Reduction of Plasma Gonadotropin Levels and Pituitary Tumor Size by Treatment with Bromocriptine in a Patient with Gonadotropinoma

Noriyoshi Yamakita, Takashi Komaki, Toshihiro Murai and Satoru Kawamura

A pituitary tumor with suprasellar extension was found by magnetic resonance imaging (MRI) in a male with diabetes mellitus. Endocrine examination revealed high plasma follicle-stimulating hormone (FSH) and \( \alpha \)-subunit levels, which increased with administration of thyrotropin (TSH)-releasing hormone (TRH). Plasma luteinizing hormone (LH) and testosterone levels were low. Pituitary gonadotropin producing tumor was diagnosed. Because the patient refused surgery, bromocriptine was administered and plasma FSH and \( \alpha \)-subunit rapidly decreased; on MRI the tumor size was gradually reduced. When pituitary operation is not feasible, bromocriptine is one choice of treatment.

(Internal Medicine 38: 266-271, 1999)

Key words: follicle-stimulating hormone, \( \alpha \)-subunit, paradoxical response, gonadotroph adenoma

Introduction

Gonadotroph cell adenoma (gonadotropinoma) was formerly rarely reported (1). However, according to recent reports (1-3), especially proven by in vitro experiments or immunohistochemical method, 3.5-17% of pituitary adenomas secrete gonadotropin. On morphological examination, so-called nonfunctioning pituitary tumors always contain secretory granules. Many of these tumors are gonadotropes (3, 4). The preoperative evaluation whether the hypergonadotropinism is primary or secondary is not easy in an aged male. The menstrual cycle also affects the plasma gonadotropin levels in females. Furthermore, hypersecretion of follicle-stimulating hormone (FSH) does not always induce any clinical abnormalities especially in aged persons. Generally, gonadotropinoma is large when discovered and is resected transsphenoidally. It was reported that medical treatment for the tumor is not effective (1, 5, 6). We report a patient with pituitary gonadotropinoma whose plasma gonadotropin level decreased and tumor size was reduced on magnetic resonance imaging (MRI) by treatment with the dopamine agonist, bromocriptine.

Case Report

A 70-year-old male with diabetes mellitus and diabetic triopathy consulted Matsunami General Hospital complaining of headache and nausea which had persisted for four months. Brain MRI revealed a pituitary tumor with suprasellar extension and invasion to the sphenoidal sinus. However, the optic nerve was intact. He had been treated with 10 mg/day glybenclamide and 10 IU/day insulin administration for 18 years. Diabetes mellitus had been poorly controlled and creatinine clearance was 0.78 ml/s, but recently the glycohemoglobin was 6.5-7.0%. About one year before admission, operation for bilateral cataracts was performed and photocoagulation therapy had been repeated for bilateral diabetic proliferative retinopathy. His visual acuity was 20/30 in the right eye and 20/150 in the left eye. However, the ophthalmologically evaluated visual field was intact.

Operation scar on the right chest wall was seen due to right upper lobectomy for pulmonary squamous cell carcinoma performed three years earlier, of which recurrence was not detected by computed tomography. Other physical examination of the chest and abdomen was unremarkable. However, bilateral Achilles tendon reflex and patellar tendon reflex were blunted due to diabetic neuropathy. Axillary and pubic hair was sparse. Routine laboratory data were unremarkable. Pathological examination of the testes was not performed.

Endocrine examinations: Basal plasma and urinary testosterone one levels were low, 0.58 nmol/l (reference range, 7–38) and 12.8-17.3 \( \mu \)mol/day (34.7–416), respectively. Basal plasma FSH level was high, 39–42 IU// (age-matched reference range,
Bromocriptine Therapy of Gonadotropinoma

