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Functional Gonadotroph Adenomas: Case Series and Report of Literature

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Abstract

Background—Functional gonadotroph adenomas (FGA) are rare tumors of the pituitary gland that secrete biologically active gonadotropins.

Objective—To advance clinical understanding of FGA.

Methods—We performed a retrospective review of adult patients who underwent resection of a pituitary lesion between August 1997 and October 2014 and remain under care at our center. We identified patients who had pathologic and biochemical confirmation of FGA, as defined by lack of serum LH/FSH suppression in the setting of elevated gonadal steroids, associated clinical symptoms, or both.

Results—FGA was documented in seven patients (five men, two women) over a 17-year period. Clinical findings at presentation included visual field deficits in five patients, headache in three, sexual dysfunction in three, and ovarian cysts in both women. Each patient underwent lesional resection (six by the endonasal transsphenoidal approach, one by craniotomy with transsphenoidal reoperation). Analysis of tumor samples revealed immunopositivity for FSH/LH in five patients and FSH only in two patients. Post-operative follow-up (median 10 mo, range 4-213 mo) indicated remission in six of seven patients.

Conclusion—FGA can pose both a diagnostic and therapeutic challenge. The tumor is often diagnosed as a nonfunctioning macroadenoma after presenting with non-specific symptoms, and is the cause of significant morbidity. FGA should be considered in the differential diagnosis of patients harboring pituitary adenomas with reproductive dysfunction. Transsphenoidal resection is

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the initial treatment of choice, and can reduce endocrine dysfunction, resolve headaches, improve visual impairment, and provide tissue for detailed analysis.

Keywords

functional gonadotroph adenoma; gonadotropins; gonadotroph adenoma; pituitary adenoma; pituitary surgery

Functional gonadotroph adenomas (FGA) are rare benign tumors of the pituitary that secrete one or both of the gonadotropins, FSH and LH, in a biologically active form.¹⁻³ Epidemiological studies of FGA are limited, in part because of their rarity and non-specific signs/symptoms, and in part because of an uncoupling of clinical presentation and pathologic evaluation of tumor specimens.^{1, 2, 4, 5} Many non-functioning pituitary adenomas develop from gonadotroph cells and are misidentified as FSH- or LH- producing on pathological analysis. The majority of clinically non-functioning pituitary adenomas express one or more of the glycoprotein hormone moieties (alpha, LH beta, FSH beta, TSH beta).^{6, 7} Several studies have shown that although non-functioning gonadotroph adenomas are common, FGA are infrequent.^{6, 8-10} Given the diagnostic and pathologic challenges associated with this condition, few case series of patients with confirmed clinical and pathologic FGA have been published.^{1, 11-22}

Unlike other functional adenomas of the pituitary gland that have characteristic presentations, the clinical signs and symptoms of FGA are often ambiguous.^{1, 4, 6, 16, 23} Clinical sequelae of FGA include polycystic ovarian syndrome (PCOS), infertility, menstrual irregularities, ovarian hyperstimulation syndrome (OHSS) in women, and testicular hypertrophy and sexual dysfunction in men.^{5, 22-28} Since these conditions may be attributed to other systemic diagnoses, gonadotropin-producing adenomas often escape detection until they become macroadenomas, with associated mass effect causing headache, visual field deficits, and hypopituitarism, which counterintuitively may include hypogonadism.^{1, 11, 13-17, 29-32} FGA are generally not responsive to medical therapy either in the form of dopamine agonists or somatostatin analogs.^{1, 12, 33}

The standard of care for FGA is tumor resection.^{2, 24, 27, 29} Operative intervention serves to decompress the optic chiasm, ameliorate endocrine dysfunction, and provide conclusive pathologic diagnosis.^{1, 24, 33, 34} Post-operative follow-up is imperative to monitor endocrine function and to detect tumor recurrence. We report seven cases of FGA patients currently under our care, with focus on presentation, diagnosis, treatment, and outcome.

