Isolated Adrenocorticotrophic Hormone Deficiency Associated with Growth Hormone Deficiency and Empty Sella

Toshimitsu HATAZOE, Yoshio MURAKAMI, Itsumi UMAKI, Motoi SOHMIYA, Hong-Yi HU and Yuzuru KATO

A 38-year-old man had an acute onset of consciousness loss, pyrexia and hyponatremia. Plasma Adrenocorticotrophic Hormone (ACTH) and cortisol levels were low. Plasma ACTH failed to respond to corticotropin-releasing hormone (CRH) and insulin-induced hypoglycemia whereas i.m. injection of ACTH-Z raised plasma cortisol. Plasma insulin-like growth factor-I (IGF-I) and urine growth hormone (GH) concentrations were also low and plasma thyroid-stimulating hormone (TSH) level was rather elevated. Plasma IGF-I and TSH levels were not completely normalized by glucocorticoid (GC) replacement alone although plasma GH responses to pharmacological stimuli were normalized. The GC replacement in combination with daily s.c. injection of recombinant human GH (rhGH) not only normalized plasma IGF-I and IGF-BP-3 levels, but also further lowered the plasma TSH level, possibly due to an increased T_4/T_3 conversion, which resulted in a beneficial change in body composition. (Internal Medicine 34: 688–691, 1995)

Key words: recombinant human growth hormone, replacement, body composition, corticotropin-releasing hormone (CRH)

Introduction

It has been reported that isolated adrenocorticotrophic hormone (ACTH) deficiency (ICD) (1) may be accompanied by deficiencies of other pituitary hormones. Impairment of growth hormone (GH) secretion was noted in 20 to 30% of ICD patients and was normalized after glucocorticoid (GC) replacement therapy (2, 3).

In the present study, we report an adult male case with ICD associated with GH deficiency in whom GH secretion was carefully investigated before and after GC replacement with or without daily s.c. injection of recombinant human GH (rhGH).

Case Report

A previously healthy 38-year-old man was brought to the local emergency hospital because of unconsciousness, pyrexia and vomiting. Laboratory data showed severe hyponatremia (107 mEq/L) and serum cortisol was not detectable (less than 1 µg/dl). These symptoms and signs were corrected by GC administration. He was transferred to our hospital for further examination.

On admission, his height was 168.5 cm and body weight (BW) was 53.5 kg. His body temperature was 36.3°C and pulse

rate was 68/min. Blood pressure was 104/60 mmHg. Chest and abdomen were normal. Neurological examination failed to reveal abnormality. Axillary and pubic hair was preserved. No pigmentation was noted in the skin and oral mucous membrane.

Laboratory investigation revealed mild anemia (Hb 12.7 g/dl) and low glycohemoglobin level (HbA_{1c} 3.9%). Serum Na, K and Cl levels were 142 mEq/L, 4.0 mEq/L and 106 mEq/L, respectively.

Endocrinological examination revealed low plasma ACTH and cortisol levels (less than 5 pg/ml and less than 1 µg/dl, respectively). Plasma GH and insulin-like growth factor-I (IGF-I) levels were considerably low and urine GH was undetectable (less than 3 pg/ml). Plasma thyroid-stimulating hormone (TSH) level was elevated (6.08 µU/ml) while serum triiodothyronine (T_3) and thyroxine (T_4) levels were within the normal range. Plasma luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL) and antidiuretic hormone (ADH) levels were all normal.

Plasma cortisol and urine 17-hydroxycorticosteroid (17-OHCS) increased on the standard ACTH test (ACTH-Z 1 mg, i.m. for 3 days) from less than 1 µg/dl to 12 µg/dl and from 0.4 mg/day to 14.9 mg/day, respectively. However, plasma cortisol did not respond to the rapid ACTH test (ACTH₁₋₂₄ 0.25 mg, i.v.). Plasma ACTH and cortisol did not respond to such

From the First Division, Department of Medicine, Shimane Medical University, Izumo

Received for publication September 14, 1994; Accepted for publication March 29, 1995

Reprint requests should be addressed to Dr. Toshimitsu Hatazoe, the First Division, Department of Medicine, Shimane Medical University, 89-1 Enya-cho, Izumo 693

provocative stimuli as corticotropin-releasing hormone (CRH), CRH+arginine vasopressin (AVP), CRH+lysine vasopressin (LVP), and repeated CRH and insulin-induced hypoglycemia (Table 1). Plasma LH, FSH and ADH well responded to LH-releasing hormone (LHRH) and 5% NaCl infusion, respectively. Plasma TSH and PRL showed exaggerated responses to thyrotropin-releasing hormone (TRH) (Table 2).

