LH- and FSH-Secreting Pituitary Adenoma in a Postmenopausal Woman

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Abstract. Gonadotropin secreting pituitary adenomas have been reported with increasing frequency in men, but they are still rarely recognized in women. We report a 52-year-old postmenopausal woman with LH- and FSH-secreting pituitary adenoma. She had increased LH (37.0 ± 13.7 IU/l) (mean $\pm$ SD) and FSH (109.9 ± 26.7 IU/l) but these concentrations were within normal ranges in 80 postmenopausal women (LH: 29.7 ± 18.3 IU/l, FSH: 104.0 ± 43.9 IU/l). The administration of GnRH and conjugated estrogen resulted in normal response of LH and FSH. No abnormal response of gonadotropin to TRH and bromocriptine was observed. After transsphenoidal adenomectomy both LH and FSH decreased (LH: 11.1 ± 4.2 IU/l, FSH: 37.0 ± 9.6 IU/l). An immunocytochemical study revealed that the adenoma cells synthesize both LH and FSH. The rarity of gonadotropin secreting pituitary adenomas in women could be the result of greater difficulty in recognition due to an increase in serum gonadotropin in postmenopausal women.

Key words: LH, FSH, Pituitary adenoma, Menopause.

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GONADOTROPIN-secreting pituitary adenomas have been reported relatively infrequently [1, 2]. The diagnosis is facilitated *in vivo* by increases in the circulating gonadotropin levels. As a result, most of the patients are males. In middle-aged females with pituitary adenomas and increased gonadotropin, the distinction between gonadotropin-secreting pituitary adenoma and nonfunctioning pituitary adenoma associated with normal postmenopausal serum concentrations of gonadotropins is difficult to make. In addition, it is not clear whether gonadotropin levels change during postmenopause. If serum gonadotropin increases with age as demonstrated in men [3, 4], the determination of gonadotropin levels may be useless in the follow-up. We report a postmeno-

pausal woman with LH- and FSH-secreting pituitary adenoma and demonstrate the relationship between age and gonadotropin levels in postmenopausal women.

Case Report

A 52-year-old woman was referred to our hospital for the evaluation of a pituitary tumor. She had experienced nasal bleeding several times during the previous 3 months and a pituitary tumor was incidentally discovered by head CT. She noticed blurred vision for about two weeks prior to admission. She had 2 children 28 and 31 years old. She noticed amenorrhea five months ago after irregular menstrual cycles for about a year. On physical examination she was a normally developed woman 158 cm tall weighing 61.5 kg. Pubic and axillary hair were normal and there was no evidence of galactorrhea. Ophthalmological

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studies revealed a small temporal defect in the visual field of the right eye.

Blood was taken in the morning after an overnight fast. Serum LH and FSH levels were determined by immunoradiometric assay (Daiichi Radioisotope, Tokyo, Japan) with reference standards of 1st IRP LH 68/40 for LH and 2nd IRP HPG 78/549 for FSH. Monoclonal antibodies were used for solid and labeled antibodies. The cross reactivity of FSH in LH assay was less than 2% and that of LH in FSH assay was negligible. Alpha subunit did not cross-react in either assay. Successive adjacent serial sections of the tumor were treated with peroxidase labeled anti-LH and FSH polyclonal antibodies (Dako, Kyoto, Japan). The cross reactivity of FSH in the LH assay was less than 5% and that of LH in the FSH assay was less than 10%. Serum PRL levels were measured by immunoradiometric assay (Dainabot, Tokyo, Japan) with a reference standard of NIH VLS#4.

Routine blood and urine chemical determinations were normal. Basal serum LH and FSH were increased (LH: 37.0 ± 13.7 IU/l, FSH: 109.9 ± 26.7 IU/l) (mean $\pm$ SD) but these were within normal ranges in 80 postmenopausal women aged from 50 to 82 yr (LH: 29.7 ± 18.3 IU/l, FSH: 104.0 ± 43.9 IU/l). No significant correlations were found between age and gonadotropin levels in postmenopausal women (LH: $r = -0.06$ NS, FSH: $r = 0.21$ NS). Serum PRL was increased (44.4 ± 5.6 μ g/l) and serum estradiol was less than 10 pg/ml. Results of loading tests are shown in Table 1. GnRH (100 μ g i.v.) elicited a normal increase in LH and FSH