Methods

We retrospectively reviewed patients who underwent resection of pituitary lesions at a single academic center to identify those who had pathologic and biochemical confirmation of FGA, and who remain under our care. Reviewed criteria included clinical symptoms, immunohistochemical staining for LH and/or FSH-beta, and either elevated FSH/LH or non-suppressed FSH/LH in the setting of elevated gonadal steroids.^{1, 2, 16, 24, 35} Demographics, presenting signs and symptoms, medical treatment, operative details, peri-operative hospital

course, endocrine laboratory studies, imaging results, and pathology findings were analyzed (Tables 1-3).

Each patient underwent a thorough endocrine evaluation prior to resection. In all cases, tissue samples obtained during surgery confirmed adenoma and were immunohistochemically assayed for TSH, prolactin, LH, FSH beta subunit, GH, and ACTH (see Supplemental Digital Content, which describes the techniques used for immunohistochemical analysis). Follow-up with a neurosurgeon and neuroendocrinologist included annual MRIs and biannual measurement of pituitary hormones.

Results

Seven patients who remain under our care were diagnosed with FGA over a 17-year period. All seven patients were followed post-operatively at our multidisciplinary pituitary center (median follow-up 10 mo, range 4-213 mo).

Case 1

A 45-year-old man presented with left temporal hemianopsia and left optic atrophy. He denied other neurologic symptoms including headache. MRI revealed a homogeneously enhancing $4.5 \times 4.5 \times 3.0$ cm lesion involving the sella turcica and suprasellar cistern, with superior displacement of the optic chiasm. Results of laboratory testing revealed elevated FSH (27.8 mIU/mL, nl 0.9-15.0 mIU/mL), LH of 4.5 mIU/mL (nl 2.4-5.9 mIU/mL), and testosterone at the low end of normal (253.9 ng/dL, nl 165-1194 ng/dL). Markers of the hypothalamic-pituitary-adrenal (HPA) axis remained normal; pre-operative TSH was normal (1.0 uU/mL, nl 0.5-5.0 uU/mL). He underwent transsphenoidal surgical resection. Tumor specimens demonstrated adenoma immunopositive for FSH, with weak focal staining for LH and TSH (Figure 1). His post-operative course was complicated by the development of diabetes insipidus (DI) and panhypopituitarism, treated with full replacement therapy. He presented to the Emergency Department on post-operative day eight with nausea, vomiting, and mild epistaxis. His sodium was found to be low (121 mmol/L, nl 136-142 mmol/L), and he was readmitted for three days while treated for symptomatic hyponatremia. One month post-operatively, his FSH had decreased to 2.6 mIU/mL (nl 0.9-15.0 mIU/mL). No further tumor growth was observed for four years, and his FSH remained within normal limits (3.1 mIU/mL, nl 0.9-15.0 mIU/mL). A three-month post-operative MRI demonstrated decompression of the optic chiasm. Eight years after initial resection, the patient experienced tumor recurrence without elevation of FSH. He underwent stereotactic radiation therapy, with stable FSH (1.8 mIU/mL, nl 1.5-12.4 mIU/mL) and no further tumor growth eight years later (16 years post-operatively).

Case 2

A 35-year-old woman presented with right lower quadrant abdominal pain. Abdominal ultrasound revealed ovarian torsion secondary to bilateral enlarged polycystic ovaries, for which she underwent right salpingo-oophorectomy. Pathology revealed a large hemorrhagic follicular cyst and numerous smaller cysts lined by granulosa cells and a layer of luteinized thecal cells. Further evaluation revealed elevated prolactin and FSH. MRI demonstrated a