High resolution computed tomography (CT) scan with enhancement and magnetic resonance imaging (MRI) examination showed an empty sella.

GH secretion was further evaluated by such provocative stimuli as GH releasing hormone (GRH), insulin-induced

hypoglycemia and insulin-propranolol stimulation before and after GC replacement. Before GC replacement, peak plasma GH levels after GRH, insulin-induced hypoglycemia and insulin-propranolol stimulation were 7.1 ng/ml, 2.5 ng/ml and 1.5 ng/ml, respectively. When these provocative tests were repeated 2 to 4 weeks after GC replacement (hydrocortisone 20 mg/day), peak plasma GH levels after GRH, insulin-induced hypoglycemia and insulin-propranolol were 13.3 ng/ml, 7.2 ng/ml and 14.8 ng/ml, respectively (Fig. 1).

Daily profiles of plasma GH were determined one month and 7 months after GC replacement (hydrocortisone 10 mg/day). Plasma samples were obtained every 20 minutes and GH concentrations were determined by highly sensitive enzyme immunoassay (EIA) as described previously (4). There were some pulsatile increases in the night time plasma GH level, but the highest peak value was 4.7 ng/ml (one month) and 3.1 ng/ml (7 months), respectively. The mean plasma GH during 24 hours was 0.48 ng/ml (one month) and 0.63 ng/ml (7 months). During the GC replacement, low plasma IGF-I levels were maintained

Table 1. Basal and Stimulated Level of Plasma ACTH

Stimulation		Basal value (pg/ml)	Peak value (pg/ml)
Insulin	(0.05 U/kg BW, i.v.)	19	21
CRF	(100 µg, i.v.)	19	21
CRF	(100 µg, d.i.v.)	6	8
Repeated CRF	(100 µg, i.v. 3 days)	12	14
CRF + AVP	(CRF: 100 µg, i.v. AVP: 0.5 U, i.v.)	6	10
CRF + LVP	(CRF: 100 µg, i.v. LVP: 10 U, i.m.)	5	7

ACTH: adrenocorticotrophic hormone, AVP: arginine vasopressin, CRF: corticotropin-releasing factor, LVP: lysine vasopressin.

Table 2. Basal and Stimulated Levels of Other Pituitary Hormones

Hormones	Provocation test	Basal value	Peak value
TSH (µU/ml)	TRH (0.5mg i.v.)	6.31	47.53
PRL (ng/ml)	TRH (0.5mg i.v.)	7.7	80.6
	metoclopramide (20mg i.v.)	10.7	149.4
LH (mIU/ml)	LH-RH (100 µg i.v.)	2.1	29.5
FSH (mIU/ml)	LH-RH (100 µg i.v.)	2.7	6.5
ADH (pg/ml)	Hypertonic saline infusion (5% NaCl)	1.7	4.1

ADH: antidiuretic hormone, FSH: follicle-stimulating hormone, LH: luteinizing hormone, LH-RH: luteinizing hormone-releasing hormone, PRL: prolactin, TRH: thyrotropin-releasing hormone, TSH: thyroid-stimulating hormone.

Figure 1. Plasma GH responses to GRH (100 µg, i.v., top panel), insulin-induced hypoglycemia (0.05 U/kg BW, i.v., middle panel) and insulin-propranolol (0.1 U/kg BW, i.v. + 10 mg d.i.v.) test (bottom) before (---) and after (—) glucocorticoid replacement.

Figure 2. Plasma IGF-I and TSH levels after GC replacement therapy.

Figure 4. Changes in body composition during rhGH replacement. Body composition was analyzed by means of bioimpedance analysis (BIA) method.

(77 ng/ml) and plasma TSH remained high (Fig. 2). Serum T_3 and free T_4 (ft_4) levels were not changed and urine GH excretion for 24 hours remained less than the minimal detect-

Figure 3. Plasma IGF-I, IGFBP-3, TSH, and serum T_3 and ft_4 levels after rhGH replacement therapy. Glucocorticoid was continuously replaced (15 mg/day).

able concentration (0.3 pg/ml) during GC replacement alone (data not shown).

We obtained written consent for the rhGH replacement therapy from this patient, and rhGH was injected daily s.c. (0.01 U/kg BW; for the initial four weeks, followed by 0.03 U/kg BW for the next four weeks) along with hydrocortisone. Plasma IGF-I and IGF binding protein-3 (IGFBP-3) were normally increased from 101 ng/ml to 230 ng/ml and 1.63 μg/ml to 2.48 μg/ml, respectively (Fig. 3).

