A Case of Hypothalamic Adrenal Insufficiency Manifested Normal ACTH Response to Insulin-Induced Hypoglycemia

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Abstract. A low plasma ACTH response to insulin-induced hypoglycemia and an exaggerated and delayed plasma ACTH response to CRH stimulation have been considered as an indicator of hypothalamic hypopituitarism. We report a case of hypothalamic adrenal insufficiency which manifested normal ACTH response to insulin-induced hypoglycemia. This case provides important information to categorize hypothalamic adrenal insufficiency caused by abnormal regulation of CRH release.

Key words: ACTH, Hypothalamic adrenal insufficiency

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ADRENAL insufficiency results from dysfunction at one or more sites in the hypothalamic-pituitary-adrenal (HPA) axis. The distinction between pituitary and hypothalamic adrenal insufficiency is of diagnostic importance, and can usually be established using imaging studies, prolactin levels, or dynamic endocrine tests consisting of CRH test and insulin tolerance test (ITT) [1]. Hypoglycemic stress induced by ITT is a powerful but indirect stimulus to cortisol production via activation of hypothalamus. Therefore, low ACTH response to ITT in combination with delayed and exaggerated ACTH response to CRH suggests the presence of hypothalamic insufficiency [1–4].

Herein we report a patient with hypothalamic adrenal insufficiency who manifested normal ACTH response to ITT. This case provides us with important information to categorize hypothalamic adrenal insufficiency caused by abnormal regulation

of CRH release.

Case report

A 65-year-old Japanese woman was admitted with persistent nausea and general malaise after recovery from common cold. She had been weary from overwork for the four months prior to the appearance of symptoms. She had never received oral administration, injection or inhalation of corticosteroids, nor did she have a history of postpartum hemorrhage, but she had experienced repeated episodes of aseptic meningitis at the age of 43, 52, 59 and 60. Her menopause occurred at age 48.

Physical examination on admission revealed that she was 147.0 cm height and weighed 38.0 kg. Blood pressure was 80/52 mmHg and pulse rate was 70/min. Consciousness was clear. Several patches of depigmentation were noted on the skin of anterior chest, upper back and both forearms. The pubic hair was preserved, but the axillary hair was lost. No goiter was palpable. There was no abnormal finding in the chest or abdomen. Laboratory studies on admission disclosed hyponatremia (127 mEq/l) and normochromic normocytic anemia (Hb 10.3 g/dl).

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Other blood chemistry findings were all within normal limits. Her symptoms, physical and laboratory findings suggested the presence of adrenal insufficiency, and the endocrinological examination revealed low serum cortisol level (less than 1.0 $\mu\text{g}/\text{dl}$) and normal ACTH level (27.2 pg/ml). Adrenal insufficiency was diagnosed and she received hydrocortisone intravenously. She made a rapid recovery from the symptoms and hyponatremia after the therapy. She was well managed by oral administration of hydrocortisone at a daily dose of 10 mg within one week after the therapy had begun.

Further endocrinological examination was performed under discontinuance of hydrocortisone (normal values are given in parentheses). Plasma ACTH level at 0600 h was 37.6 pg/ml (4.4–48.0 pg/ml), with a simultaneous serum cortisol level of 3.9 $\mu\text{g}/\text{dl}$ (5.3–24.5 $\mu\text{g}/\text{dl}$). Dehydroepiandrosterone sulfate level was 120 ng/ml (800–4600 ng/ml). Urinary 17-hydroxycorticosteroid level was 2.4 $\text{mg}/24\text{ hr}$ (1.9–6.1 $\text{mg}/24\text{ hr}$), and Urinary free cortisol level was 25 $\mu\text{g}/24\text{ hr}$ (31–99 $\mu\text{g}/24\text{ hr}$). Urinary 17-ketosteroid level was 0.2 $\text{mg}/24\text{ hr}$ (3.1–8.8 $\text{mg}/24\text{ hr}$). Circadian rhythms of both ACTH and cortisol had abnormal patterns of increase at 1600 h. Serum aldosterone level was less than 25.0 pg/ml (56.9–150.3 pg/ml) and plasma renin activity was 0.15 $\text{ng}/\text{ml}/\text{hr}$ (0.5–2.0 $\text{ng}/\text{ml}/\text{hr}$). Urinary aldosterone level was 1.2 $\mu\text{g}/24\text{ hr}$ (3.0–11.4 $\mu\text{g}/24\text{ hr}$). Urinary adrenaline, noradrenaline and dopamine levels were 2 $\mu\text{g}/24\text{ hr}$ (3–15), 95 $\mu\text{g}/24\text{ hr}$ (26–121) and 372 $\mu\text{g}/24\text{ hr}$ (190–740), respectively. Serum GH level was 1.8 ng/ml (0.6–3.7 ng/ml) and somatomedine C level was 40.0 ng/ml (121–436 ng/ml). TSH level was 2.62 $\mu\text{IU}/\text{ml}$ (0.35–3.73 $\mu\text{IU}/\text{ml}$), free triiodothyronin level was 1.2 pg/ml (2.1–4.0 pg/ml) and free thyroxine level was 0.7 ng/dl (0.8–1.8 ng/dl). Serum LH and FSH levels were 1.0 mIU/ml (7.5–56.2 mIU/ml) and 3.8 mIU/ml (9.1–124.7 mIU/ml), respectively. Estradiol level was less than 10.0 pg/ml , and prolactin level was 67.3 ng/ml (less than 15 ng/ml).