3.1 × 2.5 × 3.4 cm sellar lesion, extending into the suprasellar cistern and causing considerable compression of the optic chiasm and anterior brainstem. Laboratory testing indicated hyperprolactinemia (122.9 ng/mL, nl 2.7-26.7 ng/mL), elevated FSH (17.3 mIU/mL, nl 1.7-10.4 mIU/mL), low LH (<0.1 mIU/mL, nl 1.0-11.4 mIU/mL), and estradiol of 130 pg/mL (nl 14-188 pg/mL). She denied any visual symptoms and had intermittent mild headaches. She reported normal menses and denied galactorrhea. Two months after presentation, the patient underwent uncomplicated transsphenoidal resection of tumor. The tumor was immunonegative for all pituitary hormones, including LH and FSH, and was classified as a typical non-functioning adenoma. No hormone replacement was instituted. Eighteen months later, the patient presented with extreme fatigue and optic atrophy with a mild right superior temporal quadrantanopia. Laboratory testing revealed elevated prolactin (53.2 ng/mL, nl 2.7-26.7 ng/mL), FSH of 9.9 mIU/mL (nl 1.7-10.4 mIU/mL), LH of 2.1 mIU/mL (nl 1.0-11.4 mIU/mL), and estradiol of 89 pg/mL (nl 14-188 pg/mL). Repeat MRI revealed a residual sellar and suprasellar lesion with compression of the optic chiasm. She underwent reoperation by the transsphenoidal approach, after which her FSH (8.3 mIU/mL, nl 1.7-10.4 mIU/mL), LH (1.3 mIU/mL, 1.0-11.4 mIU/mL), and prolactin (13.3 ng/mL, nl 2.7-26.7 ng/mL) were within normal laboratory limits. Tumor specimens from the operation confirmed the presence of adenoma and stained positively for FSH and p53. The adenoma was classified as an atypical FSH-producing gonadotroph adenoma. Her second post-operative course was complicated by hypothyroidism and adrenal insufficiency, requiring hormone replacement, as well as intracerebral hemorrhage and transient diabetes insipidus. She developed amenorrhea and hypogonadism, and was treated with sex steroid replacement in the form of OCP until she self-discontinued several months post-operatively. Her visual symptoms improved. She remained on glucocorticoid and levothyroxine replacement. No evidence of tumor regrowth was observed after six-years of follow-up.

Case 3

A 52-year-old man presented after a routine examination revealed incomplete bitemporal hemianopsia. MRI demonstrated a 2.4 × 2.0 × 2.9 cm heterogeneously enhancing sellar mass, extending to the suprasellar cistern. The mass caused superior displacement of the optic tract and chiasm, and completely encompassed the left internal carotid artery. The patient reported headaches and fatigue. He denied sexual dysfunction. Laboratory testing revealed elevated FSH (159.1 mIU/mL, nl 1.3-19 mIU/mL) and alpha subunit (8.8, nl <0.6), LH of 4.2 mIU/mL (nl 1.7-8.6 mIU/mL), and testosterone of 880 ng/dL (nl 250-1100 ng/dL). All other hormone levels were normal. Because of the large size and location of the tumor, the patient underwent a left frontotemporal craniotomy. On post-operative day two, he experienced neurologic deterioration with left-sided visual loss and new right-sided hemiparesis. He was found to have an infarction in the left basal ganglia and internal capsule for which he underwent multiple angiographic procedures. He was discharged to rehabilitation on dexamethasone and made remarkable improvement in the strength of his extremities. He required no hormone replacement after a normal cosyntropin stimulation test six months post-operatively. Tumor histology confirmed adenoma and stained positively for FSH and negatively for other pituitary hormones. Eighteen months post-operatively, the patient remained blind in his left eye, but had regained independent ambulatory status. He returned 20 months post-operatively with rapidly worsening visual acuity and severe visual

field loss in his right eye. MRI demonstrated continued regrowth of residual tumor, measuring $3.4 \times 3.2 \times 3.6$ cm. His FSH remained elevated (>200.0 mIU/mL, nl 1.5-12.4 mIU/mL) with LH of 2.6 IU/L (nl 1.7-8.6 IU/L) and testosterone of 441 ng/dL (nl 193-740 ng/dL). The patient underwent reoperation via the endoscopic transsphenoidal approach, without complications, after which his gait and vision in the right eye improved. Tumor obtained stained weakly for FSH. Six weeks post-operatively the patient's vision remained stable, his FSH had decreased to 139.6 IU/L (nl 1.5-12.4 IU/L), and his LH (2.6 IU/L, nl 1.7-8.6 IU/L) and testosterone (502 ng/dL, nl 193-740 ng/dL) remained within normal limits without replacement. Twelve weeks post-operatively, an MRI demonstrated no evidence of residual tumor, and the patient's endocrine testing remained stable.

