Glucocorticoid-Dependency on GH Secretion and Tumor Growth in a GH-Producing Pituitary Adenoma with Cushing’s Syndrome

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Abstract. We report a rare case of a 40-year-old woman with Cushing’s syndrome and acromegaly. At the age of 28 she was diagnosed with Cushing’s syndrome due to a left adrenal tumor concomitant with a GH-producing pituitary tumor. Before adrenal surgery her basal GH levels were extremely high and CT scanning revealed a high-density mass in the sella turcica. A 28 g left adrenocortical adenoma was removed by adrenalectomy. During the four months after the adrenalectomy, basal GH levels dramatically decreased and the high-density mass detected by CT scanning had disappeared but the basal GH levels and IGF-1 had not been normalized. She gradually became acromegalic in the twelve years after the adrenalectomy. At the age of 40 CT scanning showed reappearance of the pituitary tumor. In order to examine the glucocorticoid dependency on GH secretion, we compared the GH secreting pattern before and after oral 8 mg dexamethasone administration for 7 days. There was no difference between before and after dexamethasone administration in the GH secreting pattern, but basal GH levels were apparently increased after dexamethasone treatment. Transsphenoidal surgery was done and pathological examination showed a GH-producing pituitary adenoma. In vitro, dexamethasone increased GH secretion from the cultured GH-producing adenoma cells in a dose-dependent manner. In this case, both GH secretion and pituitary tumor growth seemed to be dependent on glucocorticoid.

Key words: Acromegaly, Cushing syndrome, Glucocorticoid, GH

Case Report

We studied a 40-year-old woman with Cushing’s syndrome and acromegaly. At the age of 28 she was diagnosed with Cushing syndrome due to a left adrenal tumor concomitant with a GH producing pituitary tumor. At that time she had moon face, acne, central obesity, amenorrhea, and hypertension, but there was no acromegalic feature. The basal cortisol level was 30 μg/dl. The plasma ACTH level was low and urinary excretion of 17-hydroxycorticosteroid (17-OHCS) increased. Neither urinary
17-OHCS nor plasma cortisol was suppressed after ingestion of 8 mg dexamethasone. A 50 g oral glucose tolerance test revealed overt diabetes mellitus. Before adrenal surgery basal GH levels were 138-232 ng/ml. Administration of TRH and LHRH produced a paradoxical GH increase. Levodopa and bromocriptine suppressed GH secretion. CT scanning revealed an 18 mm high-density mass in the sella turcica and bitemporal hemianopsia was recognized. These data indicated the presence of a GH-producing pituitary adenoma.

Surgical adrenalectomy was done to remove 28 g of the left adrenocortical adenoma. Three weeks later her blood pressure returned to the normal range and the response of blood glucose in a 50 g glucose tolerance test also became within normal limits. Two months later, the basal cortisol levels were 4.6-5.7 µg/dl and plasma ACTH levels increased to 48-51 pg/ml. Four months later, basal GH levels decreased dramatically to 26.4-47.7 ng/ml and the high-density pituitary mass seen on CT scanning had disappeared. The visual field defect was also improved but plasma GH levels and IGF-I had not been normalized.

She gradually became acromegalic during the next twelve years after the adrenalectomy. At the age of 40 CT scanning showed a 12 mm pituitary tumor again and she decided to undergo transsphenoidal surgery. At that time basal GH levels were 8.1-18.1 ng/ml. She had acromegalic features and her heel pad thickness was 23 mm. For further examination of glucocorticoid dependency on GH secretion, a series of endocrinological tests for the pituitary gland were done before and after 8 mg oral dexamethasone administration for the next 7 days. Before and after dexamethasone administration (Fig. 1A-C) there was no difference in the GH secreting pattern for GH-releasing hormone (GHRH), TRH.
and arginine infusion tests, but basal GH levels were apparently increased to 25.5-32.1 ng/ml after dexamethasone administration. Transsphenoidal surgery was done and pathological examination showed the presence of a GH-producing pituitary adenoma. After the operation both GH and IGF-1 were normal.

GH-secreting pituitary adenoma cells were cultured in MEM medium with 10% FCS in 96-well culture dishes. At the time of confluence, the medium was changed to MEM with various concentrations of dexamethasone. 24-hours after incubation, GH levels in the medium were measured and GH levels are adjusted to the DNA content of each well. 10⁻⁶ M dexamethasone significantly increased GH release from the pituitary adenoma cells (Fig. 2).

**Discussion**

It is very interesting that this case showed a dramatic decrease both in basal GH levels and in pituitary tumor size after adrenalectomy. The possibility of ectopic production of GH or GHRH from an adrenocortical adenoma was denied because the adrenal tumor tissue did not contain a sufficient amount of these hormones (Prof. L. A. Frohman, Chicago University). Furthermore, long-term glucocorticoid administration produced a rise in basal GH levels in this patient.

The role of glucocorticoid in the regulation of GH secretion may be biphasic. GH deficiency in patients with adrenocorticotropin deficiency resolves during glucocorticoid replacement [3]. It was also reported that cortisol stimulates GH production by human pituitary tissue in culture [4]. These data indicated that a physiological concentration of glucocorticoid is necessary for secretion of GH from the pituitary but the effect of glucocorticoid with concentrations over the normal range seems to be different. It was reported that both normal men chronically treated with pharmacological doses of glucocorticoids and patients with Cushing’s disease show blunted GH responses to various stimuli [2,5]. In patients with acromegaly, because baseline and stimulated GH levels are usually decreased by treatment with pharmacological doses of glucocorticoid [1], glucocorticoid over physiological concentrations may inhibit GH secretion in vivo. Even though the precise mechanism of the increase in basal GH levels in this acromegalic patient after dexamethasone ingestion is still unclear, an in vitro experiment showed that dexamethasone directly increased GH secretion from cultured GH-secreting adenoma cells. It is therefore possible that in this case both GH secretion and pituitary tumor size were dependent on glucocorticoid. In any case, further examination should be necessary to disclose the molecular mechanism of glucocorticoid dependency on GH secretion and tumor growth.

**References**