Functioning gonadotroph adenoma

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To the Editor: Pituitary gonadotroph adenoma is a type of non-functioning pituitary adenoma of which approximately 35% secrete biologically active luteinizing hormone (LH) or follicle-stimulating hormone (FSH), and these adenomas are named functioning gonadotroph adenoma (FGA). We present three cases of FSH-secreting adenomas who were admitted to our hospital between 2014 and 2016.

Case 1: A 37-year-old woman was admitted due to menstrual irregularity and galactorrhea for 2 years. The laboratory tests showed a significantly elevated estradiol 2 (E2) level, and multiple cyst fusions could be observed by transvaginal ultrasonography. The pituitary magnetic resonance imaging (MRI) revealed an upper-right wing distension and detected a mass with a size of approximately 7.5 mm × 10.7 mm in the saddle area, and a pituitary macroadenoma was considered. The patient underwent a transsphenoidal microsurgical resection of the pituitary adenoma. The pathologic examination showed a positive result for FSH, LH, and SF-1, and a negative result for growth hormone, insulin-like growth factor 1, TPIT, and PIT1.

Case 2: A 39-year-old woman visited the endocrinology department due to menstrual irregularity for 3 years. She was diagnosed with multiple polyps at the cervix, and complete curettage of the uterine cavity was performed. The transvaginal ultrasonography revealed cystic occupying lesions of 58 mm × 62 mm × 31 mm in the right ovary and pelvic occupying lesions of 109 mm × 90 mm × 70 mm. Laboratory tests showed the results of increased FSH and E2. A 23 mm × 14 mm macroadenoma was observed through MRI. We performed a transsphenoidal microsurgical resection of the pituitary adenoma and achieved total resection. The immunohistochemical staining and pathologic examination showed positive staining for FSH, LH and SF-1, and a negative result for TPIT and PIT1.

Case 3: A 46-year-old man was admitted due to hypopsia, hemianopsia, and hypogonadism for 3 years. The hormone measurements were as follows: prolactin, 340.9 ng/mL; FSH, 70.6 U/L; LH, 0.36 U/L; and FT4, 4.41 pmol/L. His 24-h urinary-free cortisol was 63.23. An occupying lesion of 45 mm × 30 mm × 31 mm was found in the suprasellar area, and a transsphenoidal microsurgical resection was conducted at a local hospital. The immunohistochemical staining showed a positive result for FSH. Two months after the first surgery, another pituitary MRI was taken and showed an occupying lesion in the sellar area, which was diagnosed as a tumor relapse. We again performed a transsphenoidal microsurgical resection of the pituitary adenoma. The immunohistochemical staining and pathologic examination showed a positive result for FSH, LH, and SF-1, and a negative result for TPIT and PIT1.

To our best knowledge, 34 cases of FGA have been described in the literature prior to the present report. The patients' tumors can secrete functional FSH or LH and thus cause clinical manifestations. The clinical manifestations of FGA include menstrual irregularity (15/34), abdominal distension or increasing abdominal girth (13/34), amenorrhea (13/34), galactorrhea (10/34), abdominal or pelvic pain (10/34), hypomenorrhea (5/34), hypermenorrhea (2/34), and infertility (2/34).[1,2] Our summary shows that the FSH level was mostly mildly higher or within the normal range (FSH was normal in 21/34 patients and elevated in 14/34 patients). LH was decreased (31/34). Regarding prolactin, 27 of the 34 patients had hyperprolactinemia. In our reports, the two female patients' clinical manifestations included menstrual irregularity, galactorrhea, and cystic lesions in the ovary. Their blood hormone levels showed a hyperestrogenism, but their FSH levels were within normal range or mildly elevated.

The male patient of case 3 complained of sexual hypoactivity and bitemporal hemianopia. The most common symptom in males with FGA is testicular enlargement.[3] However, there are few reports regarding FGA as the cause of hypogonadism. Dahlqvist *et al*[4] reported a 56-year-old man with hypogonadism and

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bilaterally enlarged testicles (7 cm × 5 cm and 6 cm × 4 cm). In our case, the patient's leading complaint was hypogonadism, but no testicular enlargement was observed in the physical examination. In Sertoli cells, FSH stimulates the secretion of androgen-binding protein, which provides a high local concentration of T in the seminiferous tubules. A pituitary adenoma with a mass effect on the normal pituitary often results in LH and T insufficiency. Very low T levels might impede the synergistic trophic effects of FSH in the seminiferous tubuli.[4] In addition, the FGA production of multiple FSH species with variable biologic activity in Sertoli cells is hypothesized to be significant in the enlargement of the testicles. Regarding hypogonadism, high FSH levels can lead to a decreased sperm count. However, there are also reports of an increased sperm count.[5] Regarding the hormone levels, in contrast to female patients, almost all male patients with FGA have a high level of FSH. The reported cases include LH and T levels that are below reference, normal, or increased. In case 3, his FSH level was significantly elevated before the first operation and slightly elevated before the second operation. His LH level was below the normal range. There was no distinctive change in his T level. Ultrasound of the scrotum, in cases with testicular enlargement, has demonstrated increased testicular volumes without cystic or solid masses.[4] Most male patients first present with a visual disturbance or hemianopia because their symptoms are not as distinctive as those in female patients, which leads to a larger tumor size at diagnosis.

Transsphenoidal resection is regarded as the most effective therapy. The enlarged ovarian cysts and cystic lesions in the pelvis may gradually regress after surgery. The elevated E2 or FSH level can decrease to within normal range days after the total resection of the tumor. Importantly, a diagnosis of FGA must be considered before any surgical intervention to avoid an unnecessary ovary laparotomy.

There are reports regarding the use of radiotherapy for recurrent FGA. However, because these are only case reports and do not contain long-term follow-up results, the effectiveness of radiotherapy in FGA patients remains unknown. Our three patients did not receive radiotherapy because of its unknown effects.

FGA is a rare disease comprising only a small portion of pituitary adenomas. Early diagnosis is important to avoid unnecessary surgery procedures. FGA in reproductive-aged women is relatively rare, and awareness in endocrinologists, gynecologic clinicians, or even neurosurgeons is limited.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the article. The patients understand that their names and initials will not be published and due efforts will be made to conceal the identity of the patient, although anonymity cannot be guaranteed.

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Conflicts of interest

None.

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