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Follicle-Stimulating Hormone-Secreting Pituitary Adenomas

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ABSTRACT. This retrospective study concerns 40 patients with an apparently nonsecretory pituitary adenoma who were operated on during an 11-yr period from 1971 to 1981. Among them, 6 men had elevated serum FSH levels. LH levels were normal in 5 and slightly elevated in 1. Testosterone levels were low in 2 patients and within normal limits in 2 others. Sexual impotency had developed from 6 months to 1 yr before surgery in all patients. Primary hypogonadism could be eliminated on clinical grounds (recent onset of hypogonadism, previous fertility of 5 of the 6, and postoperative improvement). After transsphenoidal adenomectomy, FSH levels returned to normal values in all, and clinical recovery occurred in most patients. Tumor tissue obtained at operation stained positively for the gonadotropins, but was negative for other pituitary hormones in all patients. The most probable explanation for these findings was that the tumors were responsible for the elevated FSH secretion. This explanation is supported by the immunocytochemical identification of gonadotropin-containing cells in the tumors.

We conclude that these 6 men from a series of 40 patients who presented with pituitary tumor but no GH, PRL, or ACTH hypersecretion had primary gonadotropinomas. (*J Clin Endocrinol Metab* **61:** 525, 1985)

CLASSICALLY, pituitary tumors have been divided into two groups: nonsecreting adenomas and those hypersecreting GH, ACTH, and/or PRL. Glycoprotein-secreting adenomas are rare.

About 40 patients with TSH secreting adenomas have been described since the first report by Jailer and Holub (1). Gonadotropinomas, as a phenomenon secondary to long-standing primary hypogonadism, also have been described (2–8), but primary gonadotropinomas are rare (9–19). That patients with primary gonadotropinomas are seldom reported could be due to the absence of specific clinical symptoms of gonadotropin hypersecretion. The availability of simple hormone RIAs has allowed the efficient study of patients with apparently nonfunctioning pituitary adenomas, and such studies have indicated that the proportion of pituitary adenomas that are nonsecreting is smaller than previously estimated. Immunocytochemistry has proved to be an additional effective method to identify different types of pituitary adenomas and to correlate hormone hypersecretion with pathological results.

This report describes the clinical, biochemical, and pathological findings in 6 men with elevated plasma FSH levels identified from a larger group of 40 patients who had no evidence of GH, PRL, or ACTH hypersecretion.

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Subjects and Methods

A total of 182 pituitary adenoma patients were operated on by 1 of us (A.S.), using a transsphenoidal approach, during an 11-yr period from 1971 to 1981. Of them, 21 patients had ACTH hypersecretion, 59 had hyperprolactinaemia, and 62 had acromegaly. Forty patients (28 men and 12 women) had a pituitary tumor without evidence of hypersecretion of GH, PRL, or ACTH. From these 40 patients, 6 were found to have an elevated serum FSH level.

These six patients were all men, ranging in age from 36–57 yr. All had macroadenomas, and five had pneumoencephalographic evidence of suprasellar extension. Tumor specimens were available for microscopic studies from all six men. Gonadal function was evaluated clinically and biologically before and 3 months after operation. Basal serum LH and FSH concentrations were determined in all subjects, and basal testosterone was measured in four patients. LH and FSH responses to a 25-μg iv bolus dose of GnRH also were determined. Thyroid function was evaluated by determining the basal serum concentrations of T_4 and TSH and the TSH response to a 200-μg iv bolus dose of TRH; basal serum PRL and GH and serum and urinary cortisol also were determined in most patients. None had received therapy of any type before these studies. Semen analyses were not done. Serum concentrations of all hormones were measured by RIA using commercial kits. Normal reference ranges are shown in Table 1.

