Paradoxical Prolactin Response to Growth Hormone-Releasing Hormone in a Patient with Hyperprolactinemia and Empty Sella

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Abstract. In a 30-year-old woman with amenorrhea due to hyperprolactinemia, serum PRL increased to twice the basal amount in response to growth hormone-releasing hormone (GHRH). Roentgenological studies revealed no pituitary adenoma but empty sella. Bromocriptine therapy normalized serum PRL and made the paradoxical response to GHRH disappear. The paradoxical response did not occur in any of eight other patients with hyperprolactinemia due to prolactinoma. Although this case is rare, GHRH stimulates PRL as well as GH release remarkably in some cases with hyperprolactinemia without a GH-producing tumor.

IT HAS been well documented that about 50% of patients with acromegaly exhibit a paradoxical PRL response to GHRH [1]. However, PRL response to GHRH in patients with hyperprolactinemia has not yet been well established. Serri et al. [2] recently reported a statistically significant PRL increase after GHRH load in 13 patients with microprolactinoma. However, the magnitude of the increase expressed in terms of the area under the curve is only 109% on average, taking the basal level as 100%. Their report fails to answer the question whether some cases with hyperprolactinemia as well as acromegaly would exhibit a clearly paradoxical PRL response to GHRH.

We experienced a case of hyperprolactinemia without acromegaly which showed remarkable PRL response to GHRH. We also examined the PRL response to GHRH in 8 other cases with prolactinoma in order to determine whether the basal serum PRL concentration in hyperprolactinemia is correlated with the response of PRL to GHRH as reported by Serri et al. [2] and to compare their PRL response with that of this remarkable case.

Case Report
A 30-year-old woman visited Toranomon Hospital in July 1987 with an eight-year history of secondary amenorrhea and a twelve-year history of hirsutism. Her history and the family history were unremarkable. She was receiving no medication. On examination, she was obese and hirsute. Neither galactorrhoea nor acromegalic features were observed. Her height was 158.2 cm and her weight was 66.8 kg. Blood pressure was 130/70 mmHg. Endocrine studies showed a serum PRL level of 90 ng/ml (normal, <30 ng/ml), testosterone of 96 ng/ml (20–60), dehydroepiandrosterone (DHEA) of 9.0 ng/ml [1.2–7.5], dehydroepiandrosterone sulfate (DHEA-S) of 2590 ng/ml (500–3000) and 24 h-urinary 17-KS of 10.2 mg/day (3.1–8.8). The serum GH level was 1.3 ng/ml (<5), LH 6.0 mIU/ml and FSH 5.9 mIU/ml. The serum cortisol level was 13.5 μg/dl at 0800 h (5–12) and 1.2 μg/dl at 2300 h (<5). The free thyroxine

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concentration determined by calculation [3] was 1.37 ng/dl (0.8–2.5) and TSH by highly sensitive radioimmunoassay was 0.97 μU/ml (0.5–5.5).

The results of pituitary function studies were as follows. Her responses of LH and FSH to LHRH, GH to GHRH and TSH to TRH were normal (Table 1). PRL after TRH injection increased to more than twice the basal concentration. PRL after GHRH injection also increased to twice the basal concentration, namely close to the level obtained with TRH (Fig. 1A). Serum PRL did not increase after LHRH injection (Table 1).

A plain film of the skull and tomography of the sella demonstrated an enlargement of the sella turcica. A CT scan revealed diffuse lucency of the intrasellar region. Methorizamide CT scan confirmed the diagnosis of empty sella. Ultrasonography of the ovaries showed normal sized ovaries without cysts.

An ACTH injection (250 μg iv Cortrosyn®, Organon) increased the serum 17-hydroxyprogesterone concentration from 0.3 ng/ml to 1.2 ng/ml within 60 min. This response was not compatible with the diagnosis of 21-hydroxylase deficiency. Dexamethazone (1 mg via the oral route at 2300 h) suppressed the serum testosterone concentration from 96 to 35 ng/dl at 0900 h the next morning.

One month after she had received bromocriptine 2.5 mg twice a day, the basal level of PRL decreased to 9.0 ng/ml and the response of PRL to GHRH disappeared (Fig. 1B). Regular periods of menstruation appeared. However, the concentration of testosterone and that of DHEA did not alter 6 months after bromocriptine treatment. They decreased to the normal range and hirsutism improved after the reduction of her body weight by dieting.

