Reversible Pituitary Dysfunction in a Patient with Cushing’s Syndrome Discovered as Adrenal Incidentaloma

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Abstract. We report a 45-year-old woman with Cushing’s syndrome showing reversible pituitary dysfunction. Left adrenal tumor was incidentally discovered by a screening examination of abdominal computed tomography. Although this patient lacked typical Cushingoid features except hypertension and leg edema, endocrine examinations revealed moderate suppression of plasma ACTH (~6.3 pg/ml) with relatively high levels of serum cortisol (~22.9 μg/dl) without normal circadian rhythm. Plasma ACTH failed to respond to either CRH or metyrapone, and dexamethasone failed to suppress her daily steroid production. Surgical removal of left adrenocortical adenoma and 6-month replacement of hydrocortisone have ameliorated both ACTH and cortisol responses to CRH loading test. Postoperative responses of TSH and GH to TRH and GRH, respectively, were two fold higher than the preoperative levels. In contrast, basal and TRH-induced levels of serum PRL were decreased after surgery although both the basal and stimulated PRL levels were markedly high before surgery. In addition, gonadotropin response to GnRH examined in the same ovarian cycle was decreased in accordance with an increase in serum estradiol and progesterone levels after surgery. Improvement of hypercortisolemia even in a moderate case of Cushing’s syndrome not only ameliorated hypertension, obesity and glucose intolerance, but also restores the accompanying dysfunctions of anterior pituitary, suggesting the clinical importance of early discovery and treatment of functioning adrenocortical incidentalomas.

Key words: Cushing’s syndrome, Prolactin (PRL), Gonadotropin, Adrenocorticotropin (ACTH), Hypercortisolemia, Incidentaloma

Anterior pituitary functions can be affected by endogenous as well as exogenous glucocorticoids to greater or lesser degree. In particular, blunted response of TSH secretion by excessive glucocorticoids has been widely recognized [1, 2] and this phenomenon is also observed in patients with Cushing’s syndrome [3, 4]. Subsequent research has shown that pituitary responses of TSH and GH were likely to be impaired by glucocorticoid excess in such Cushing conditions [5–7]. The difference of secretory capacity of anterior pituitary hormones in the patients with hypercortisolemia due to Cushing’s syndrome has been demonstrated in Demura et al. [6] and Hashimoto [7], which shows the presence of a certain suppressibility of the anterior pituitary hormones caused by Cushing’s syndrome.

We herein showed dynamic changes in pituitary hormones in a patient with Cushing’s syndrome caused by adrenocortical adenoma before as well as after surgery. This case provides important evidence that reversible dysfunction of anterior pituitary can be observed even in a moderate case of Cushing’s syndrome [8, 9]. This report extends our understanding of the effect of hypercortisolemia on the secretory capacity of pituitary hormones, and indicates that incidentally-discovered adrenal tumors, so-called adrenal incidentalomas [10], should be carefully evaluated with regard to excess steroid production.
Case Report

A 45-year-old Japanese woman, who had been treated with antihypertensive drugs and diuretics for hypertension, leg edema and weight gain (~9 kg for 1 year), incidentally underwent CT scan for a screening examination. Abdominal CT revealed a left adrenal tumor, which brought this patient to our hospital for further examination. Her past medical history was negative except one-year medication for hypertension and her family history was unremarkable. Her physical status on admission was height 154 cm, body weight 69.2 kg and body mass index 29.2 kg/m². Blood pressure was 146/96 mmHg, pulse rate was regularly ~80 bpm, and brachial-ankle pulse wave velocity (baPWV) index was very high (left and right; 1630 and 1722 cm/s, respectively) for her age-matched score. Her complaint of leg edema was not remarkable on admission.

Fig. 1. Radiological findings of left adrenocortical tumor. A) Plain abdominal CT, B) enhanced CT scan, C) ultrasonography and D) 131I-adosterol scintigraphy. Arrows indicate the adrenal mass.