6.1- 19.8). Plasma α-subunit, of which the measuring method is described elsewhere (reference range, <1.2 ng/ml) (7), was also high, 1.9–2.5 ng/ml. However, the basal plasma luteinizing hormone (LH) level was low, 0.6–1.4 IU/l (age-matched reference range, 2.6–10.8). After the administration of 100 μg gonadotropin-releasing hormone (GnRH), plasma FSH and α-subunit increased from 40 to 48 and 1.9 to 3.5, respectively. The increase of plasma LH was inadequate, from 0.6 to 1.4. Administration of 500 μg thyrotropin-releasing hormone (TRH) paradoxically increased plasma FSH and α-subunit levels from 40 to 62 and from 2.2 to 3.2, respectively (Fig. 1A). However, during this stimulation, no increase was seen in the plasma LH level. Single oral administration of 2.5 mg bromocriptine slightly decreased plasma FSH and α-subunit from 41 to 34 and from 2.5 to 1.8, respectively, but did not decrease plasma LH levels. Subcutaneous administration of 100 μg octreotide acetate showed no effect on the plasma levels of FSH, α-subunit, and LH. Thyroid function was slightly decreased; plasma free triiodothyronine and free thyroxine were 2.65 pmol/l (3.80–6.68) and 11.6 nmol/l (12.5–23.0), respectively. Basal plasma TSH level was within the normal range, 2.01 μU/l (0.34–3.5), but its response to TRH was slightly blunted, from 2.0 to 6.6. The increase of plasma growth hormone level after 100 μg growth hormone-releasing hormone was also blunted, from 0.42 μg/ml to 3.95. The response of plasma prolactin to TRH and the pituitary-adrenal function evaluated by the administration of corticotropin-releasing hormone were normal. From the results of these endocrine examinations, gonadotropin-producing pituitary tumor associated with partial hypopituitarism was diagnosed. The patient refused an immediate operation of the pituitary tumor, because the tumor was not in contact with the optic nerve on MRI and the visual field was still intact, and the visual acuity was already severely impaired due to diabetic proliferative retinopathy.

Accordingly, bromocriptine was administered. As shown in Fig. 2 plasma FSH and α-subunit levels rapidly decreased to 6.0 and 0.6, respectively, when the dose of bromocriptine increased to 11.25 mg/day. However, plasma α-subunit level increased to a supra-normal level three months after the start of the treatment, although plasma FSH level was still in the normal range. The dose of bromocriptine was gradually increased to 20 mg/day. Plasma α-subunit level decreased again and remained in the normal range. During the treatment, the plasma testosterone level slightly increased to 2.48 and 2.68 nmol/l, which were still sub-normal levels, two and five months after the start of the treatment, respectively. The glycohemoglobin level did not change during the treatment. Five months after the start of the bromocriptine treatment, the paradoxical response of plasma FSH and α-subunit levels to the administration of TRH was completely resolved (Fig. 1B). The tumor

Figure 1. The responses of plasma gonadotropin and α-subunit levels during the stimulation with TRH. Plasma FSH and α-subunit levels paradoxically increased during the stimulation. Plasma LH level, however, did not change A). However, five months after the start of bromocriptine treatment the paradoxical increase of FSH and α-subunit was completely resolved B). closed circle: plasma FSH level, open circle: plasma α-subunit level, open triangle: plasma LH level.
Figure 2. The change of plasma gonadotropin and α-subunit levels during the treatment with bromocriptine. The dose of bromocriptine was gradually increased from 2.5 mg/day to 20 mg/day. Plasma FSH and α-subunit levels rapidly decreased. However, plasma LH level did not decrease, rather it slightly increased. closed circle: plasma FSH level, open circle: plasma α-subunit level, open triangle: plasma LH level, shaded area, reference ranges of hormones.

Figure 3. Change of the tumor size on MRI during the treatment of bromocriptine. The size of the pituitary tumor gradually decreased by the treatment with bromocriptine. Before the start of bromocriptine treatment (Sep. 24, ’97 A), Dec. 18, ’97 B), Apr. 2, ’98 C). Arrows indicate gonadotropinoma.
size on MRI was reduced seven months after the start of bromocriptine treatment (Fig. 3).

Discussion

In this patient, we did not confirm the diagnosis pathologically. However, not only was the basal plasma level of FSH high compared with the age-matched reference range, but also the plasma α-subunit level was high in the pre-treatment period. On the other hand, the basal plasma LH level was low and testosterone levels in plasma and urine were also low. The discrepancy in plasma FSH and LH levels indicated that a secondary increase of plasma FSH level due to aging was unlikely. Furthermore, during the stimulation with TRH, plasma FSH and α-subunit levels paradoxically increased. These findings were consistent with previous reports on the endocrine characteristics of patients with gonadotropinoma (8–12). Only a few patients who showed autonomous secretion of only LH but not FSH were reported (1, 13). Almost all reported patients with gonadotropinoma showed high plasma levels of FSH (1). More than half of the patients show normal or low plasma LH levels similar to the present patient. Even in patients with high plasma LH levels, plasma testosterone levels were low, probably because apparently supranormal plasma LH levels were not intact LH, but, instead, were the uncombined α-subunits and LH-β (10).