During the GC replacement therapy with rhGH, plasma TSH decreased from 8.3 μ U/ml to 3.1 μ U/ml while serum T_3 levels increased from 80 ng/dl to 100 ng/dl without any considerable change in serum free T_4 (Fig. 3). In addition, his lean body mass determined by bioimpedance analysis (BIA) (5) was increased from 48 to 51 kg whereas fat mass decreased from 7 to 4 kg (Fig. 4).

Discussion

GC exerts dual effects on GH secretion. Pharmacological doses of GC inhibit growth and plasma GH responses to provocative stimuli while GC enhances GH release at the pituitary level (6).

It has been reported that GH secretion is impaired in 20–30% of the patients with isolated ACTH deficiency (2, 3). Giustina et al (7) reported that GH deficiency in patients with idiopathic ACTH deficiency is resolved during GC replacement therapy and that short-term GC deprivation impairs the GH response to GRH in these patients, suggesting that physiological plasma cortisol levels are necessary for a normal plasma GH response to provocative stimuli.

In the present study, we demonstrated that the impaired GH response to provocative stimuli was partly corrected by GC replacement alone, whereas spontaneous GH secretion determined by 24 hours blood sampling was not normalized even after 7 months of GC replacement therapy. Plasma IGF-I and IGFBP-3 levels were normalized 4 weeks after daily s.c. injection of rhGH. An increase in serum T_3 and a further decrease in plasma TSH were demonstrated in the course. It might be possible that GH and subsequently the normalized plasma IGF-I stimulated the peripheral conversion of T_4 to T_3 (8) and that the increased active hormone levels available thereby inhibited TSH secretion from the pituitary gland.

It is generally agreed that GH replacement therapy is beneficial for adult patients with GH deficiency. In the present patient, after 4 weeks of rhGH replacement, his lean body mass increased and fat mass decreased although his body weight was unchanged. These findings are the same as those of Whitehead et al (9), in that total body weight was not changed during rhGH treatment and that rhGH treatment had anabolic and lipolytic

effects. Salomon et al (10) also reported beneficial effects of GH replacement on body composition and metabolism in a randomized double-blind placebo-controlled trial of rhGH administration in GH-deficient adults.

In summary, we report a case of ICD, in which GC replacement alone failed to restore normal GH secretion. Daily s.c. injection of rhGH resulted in beneficial effects such as normalization of plasma IGF-I and IGFBP-3 levels as well as promotion of conversion of T_4 to T_3 and a change in body composition.

References

- 1) Sternberg A, Shechter FR, Segal HI. True pituitary Addison's disease: a pituitary unitrophic deficiency (fifteen-year follow up). *J Clin Endocrinol* **14**: 1519, 1954.
- 2) Hashimoto K, Nishioka T, Iyota K, et al. Hyperresponsiveness of TSH and prolactin and impaired responsiveness of GH in Japanese patients with isolated ACTH deficiency. *Folia Endocrinol* **68**: 1096, 1992.
- 3) Yamamoto T, Fukuyama J, Hasegawa K, Sugiura M. Isolated corticotropin deficiency in adults. Report of 10 cases and review of literature. *Arch Intern Med* **152**: 1705, 1992.
- 4) Sohmiya M, Kato Y. Renal clearance, metabolic clearance rate and half-life of human growth hormone in young and aged subjects. *J Clin Endocrinol Metab* **75**: 1487, 1992.
- 5) Hu H-Y, Yamamoto H, Sohmiya M, Abe T, Murakami Y, Kato Y. Body composition assessed by biochemical impedance analysis (BIA) and the correlation with plasma insulin-like growth factor I (IGF-I) in normal Japanese subjects and patients with acromegaly and GH deficiency. *Endocr J* **41**: 63, 1994.
- 6) Adams EF, Brajkovich IE, Mashiter K. Growth hormone and prolactin secretion by dispersed cell cultures of human pituitary adenomas: long-term effects of hydrocortisone, estradiol, insulin, 3,5,3'-triiodothyronine and thyroxine. *J Clin Endocrinol Metab* **53**: 381, 1981.
- 7) Giustina A, Romanelli G, Candrina R, Giustina G. Growth hormone deficiency in patients with idiopathic adrenocorticotropin deficiency resolves during glucocorticoid replacement. *J Clin Endocrinol Metab* **68**: 120, 1989.
- 8) Pirazzoli P, Cacciari E, Mandini, et al. Growth and thyroid function in children treated with growth hormone. *J Pediatr* **121**: 210, 1992.
- 9) Whitehead HM, Boreham C, McIlrath EM, et al. Growth hormone treatment of adults with growth hormone deficiency: results of a 13-month placebo controlled cross over study. *Clin Endocrinol* **36**: 45, 1992.
- 10) Salomon F, Cuneo RC, Hesp R, Sonksen PH. The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. *N Engl J Med* **321**: 1797, 1989.