed to be at an advanced age. In addition, titers of both anti-GAD antibody and anti-islet cell antibody were high, and he was treated with oral hypoglycemic agents at the beginning. Such evidence strongly indi-

cated that he suffered from SPIDDM.

Type 1 DM including SPIDDM is usually known to be an autoimmune disease, and is often complicated by other autoimmune diseases. The present case showed hypogonadism due to aging and CPHD; however, no other autoantibodies were detected. In order to address whether these impaired GH, TSH and PRL secretions were elicited by autoantibodies or not, we performed some immunological studies. A single band was detected with a size of 65 kD, which we supposed anti-GAD antibody. There was a high possibility that the band detected with western blotting was intracellular GAD, hence we could not obtain direct evidence of autoimmune disease on immunostaining.

To clarify the cause of CPHD in this case, we sought for his prior history of trauma, tumor, medical side effect, emotional disturbance, cerebrovascular disorder and inflammation, but the reason remained unclear. In addition, MRI of the pituitary showed no significant findings and the pattern of CPHD in this patient was different from those often impaired. However, a previous study on patients with lymphocytic hypophysitis reported that the cases who showed normal MRI findings were 3.4%, and that dysfunction of ACTH or gonadotropins were detected in 61.1% and 38.9%, respectively [4]. Moreover, it showed that IDDM was present in 2 of 124 patients with lymphocytic adenohypophysitis, and in 20 cases who were examined the human leukocyte antigens, A2, B35, CW1, CW3 and DR2 also detected in the present case were observed in 10, 4, 4, 4 and 4 cases, respectively [4]. This finding indicates that lymphocytic hypophysitis has a close link with certain HLA types, and that the HLA types frequently detected in lymphocytic hypophysitis were recognized in the present case. Such evidence does not absolutely prove the existence of hypophysitis, and the diagnosis of hypophysitis could not be made with certainty. However, we think that they indicate the possibility that CPHD in this case was caused by lymphocytic hypophysitis.

The present case showed a high concentration of serum FSH. Some cases who had FSH-producing pituitary tumors have been reported. Dizon and Vesely reported a 61-year-old male who showed high plasma levels of FSH, LH, PRL and total T [10]. In addition, some reports showed female cases who showed high levels of FSH and estradiol [11–13]. Moreover, Shimon *et al.* reported a case of a 28-year-old female with a high concentration of FSH and a normal level of estradiol [14]. These case reports indicate that high plasma levels of FSH induce hyper- or normal secretion of sex hormones. On the other hand, Haji *et al.* showed that serum free T concentration declined linearly and FSH level increased with aging in healthy Japanese men [15]. In addition, the Sertoli cell function of diabetic patients was shown to be decreased in comparison with healthy subjects [16]. In the present case, the plasma free T level was very low and the serum FSH level was conversely high. Furthermore, LH-RH administration elicited a normal induction of FSH and treatment with HCG for 3 days increased T concentration only very slightly. These data suggest that increase in FSH level was caused by the decline of T, and that hypogonadism was the fundamental cause.

The pituitary-specific transcription factor *Pit-1* is known to play a key role in the regulation of biosynthesis of PRL, GH and TSH [17]. In addition, previous reports indicated that in some types of *Pit-1* gene mutation, GH and PRL secretion are completely deficient, while TSH secretion is partially maintained [18, 19]. Moreover, it is reported that heterogenous mutation elicits adult onset *Pit-1* disorder. Therefore we surveyed all six exons of *Pit-1* gene in this patient, but no mutation was detected. In addition, the results of ultrasensitive enzyme immunoassay of GH did not strongly support the involvement of *Pit-1* disorder. It was then considered that a direct pathophysiological role of *Pit-1* was less important in the present case.

It is commonly known that among pituitary hormones, ACTH could be relatively obstructed. On the other hand, PRL is rarely impaired in the caase of hypophysitis [4]. The CPHD of this case differs entirely from the typical pattern and it has rarely been reported in cases of hypophysitis. Although it is unclear that the CPHD of this case was elicited by the functional disorder of *Pit-1*, the pattern of CPHD closely resembles it. Previous reports showed two cases that had complete GH and PRL deficiency and incomplete TSH deficiency [18, 19]. Both cases had heterozygous C-T substitutions in the *Pit-1* gene, which resulted in a proline to leucine substitution. Two mutations resulted at different positions, one at codon 14 and the other at codon 24, but both mutations in the two patients were located in the same, highly conserved region of the main transactivation domain in *Pit-1* [20]. Disruption of the predicted major transactivation domain by the amino acid substitution severely compromises transactivation of *Pit-1* target genes. On the other

hand, some reports showed that several extracellular factors could elicit functional abnormality of *Pit-1*. Retinoic acid, GHRP-6 and ghrelin have been shown to have an important role in activation of *Pit-1* [21, 22]. As mentioned above, type 1 DM often complicate other autoimmune diseases, hence functional disorder of these molecules may be caused immunologically. However, to our knowledge, the unique pattern of CPHD shown in the present case has not been reported to be induced by an exogenous cause, that is to say, a factor that compromises the transactivation of *Pit-1* target genes has not been identified. Although previous reports have suggested that the disorder of certain factors which regulate *Pit-1* function might induce CPHD, these evidences predict only the possibility to induce CPHD, and unique pattern of CPHD in the present case could not have been induced. We consider that an unknown factor would have elicited acquired functional disorder of *Pit-1* if the cause of CPHD in the present case is associated with *Pit-1*. Hence further study is required to elucidate the pathogenesis of this patient.

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