Rapid ACTH test (Cortrosyn 0.25 mg, i.v.) revealed delayed and low response of serum cortisol. However, serum cortisol and urine 17-hydroxycorticosteroid increased on the standard ACTH test (Cortrosyn Z 1 mg, i.m. for 3 days). A single administration of human CRH (100 μg , i.v.) induced exaggerated and delayed ACTH response (Fig. 1,

top). Following insulin-induced hypoglycemia (regular insulin 0.05 U/kg), a test examining stress-mediated ACTH release, the plasma ACTH level rose to 101.0 pg/ml , a normal response (Fig. 1, bottom). The cortisol response to insulin-induced hypoglycemia was slightly low and that to CRH stimulation revealed delayed pattern. While the GH response to insulin-induced hypoglycemia was low rising to 4.4 ng/ml , the response after injection of GH releasing hormone (GRF 100 μg , i.v.) was almost normal rising to 14.0 ng/ml . The response of LH and FSH to a single administration of LHRH (100 μg , i.v.) was low. However, an augmented response of LH and FSH to LHRH was observed after five successive days of LHRH pretreatment (LHRH 100 $\mu\text{g}/\text{day}$, i.m.). A peak rise in LH level was 10.7 mIU/ml and that in FSH level was 28.1 mIU/ml . Serum TSH showed low and delayed response to TRH (500 μg , i.v.) rising to a peak of 3.95 $\mu\text{IU}/\text{ml}$ at 90 minutes after injection (basal: 2.28 $\mu\text{IU}/\text{ml}$). Serum prolactin showed low response to TRH (500 μg , i.v.) rising to 92.1 ng/ml (basal: 75.1 ng/ml). Hypertonic saline infusion test (5% NaCl) revealed no response of anti-diuretic hormone (ADH) secretion to the increase of serum osmolality (Osm). ADH level and serum Osm at the beginning of the test were 0.4 pg/ml and 285 $\text{mOsm}/\text{kg H}_2\text{O}$, respectively. A peak rise in serum Osm was 303 mOsm/kg and the ADH level at that point was 0.3 pg/ml .

Antibodies against adrenal cortex and pituitary gland were not detected. Furthermore, anti-thyroglobulin autoantibody, anti-microsomal autoantibody and anti-glutamic acid decarboxylase antibody were negative.

MRI examination of the brain showed partial empty sella. No abnormal findings were detected in the hypothalamus.

The diagnosis of hypothalamic panhypopituitarism was made in this patient. She has been in good condition by the daily administration of hydrocortisone (10 mg) alone.

Discussion

Elevated serum prolactin level and increases in pituitary hormone release after direct or successive stimulation of pituitary gland with releasing hormones are consistent with hypothalamic damage as

CRH test ; CRH 100 μ g, i.v.

Insulin tolerance test : insulin, 0.05U/ml i.v.

BS: 85 mg/dl (0 min) $\rightarrow$ 29 mg/dl (30 min)

Fig. 1. Response of plasma ACTH and serum cortisol to CRH stimulation (top) and insulin-induced hypoglycemia (bottom).

a cause of hypopituitarism. In the present case, the symptoms of adrenal insufficiency induced by stress led to a diagnosis of hypothalamic pan-

hypopituitarism. The abnormal circadian rhythm of ACTH may also indicate the adrenal insufficiency of hypothalamic origin.

Low plasma ACTH response to insulin-induced hypoglycemia and exaggerated and delayed plasma ACTH response to CRH stimulation have been considered as an indicator of hypothalamic hypopituitarism [4]. However, in this case, the ACTH response to insulin-induced hypoglycemia was normal. This retention of stress-induced ACTH release would imply that the reserve of ACTH release regulator (CRH and other neurotransmitters) in hypothalamus was normal. Therefore, together with no appreciable anatomical abnormalities in hypothalamus on the MRI examination, we conjectured that some functional abnormalities (neuroendocrine abnormalities) in the hypothalamus may be the cause of adrenal insufficiency in this case.

The HPA axis manifests prominent circadian rhythmicity as well as episodic or pulsatile modes of hormone release [5]. The intermittency of secretory activity has been considered to help prevent down-regulation (desensitization) of the target cells by releasing factor or trophic agent [6, 7]. This helps to account for the pathogenesis of adrenal insufficiency in the present case. Namely, in this patient, although basal mode of CRH release was preserved, we speculated that intermittent burstlike CRH secretion from the hypothalamus were diminished. The subsequent loss of pulsatile ACTH release of long duration would then lead to the desensitization of adrenocortical cells, presenting secondary adrenal insufficiency [8, 9]. A stress mechanism of ACTH release could not possibly work to release the sufficient cortisol for the increased requirements.

Although we cannot definitively account for the etiology of hypothalamic disorder seen in this patient, it is possible that, together with the presence of the partial empty sella, her repeated episodes of aseptic meningitis might have affected the hypothalamus, disturbing the neuroendocrine regulation of pituitary hormones. It should be noted that viral infections can also alter neurotransmitter and/or neuroendocrine regulation [10]. Repeated viral infections in this patient might have altered a variety of inhibitory or excitatory neurochemical systems known to modulate hypothalamic CRH release.

An etiologic classification of hypothalamic adrenal insufficiency could be subdivided according to at least two abnormalities, CRH deficiency (decreased CRH reserve) and functional disturbance of CRH release. CRH deficiency has been well documented to be the result of destruction of hypothalamic tissue such as tumors, inflammation, or post-radiation. Primary hypothalamic CRH deficiency is another rare cause [4, 11], but as of yet we have only limited information on the functional disturbance of CRH release. The mild central adrenal insufficiency observed in patients with chronic fatigue syndrome may be classified as a functional disturbance of CRH release [12]. Neurobiological regulation of CRH-ACTH release has not been elucidated, and the clinical significance of diminished pulsatile ACTH release represents an area for future investigation. The present case thus provides important information to categorize hypothalamic adrenal insufficiency caused by abnormal regulation of CRH release.

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