Fig. 2. Endocrine profiles of preclinical Cushing’s syndrome. A) Daily changes of plasma ACTH and serum cortisol levels (shown as mean ± SEM) and the effect of 1.5 g metyrapone (Met) administration. B) Effects of 2 and 8 mg dexamethasone (Dex) on urinary 17-hydroxycorticosteriod (U-17OHCS) and 17-kedosteroid (U-17KS) levels.
The patient showed no Cushingoid specific features including moon face, central obesity, buffalo hump, striae cutis and specific skin lesions including pigmentation and fragility, muscle weakness, or hirsutism, but her menstruation became irregular for one year. Laboratory examinations revealed lack of eosinophil and impairment of glucose tolerance. Electrolytes levels, liver and renal functions and bone density in her lumbar spine were found to be normal. Adrenal CT exhibited a left adrenal mass sized ~3 cm in diameter (Fig. 1A) and barely enhanced (Fig. 1B), while the right adrenal gland was normally detected. Left adrenal tumor was observed as a low-echoic mass by ultrasound examination (Fig. 1C). Abdominal scintigraphy using $^{131}$I-adosterol exhibited a fine accumulation in the left adrenal region (Fig. 1D). On endocrine examinations, serum cortisol concentrations at 8:00 a.m. were within upper limit of normal range (mean ± SEM: 22.9 ± 1.2 μg/ml, n = 5; normal, 8–25), while plasma ACTH levels were relatively lowered (6.25 ± 0.3 pg/ml, n = 5; normal, 9–52). Dehydroepiandrosterone sulfate (DHEA-S) level was low at 12 μg/dl (normal: 21–212). Daily profile of ACTH and cortisol lacked normal circadian rhythm (Fig. 2A) and ACTH secretion was not induced by metyrapone (1.5 g). Dexamethasone (2 and 8 mg) failed to suppress daily secretions of urinary 17-hydroxycorticosteroid and 17-ketosteroid (Fig. 2B). Upon confirming the diagnosis with preclinical Cushing’s syndrome, left adrenalectomy was laparoscopically performed. The resected tumor (Fig. 3A) was pathologically diagnosed as an adrenocortical adenoma (Fig. 3B). Her blood pressure, baPWV score (left and right, 1210 and 1291 cm/s), glucose tolerance and menstruation have gradually normalized after surgery followed by the replacement therapy using a physiologic dose of hydrocortisone alone. As shown in Fig. 4, ACTH response (A) to CRH (100 μg iv.) has become markedly increased with semi-normalized

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**Fig. 3.** Pathological finding of resected left adrenal tumor. (A) Macroscopic finding and (B) its histological assessment using hematoxylin-eosin staining (× 400).

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**Fig. 4.** CRH loading test. Time-course response of ACTH (A) and cortisol (B) to CRH (100 μg iv.) injection was evaluated before (closed circles) and after adrenal surgery (open circles).
response of cortisol (B) after surgery, although none of ACTH and cortisol was responsive to exogenous CRH before surgery. The patient had no morphologic abnormality in the pituitary by MRI examination. The slightly blunted TSH induction by TRH (500 μg iv.) was clearly recovered up to 1.8-fold higher than the preoperative level (Fig. 5A, left). Thyroid dysfunction showing low FT3 with low TSH was also improved 6 months after surgery (Fig. 5, bottom). Before surgery, increased levels of serum PRL were found and TRH stimulation (500 μg iv.) superfluously induced PRL secretion (Fig. 5A, right). However, the excess of PRL secretion has become completely normal 6 months after treatment. GH response to GRH, which was moderately blunted before surgery, has been increased to two fold higher than the preoperative peak (Fig. 5B).

![Fig. 5. TRH and GRH loading tests. Time-course responses of TSH (A, left panel), PRL (A, right panel) and GH (B) to TRH (500 μg iv.) and GRH (100 μg iv.) injections, respectively, were evaluated before (closed circles) and after adrenal surgery (open circles). Lower panel shows changes in thyroid function before and after surgery.](image)

![Fig. 6. GnRH loading test. Time-course response of FSH (A) and LH (B) to GnRH (100 μg iv.) injection was evaluated before (closed circles) and after (open circles) adrenal surgery. Lower panel shows changes in estradiol (E2) and progesterone (P4) levels before and after surgery.](image)
As shown in Fig. 6, the increments of FSH (A) and LH (B) to GnRH (100 μg iv.) at her mid-follicular phase were marginally decreased compared to the preoperative response, while serum estradiol (E2) and progesterone (P4) levels (Fig. 6, bottom) were found to be increased 6 months after treatment.