TABLE 1. Clinical and laboratory data from six patients with gonadotropinomas

Case no.	Preoperative period										Postoperative period[a]			
	Sexual potency	RX grading[b]	Testosterone (μg/liter)	LH (mU/ml)	FSH (mU/ml)	PRL (μU/ml)	GH (ng/ml)	T_4 (μg/dl)	TSH (μU/ml)	ΔTSH (μU/ml)[c]	Gonadal function	Testosterone (μg/liter)	LH (mU/ml)	FSH (mU/ml)
1	↓	II 0		11.0	25.0		0.4	8.4			Restored to normal	5.0	1.5	2.2
2	↓	II B		3.9	34.0	327	0.3	8.4	1.2	7.6				
3	↓	IV C	2.1	3.4	77.0	359	0.2		4.4	4.8	Improved		0.9	4.5
4	↓	II A	0.4	9.0	15.0	1045	0.7	2.9	3.5	23.5	Restored to normal	3.6	6.4	9.4
5	Normal	III B	2.7	4.3	9.5	756	1.6	5.1	2.4	3.3	Unaltered	3.6	4.1	4.6
6	↓	II B	5.0	5.8	20.8	250	0.1	8.8	2.9	0.0	Restored to normal	5.8	4.3	4.6
Normal			2.5–10	3–9	2–7	100–400	0.2–6.5	5.5–12.5	0.4–4.5					

[a] Three months.
[b] Radiographic grading, according to Vezina and Maltais (21) and Guiot *et al.* (22).
[c] Maximum change after 200 μg TRH, iv.

The peroxidase-antiperoxidase immunocytochemical method was applied to pituitary tissue slices, as previously described (20), using antisera specific to the β-subunits of the glycoprotein hormones and, in three instances, antisera to the glycoprotein hormone α-subunit.

Results

Gonadal function studies are summarized in Table 1. Preoperatively, clinical hypogonadism was present in five patients. Primary hypogonadism was considered unlikely because of the proximity of onset of hypogonadism (from 6 months to 1 yr) in relation to the time of diagnosis and treatment of the pituitary macroadenoma, previous fertility in five of the six patients, and postoperative improvement.

Before operation, serum testosterone concentrations were within normal limits in two patients and diminished in the others. Basal serum FSH levels were elevated in all patients, ranging from 9.5–77 mU/ml, and did not respond to GnRH except in two patients (no. 5 and 6). Only one patient (no. 1) had slightly elevated LH levels, and LH levels were normal in the remainder. Two patients (no. 5 and 6) had a normal LH response to GnRH, and the other four had no response.

Three months after operation, clinical improvement with restoration of sexual activity and ejaculation occurred in all five patients who had preoperative hypogonadism. Serum FSH was within the normal range in all patients except one, in whom it was only slightly increased (9.4 mU/ml). Serum LH was lower in all patients in whom it was measured, but the decline was small except in patient 1. The serum FSH and LH responses to GnRH were normal in the two patients tested. Postoperative serum testosterone levels were normal in four patients, but an unequivocal increase in serum testosterone occurred in only one patient (no. 4).

One patient (no. 4) had clinical hypothyroidism and a low serum T_4 value (2.9 μg/100 ml), but a substantial response of TSH to TRH. After the operation, the hypothyroidism disappeared, the serum T_4 level increased, and the serum TSH response to TRH decreased.

Pathological examination revealed chromophobic adenomas in all patients. The immunocytochemical results are summarized in Table 2. Four of the five tumors that were studied contained cells staining for FSH and LH, and one stained for FSH only. No immunostaining with anti-TSH, anti-PRL, anti-GH, or anti-ACTH was seen.

Discussion

Elevated serum FSH levels in patients with pituitary adenomas could be due to one of several abnormalities. Long-standing hypogonadism may result in the development of adenomas as well as FSH hypersecretion. X-Ray evidence of sellar enlargement has been described in patients with both Klinefelter's and Turner's syndromes (23), and a few patients with long-standing primary gonadal failure of other causes have had pituitary enlargement. This possibility could be eliminated in our patients on clinical grounds and by the postoperative improvement.

Elevated trophic hormone levels in the presence of

TABLE 2. Peroxidase-antiperoxidase immunostaining of pituitary tumor sections

Case no.	α-Subunit	LH	FSH	TSH	PRL	GH	ACTH
2[a]		+	+	—	—	—	—
3[a]		+	+	—	—	—	—
4[a]	+	+	+	—	—	—	—
5[b]	+	+	+	—	—	—	—
6[c]	+	−	±	—	—	—	—

[a] Approximately 20% of cells positive.
[b] Approximately 10% of cells positive.
[c] Few positive cells.

secondary peripheral organ failure also could be explained by diminished pituitary secretion of unknown factors, necessary for peripheral endocrine organ function. Thus, the development of a nonfunctioning pituitary adenoma might result in deficiency of such factors, with consequent peripheral organ hypofunction. In such a situation, the pituitary would then respond through negative feedback to the decreased peripheral organ secretion by secreting elevated amounts of the appropriate trophic hormone, such as FSH. In such an instance, however, the tumor should not contain the trophic hormone(s).