Table 1. Endocrine function tests

Test	Hormone	Basal	Peak
TRH	PRL (μ g/l)	45.1	184.3
	TSH (mU/l)	2.2	15.6
	LH (IU/l)	26.9	30.3
	FSH (IU/l)	83.9	100.3
GnRH	LH (IU/l)	33.0	94.3
	FSH (IU/l)	100.0	170.4
ITT	Cortisol (μ g/dl)	6.0	27.4
	GH (μ g/l)	<1.5	25.0
		Basal	Nadir
Bromocriptine	PRL (μ g/l)	37.2	4.8
	LH (IU/l)	48.8	43.9
	FSH (IU/l)	122.7	120.2
Estrogen	LH (IU/l)	56.4	17.1
	FSH (IU/l)	155.8	60.4

Fig. 1. Postcontrast sagittal T1-weighted MR image shows a pituitary adenoma with suprasellar extension.

Fig. 2. Immunostaining for LH (above) and FSH (below). Note that both hormones are positive in the adjacent adenoma cells with morphological similarity.

Fig. 3. Changes in serum LH, FSH and PRL levels before and after transsphenoidal adenomectomy in a postmenopausal woman with LH- and FSH-secreting pituitary adenoma.

levels. Administration of conjugated estrogen (Premarin, Toyo Johzo, 20 mg i.v.) resulted in normal suppression of LH and FSH during 72 h. No abnormal response of gonadotropins to TRH (500 μg i.v.) or bromocriptine (5 mg p.o.) was observed. Skull X-ray, head CT and MRI (Fig. 1) were consistent with a pituitary adenoma with suprasellar extension.

Transsphenoidal pituitary adenomectomy was performed and most of the pituitary tumor was removed, although a residual tumor surrounding the left carotid artery remained. The adenoma cells showed positive immunostaining for LH and FSH antisera but not for prolactin. The immunostaining cells were arranged in clusters and dispersed in the tumor. When comparing adjacent serial sections immunostained with anti-LH and FSH, we found that both hormones were positive in the adjacent cells with morphological similarity (Fig. 2). Immediately after surgery, the basal levels of LH and FSH decreased (LH: 11.1 ± 4.2 IU/l, FSH: 37.0 ± 9.6 IU/l) but had a tendency to increase one year later. (Fig. 3).

Discussion

Gonadotropin-secreting pituitary adenomas are uncommon, and, in particular, tumors which secrete both LH and FSH have been reported by

only a few investigators [5–7]. However, recent studies have shown that most clinically nonfunctioning pituitary adenomas contain or release gonadotropins *in vitro* [8, 9]. This discrepancy can be explained by low levels of hormone release [9].

We had a postmenopausal woman with increased gonadotropin and a pituitary adenoma, and were confronted with 1) whether an increased gonadotropin concentration was due to the pituitary adenoma or to postmenopause, and 2) whether the determination of gonadotropin levels would be useful as a tumor marker in the follow-up if she had a gonadotropin-secreting pituitary adenoma. Her LH and FSH levels were within the normal range for postmenopausal women, and could not be useful a differential diagnosis of gonadotropin secreting pituitary adenoma and nonfunctioning adenoma. An abnormal response of gonadotropins to TRH and/or dopamine was reported in some patients with gonadotropin secreting pituitary adenomas [10, 11]. We did not, however, observe these abnormalities. Gonadotropin responses to GnRH and estrogen in patients with gonadotropin secreting pituitary adenomas are varied: administration of GnRH causes exaggerated, normal or subnormal responses of gonadotropins and administration of estrogen results in suppression, stimulation or no change in gonadotropin levels [7]. Our patient showed normal gonadotropin responses to GnRH and estrogen, suggesting that hypothalamic regulation is preserved. Only immunocytochemistry was useful, revealing that immunostaining for LH and FSH were localized in the tumorous cell cytoplasm and that the immunostaining cells were arranged in clusters and dispersed in the tumor. The immunostaining of adjacent serial sections with LH and FSH showed that both hormones were positive in the adjacent cells which were morphologically similar, suggesting that the tumor synthesized both LH and FSH simultaneously.

Since we did not find an increase in LH and FSH levels with advancing age during postmenopause, which was in agreement with a previous report [12], the measurement of gonadotropin levels could be used for detecting re-growth of the adenoma even in a postmenopausal woman. However, it should be remembered that gonadotropin levels fluctuate and basal hormone levels do not necessarily represent the bulk of the tumor as shown by the preoperative data.

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