To determine the specificity of the increase in serum PRL after GHRH in this patient, PRL response to GHRH was studied in patients with hyperprolactinemia due to prolactinoma.

Materials and Methods

The serum concentration of each hormone was measured by radioimmunoassay with a commercial kit (GH, Dinabot Co.; PRL, LH, FSH, TSH and cortisol, Daiichi Radioisotope Labs; T4, T3 and testosterone, Eiken Chemical Co.; DHEA and DHEA-S, Wein Laboratories; 17α-hydroxyprogesterone, DPC. Chemical Co.; TBG, Hoechst Japan). Internal standards used for LH and FSH assay were both WHO 2nd IRP HMG 67/161. Synthetic GHRH (used 1 μg/kg BW iv for the test) was purchased from Sumitomo Pharmaceuticals Co. TRH and LHRH (used 500 μg and 100 μg iv, respectively) were purchased from Tanabe Pharmaceuticals Co.

Eight patients with hyperprolactinemia and prolactinoma were studied. The concentration of PRL was measured in sera obtained during the GHRH tests which were undertaken to evaluate pituitary function. Six of them were female and two were male, aged 23 to 45 years. Six had macroprolactinomas proven by CT scan and two were supposed to have microprolactinomas, although morpholo-
Results

The maximum positive response of serum PRL to GHRH in the 8 patients with hyperprolactinemia due to prolactinoma was less than 120% in terms of the percentage of the basal level (Fig. 2). The PRL response to GHRH in the presented case (Fig. 1) was remarkably high compared to those in the other 8 patients with prolactinoma (Fig. 2). In the 8 patients with prolactinoma, there was no statistically significant correlation between the basal serum PRL level and the PRL response at 15 min or 30 min after the GHRH injection, \( r=0.402 \) or \( r=0.107 \).

Discussion

We reported the first case with hyperprolactinemia and empty sella whose serum PRL increased in response to GHRH to more than twice the basal level. The serum PRL response to GHRH in normal subjects is reported to be either negative or slight if any [1]. There is the possibility that GHRH might be a weak stimulator of PRL release in the physiological condition. However, the magnitude of the increase so far reported is always less than the basal level.

Serri et al. [2] have recently reported a statistically significant PRL increase after GHRH injection compared with saline in 13 patients with microprolactinoma. They also stated that this increase is positively correlated with the basal PRL level. In contrast to Serri’s observation, our 8 patients with prolactinoma showed no significant correlation between the basal serum PRL level and the PRL response to GHRH. Even in Serri’s cases, the correlation recalculated by us after eliminating one case whose basal PRL level is the highest among the 13 cases showed no significant correlation. These two results indicate that PRL usually does not respond to GHRH more dramatically in prolactinoma than in normal subjects. An in vitro study by Ishibashi et al. [4] in which GHRH did not stimulate PRL release from cultured cells of prolactinoma also confirms our results. On the other hand, the serum PRL response to GHRH of the case presented is much greater than that obtained in normal subjects.

The mechanism of the paradoxical response in the present case needs some discussion. In general, paradoxical response of pituitary hormones to hypothalamic releasing hormones has been documented in pituitary adenomas; GH to TRH
or LHRH [6, 7] and PRL to GHRH in acromegaly [1], ACTH to LHRH in Cushing's disease [8], LH or FSH to TRH in gonadotropin secreting adenoma [9] and in systemic diseases; GH to TRH in chronic liver disease, chronic renal failure, IDDM, pellagrin [10], depression [11] and anorexia nervosa [12]. The present case represents no acromegalic features, no pituitary disease listed above or systemic disease. The roentgenological studies revealed only empty sella in this case. The coexistence of microprolactinoma and empty sella is well known [13, 14]. Although serum PRL does not respond to TRH in most patients with prolactinoma, it does respond in 10-20% of them [15]. It may therefore be reasonable to conclude that hyperprolactinemia and the paradoxical response of PRL to GHRH in the present case might be caused by microprolactinoma.

In conclusion, most cases of prolactinoma do not show significant PRL response to GHRH but we found a rare case of hyperprolactinemia probably due to prolactinoma who showed paradoxical PRL response to GHRH. Further search for additional cases with the paradoxical PRL response to GHRH is necessary in order to determine if cases with the paradoxical response to GHRH form a subgroup of hyperprolactinemia clinically distinct from that without paradoxical PRL response to GHRH.

References