More likely, these men had primary FSH-secreting gonadotropinomas. Such tumors have been reported occasionally in the last 10 yr. All of the reported patients (9–18) except one (19) were men. This fact is probably due to the greater difficulties in appreciating the significance of high gonadotropin levels in women. In some patients, high serum LH and/or testosterone levels as well as high serum FSH levels were present (10, 15, 18). Clinically, however, most patients have had varying degrees at hypogonadism. When studied, circulating α-subunit was usually elevated (14, 16, 17, 19), as is found in patients with TSH-secreting pituitary adenomas. As in other situations of primary pituitary hypersecretion, abnormal responses to stimulation and/or suppression tests also have been reported (11, 13, 19). In addition, in a series of 50 patients with pituitary adenomas, Snyder *et al.* (24) found elevated FSH levels in 9 patients and an exaggerated FSH response to GnRH in 3 other patients. Furthermore, abnormal LH and FSH responses to TRH and abnormal FSH subunits responses to GnRH have been described in men with pituitary adenomas and FSH hypersecretion (25, 26).

Gonadotropinomas also were recognized by immunohistochemical criteria (20, 27–30). Trouillas *et al.* (29) and Mukai (30) reported that 3.5% of pituitary adenomas contained gonadotropins, a figure similar to that in our series (3.3%). Immunocytochemical studies may demonstrate hormone-containing cells even when the tumor is nonsecreting, so the distinction between secreting and nonsecreting tumors may depend more on whether one is describing clinical and/or biochemical abnormalities or only the anatomical presence of hormone in tumor cells. Moreover, immunohistochemistry may not detect hormones in cells that are hypersecreting but do not store enough hormone to be detected. This could result in underestimation of the true prevalence of primary hypersecretion when immunocytochemistry is the only approach.

From our data and those in the literature, gonadotropinomas appear to occur more frequently than previously estimated. The clinical picture of these patients does not yet permit the description of a characteristic syndrome. Nevertheless, the following criteria can be considered as positive arguments for the diagnosis of primary gonadotropinoma: elevated plasma gonadotropin levels, absence of primary hypogonadism, pathological proof of a pituitary adenoma, demonstration of FSH- and/or LH-secreting cells by immunocytochemical methods, and postoperative clinical recovery with normalization of gonadotropin and/or gonadal steroid levels. Fulfillment of all of these criteria is not required to establish the diagnosis; for example, as discussed above, it is clear that negative immunocytochemical results cannot rule out the diagnosis.