Discussion

The functional reserve of the anterior pituitary was evaluated in patients with Cushing's syndrome by Hashimoto [7]. In that study, GH secretion in response to insulin-induced hypoglycemia and TSH release in response to TRH were impaired in most of the cases, while gonadotropin and PRL release to the stimuli of GnRH and TRH, respectively, were sufficiently preserved [7]. On the basis of improved levels of pituitary hormones after adrenalectomy, that study established the difference of susceptibility to hypercortisolemia among the pituitary hormones as follows: ACTH > GH > TSH > LH and FSH > PRL. From this point of view, Watanabe et al. have presented an interesting Cushing's case that showed suppression of all anterior pituitary hormones including LH, FSH and PRL before adrenal surgery, which were ameliorated after surgery [11], implying the prolonged hypersecretion of endogenous cortisol or undefined steroids may directly inhibit multiple secretion of anterior pituitary hormones.

The in vivo relationship between glucocorticoid and PRL was reported by Sower et al. [2] and Hubina et al. [12], showing that dexamethasone suppresses basal and TRH- or metoclopramide-induced PRL secretion in non-Cushing patients. Kasperlik-Zaluska and Jeske also presented a similar result that the PRL response to metoclopramide is suppressed in hypercortisolemia patients due to Cushing’s disease, which can be recovered by bilateral adrenalectomy [13]. Hence the pituitary capacity of PRL secretion seems to be diminished in conditions of hypercortisolemia. These findings were supported by an in vitro study showing that dexamethasone directly suppresses the PRL mRNA expression by rat pituitary lactotrope cells [14].

On the contrary, Meij et al. performed an intriguing in vivo study using dogs having a pituitary-dependent hyperadrenocorticism (PDH), an appropriate model of ACTH-dependent Cushing’s syndrome [15]. In their study, pituitary responses were evaluated by a combination stimulus of hypothalamic hormones, which showed that the PDH dogs had augmented PRL response clearly higher than normal dogs. Another in vivo study using the dogs with hyperadrenocorticism due to adrenocortical tumors (ATH) also exhibited increased levels of serum PRL [16], although the PRL secretion in the ATH dogs normally responded to exogenous bromocriptine or TRH [16]. Given that amelioration of hypercortisolemia by adrenalectomy has normalized serum PRL levels in our Cushing’s case, hypercortisolemia is most likely to be involved in the coexisting hyperprolactinemia.

The disturbance of PRL release in Cushing’s syndrome provides the insight that the endogenous dopamine signal, which negatively controls PRL release from the anterior pituitary, could be altered in the Cushing condition. However, it is also reported that hypothalamic as well as striatal dopamine contents were not significantly different among PDH, ATH and cortisone- or ACTH-treated dogs [17]. Taken together, the regulation of pituitary PRL secretion in Cushing’s syndrome seems individually divergent but closely associated with hypercortisolemia. This could be due to the difference of lactotrope sensitivity to glucocorticoid excess although the underlying mechanism remains to be clarified.

As for the gonadotropins, the capacity of gonadotropin to release FSH and LH during hypercortisolemia due to Cushing’s syndrome is either impaired or not altered in the previous reports [6, 7, 18]. Additionally, Lado-Abeal et al. found that menstrual abnormality in women with Cushing’s diseases can be correlated with hypercortisolemia rather than increased androgen levels caused by ACTH excess [19].

Our case showed rather blunted responses of gonadotropins to GnRH stimulation with increased levels of serum E2 and P4 after the surgical removal of adrenal tumor, indicating the possibility that hypercortisolemia directly suppressed the steroid synthesis in the ovary. In this regard, Suzuki et al. showed that hydrocortisone decreases the FSH-induced E2 and inhibin production by reducing the FSH sensitivity in rat granulosa cells [20]. Valli et al. further demonstrated that the E2 and P4 production in rat granulosa and/or thecal cells obtained from hydrocortisone-treated rats were significantly suppressed compared to normal rats through reducing activities of steroidogenic enzymes including 3β- and 17β-hydroxysteroid dehydrogenase [21]. Therefore, it is most likely that the reduction of ovarian
steroids by hypercortisolemia in vivo led to an enhanced response of gonadotropin secretion from the pituitary. Given that the physiologic dose of glucocorticoid replacement is important to preserve the anterior pituitary functions [22], early release of hypercortisolemia and its appropriate replacement are of great importance to maintain the normal hormonal axis comprised of hypothalamus, pituitary and peripheral endocrine glands.

Collectively, it appears that amelioration of systemic cortisol level can lead to a functional normalization of the hypothalamo-pituitary-adrenal/thyroid/gonadal axes in the Cushing state although there seems to be a variety of pituitary dysfunctions related to hypercortisolemia. This further suggests the clinical significance of early diagnosis and early removal of functional adrenocortical incidentalomas.

References