Bromocriptine, a dopamine agonist, is effective not only in decreasing the plasma prolactin level but also in reducing the tumor size in patients with prolactinoma (14, 15). In healthy subjects, bromocriptine decreases the plasma prolactin level, but not the gonadotropin level (16). Sufficient effects of this drug were reported in some patients with growth hormone- (14, 17, 18) or corticotropin- (19) producing pituitary adenoma. In patients with thyrotropin-producing adenoma bromocriptine is generally not effective (20). Reduction of the plasma hormone level by bromocriptine treatment was reported in a few patients with gonadotropinoma (5, 21–23). A few case reports have suggested that the occasional nonfunctioning pituitary tumor may decrease in size in response to dopamine agonist treatment (24–28). Almost all of these tumors are likely to be gonadotropinomas, because the majority of clinically nonfunctioning pituitary adenomas are gonadotropinomas (3, 4). In a review of 84 patients with clinically nonfunctioning pituitary adenoma described in seven series between 1984 and 1989 (29), 76 of 84 tumors showed no change and one an increase in size during dopamine agonist treatment; 79 patients were treated with bromocriptine, four with mesulergine and one with pergolide. Seven of these patients showed a small decrease in tumor size (8.3%). Bromocriptine generally has an inadequate effect on reducing the size of gonadotropinomas (1, 29). In the present patient bromocriptine clearly decreased plasma FSH and α-subunit levels, and their paradoxical increase during TRH stimulation disappeared five months after the start of bromocriptine treatment. It was reported that the paradoxical response of gonadotropin to TRH stimulation seen before the treatment was resolved after the treatment of bromocriptine in a patient, as in the present patient (23). Furthermore, the size of the tumor on MRI was reduced. Renner et al (30) reported that the inhibition of [3H]-thymidine incorporation into gonadotropinomas by bromocriptine was found in gonadotropinomas in which the mRNA of the D2short (1) isoform was predominantly or equally expressed compared with the D2long (1) receptor subtype. The presence of D2 short isoform in gonadotropinomas may favor the growth suppressive response to bromocriptine, although further investigation is needed.

The most suitable dose and duration of bromocriptine treatment to achieve clinical improvement and/or reduction in gonadotropinoma size are not consistent in individual cases (5, 14, 23, 24, 29). The dose and duration reported ranged from less than 7.5 mg/day to more than 20 mg/day and from one week to longer than one year, respectively. However, it was reported that withdrawal of bromocriptine treatment led to a rapid increase in tumor size (26). It is conceivable that bromocriptine should be administered as long as possible if a clinical effect is obtained and no severe side effects are noted.

Treatment with somatostatin analog octreotide in patients with clinically nonfunctioning pituitary adenoma or gonadotropinoma has not been well established yet, although its effectiveness in acromegaly patients has been well documented (31). Specific somatostatin receptors have been identified on the cell membrane of clinically nonfunctioning pituitary adenomas (32, 33). Octreotide was shown to inhibit the secretion of gonadotropin in patients with gonadotropinoma (6, 34). Katznelson et al (6) reported that octreotide reduced tumor size with or without an accompanying decrease in serum tumor marker levels in a small percentage of patients with clinically nonfunctioning pituitary tumors and α-subunit hypersecretion. De Bruin et al (35) reported that high-dose, 1,200 μg/day, octreotide treatment induced improvement of visual field defects in three of four patients with clinically nonfunctioning pituitary adenoma and the effect of a single injection of octreotide on the gonadotropin levels had no correlation with the improvement of the clinical efficacy. Hofland et al (36) reported that, from the results of the relation of the expression of five somatostatin receptor subtypes with the effect of somatostatin and its analogs on the secretion of gonadotropin from gonadotropinoma cells in culture, novel somatostatin receptor subtype specific somatostatin analogs might be of benefit in the treatment of selected patients with somatostatin receptor positive secreting tumors not responding to octapeptide somatostatin-analog.

Pure antagonists of GnRH, even in single doses, can cause profound hypogonadism in normal subjects (37). McGrath et al (38) reported that in five men with FSH-secreting pituitary adenomas, the GnRH antagonist Nal-Glu GnRH administered for 3–12 months decreased serum FSH concentrations to normal or below normal. Adenoma size, however, did not change during the treatment in any of the five patients.

GnRH stimulates the secretion of gonadotropin. However, a large amount of GnRH induces the down-regulation of the GnRH-receptor and decreases the production and secretion of the gonadotropin (39). It was reported that GnRH receptor was
present in gonadotropinoma cells (40). Based on this, treatment with GnRH agonist was tried in patients with gonadotropinoma. The results of this trial, however, were not consistently successful (41, 42).

Considering the many reports mentioned above, the efficacy of medical treatment of gonadotropinoma is not established. It is important to reduce hormone hypersecretion and tumor size reduction after unsuccessful surgery or in patients unable to undergo surgery.

References

Bromocriptine Therapy of Gonadotropinoma