References

1. Jailer JW, Holub DA 1960 Remission of Graves' disease following radiotherapy of a pituitary neoplasm. Am J Med 22:497
2. Bower BF 1968 Pituitary enlargement secondary to untreated primary hypogonadism. Ann Intern Med 69:107
3. Burke CW, Marshall JC 1971 Ovarian failure with probable pituitary tumour. Proc R Soc Med 64:40
4. Kelly LW 1963 Ovarian dwarfism with pituitary tumor. J Clin Endocrinol Metab 23:50
5. Kovacs K. Horvath E, Rewcastle NB, Ezrin C 1980 Gonadotroph cell adenoma of the pituitary in a woman with long-standing hypogonadism. Arch Gynecol 229:57
6. Leiba S, Landau B, Ber A 1960 Target gland insufficiency and pituitary tumours. Acta Endocrinol (Copenh) 60:112
7. Lloyd CW 1963 Central nervous system regulation of endocrine function in the human. In: Nalbandov AV (ed) Advances in Neuroendocrinology. University of Illinois, Urbana, p 468
8. Woolf PD, Schenk EA 1974 An FSH-producing pituitary tumor in a patient with hypogonadism. J Clin Endocrinol Metab 38:561
9. Cunningham GR, Huckins C 1977 An FSH and prolactin-secreting pituitary tumor: pituitary dynamics and testicular histology. J Clin Endocrinol Metab 44:248
10. Demura R, Kubo O, Demura H, Shizume K 1977 FSH and LH secreting pituitary adenoma. J Clin Endocrinol Metab 45:653
11. Friend JN, Judge DM, Sherman BM, Santen RJ 1976 FSH-secreting pituitary adenomas: stimulation and suppression studies in two patients. J Clin Endocrinol Metab 43:650
12. Koide Y, Kugai N, Kimura S, Fujita T, Kameya T, Azukizawa M, Ogata E, Tomono Y, Yamashita K 1982 A case of pituitary adenoma with possible simultaneous secretion of thyrotropin and follicle-stimulating hormone. J Clin Endocrinol Metab 54:397
13. Kovacs K. Horvath E, Van Loon GR, Rewcastle NB, Ezrin C, Rosenbloom AA 1978 Pituitary adenomas associated with elevated blood follicle-stimulating hormone levels: a histologic, immunocytologic and electron microscopic study of two cases. Fertil Steril 29:622
14. Peterson RE, Kourides IA, Horwith M, Vaughan ED, Saxena BB, Fraser RAR 1981 Luteinizing hormone and alpha subunit secreting pituitary tumor: positive feedback of estrogen. J Clin Endocrinol Metab 52:692
15. Synder PJ, Sterling FH 1976 Hypersecretion of LH and FSH by a pituitary adenoma. J Clin Endocrinol Metab 42:544
16. Warnet A, Lubetzki J, Gueris J, Franchimont P, Mikol J, Dubois MP, George B 1982 Les adénomes gonadotropes. Ann Med Intern 133:26
17. Borges JLC, Ridgway C, Kovacs K, Rogol AD, Thorner MO 1984 Follicle-stimulating hormone-secreting pituitary tumor with concomitant elevation of serum α-subunit levels. J Clin Endocrinol Metab 58:937
18. Nicolis GL, Modhi G, Gabrilove JL, 1982 Gonadotropin producing pituitary adenomas. A case report and review of the literature. Mt Sinaï J Med 49:297
19. Wide L, Lundberg PO 1981 Hypersecretion of an abnormal form of follicle-stimulating hormone associated with suppressed lutein-

izing hormone secretion in a woman with a pituitary adenoma. J Clin Endocrinol Metab 53:923
20. Mashiter K, Adams E, Van Noorden S 1981 Secretion of LH, FSH and PRL shown by cell culture and immunocytochemistry of human functionless pituitary adenomas. Clin Endocrinol (Oxf) 15:103
21. Vezina JL, Maltais R 1973 La selle turcique dans l'acromégalie. Etude radiologique. Neurochirurgie [Suppl 2] 19:35
22. Guiot G, Oproiu A, Hertzog E, Fredy D, 1969 Adénomes hypophysaires. EMC Paris 17:340
23. Samaan NA, Stepanas AV, Danziger J, Trujillo J 1979 Reactive pituitary adnormalities in patients with Klinefelter's and Turner's syndromes. Arch Intern Med 139:198
24. Snyder PJ, Bigdell H, Gardner DF, Mihailovic V, Rudenstein RS, Sterling FH, Utiger RD 1979 Gonadal function in fifty men with untreated pituitary adenomas. J Clin Endocrinol Metab 48:309
25. Snyder PJ, Muzyka R, Johnson J, Utiger RD 1980 Thyrotropin-releasing hormone provokes abnormal follicle-stimulating hormone (FSH) and luteinizing hormone responses in men who have pituitary adenomas and FSH hypersecretion. J Clin Endocrinol Metab 51:744
26. Snyder PJ, Johnson J, Muzyka R 1980 Abnormal secretion of glycoprotein alpha-subunit and follicle-stimulating hormone (FSH) beta-subunit in man with pituitary adenomas and FSH hypersecretion. J Clin Endocrinol Metab 51:579
27. Cravioto H, Fukaya T, Zimmerman EA, Kleinberg D, Flamm ES 1981 Immunohistochemical and electron-microscopic studies of functional and non-functional pituitary adenomas including one TSH secreting tumor in a thyrotoxic patient. Acta Neuropathol (Berl) 53:281
28. Kovacs K, Horvath E, Ryan N, Ezrin C 1980 Null cell adenoma of the human pituitary. Virchows Arch [Pathol Anat] 387:165
29. Trouillas J, Girod C, Sassolas G, Claustrat B, Lheritier M, Dubois MP, Goutelle A 1981 Human pituitary gonadotropic adenoma; histological, immunocytochemical, and ultrastructural and hormonal studies in eight cases. J Pathol 135:315
30. Mukai K 1983 Pituitary adenomas. Immunocytochemical study of 150 tumors with clinicopathologic correlation. Cancer 52:648