Case 4

A 32-year-old G1P1 woman presented to a reproductive endocrinologist with an 18-month history of oligomenorrhea and failure to conceive after her first pregnancy, two and a half years prior. Testing revealed that her FSH (9.8 mIU/mL, nl 2.7-15.4 mIU/mL) was not suppressed in the setting of an estradiol of 106.5 pg/mL (nl 21.8-83.7 pg/mL) and multiple follicular cysts, for which she was treated by transvaginal aspiration. Serial laboratory testing over three months revealed persistently elevated estradiol. MRI revealed a sellar mass measuring $1.4 \times 0.9 \times 1.1$ cm, with suprasellar extension and slight mass effect on the optic chiasm (Figure 2). On presentation to our clinic, the patient reported two months of retro-orbital headaches, exacerbated by recumbence and fatigue. She reported visual disturbance over the past month, described as a dimming of peripheral vision with blurry spots. Other symptoms included decreased energy, decreased libido, intermittent hot flashes, and new-onset nocturia. Laboratory testing pre-operatively indicated non-suppressed FSH (9.4 mIU/mL, nl 3.5-12.5 mIU/mL) in the setting of elevated estradiol (458 pg/mL, nl 14-188 pg/mL), and mildly elevated prolactin (45.9 ng/mL, nl 4.79-23.3 ng/mL). Her LH was low (0.04 mIU/mL, nl 1.0-11.4 mIU/mL). She underwent uncomplicated transsphenoidal resection of the lesion. The tumor was immunopositive for FSH and LH and negative for all other pituitary hormones, with the final pathologic diagnosis consistent with FSH-producing pituitary adenoma. Post-operatively, the patient reported improvement in headaches and resolution of visual difficulties. She did not require hormone replacement. Three months post-operatively, her FSH (13.2 mIU/mL, nl 3.5-12.5 mIU/mL) had returned toward normal and her LH (11.7 mIU/mL, nl 2.4-12.6 mIU/mL), estradiol (153 pg/mL, nl 14-188 ng/mL), and prolactin (8.7 ng/mL, nl 4.79-23.3 ng/mL) were within normal laboratory limits. Nine months post-operatively, the patient was pregnant and her laboratory testing remained stable.

Case 5

A 71-year-old man presented with dizziness and blurred vision. MRI demonstrated a heterogeneously enhancing sellar and suprasellar mass, measuring $2.4 \times 1.8 \times 2.1$ cm, with compression of the optic chiasm. He denied headaches, weakness, nausea and vomiting, syncope, vertigo, polyuria, and polydipsia. He reported erectile dysfunction and decreased libido over the prior five years, which had worsened during the year prior to presentation but for which he had not sought medical attention. The patient had pre-existing legal blindness in his left eye. Laboratory testing indicated FSH excess (125.3 mIU/mL, nl 1.5-12.4 mIU/mL) and LH of 2.5 mIU/mL (nl 1.7-8.6 mIU/mL). The patient had low testosterone

(48.0 ng/dL, nl 193-740 ng/dL), elevated TSH (6.17 mIU/L, nl 0.5-5.7 mIU/L), and low free T4 (3.9 ug/dL, nl 4.6-10.7 ug/dL). Levothyroxine replacement was initiated. There was concern for possible central adrenal insufficiency despite a normal cortisol in the setting of hypothyroidism; therefore, he was started on glucocorticoid replacement pre-operatively. The patient underwent transsphenoidal resection of the tumor. Pathological examination showed findings consistent with an FSH-producing adenoma, and the tumor cells stained positively for FSH and LH. Three months post-operatively, the patient showed biochemical evidence of remission with an FSH of 7.1 mIU/mL (nl 1.5-12.4 mIU/mL), an LH of 2.9 mIU/mL (nl 1.7-8.6 mIU/mL), and a testosterone of 358.3 ng/dL (nl 193-740 ng/dL). He also reported significant improvement in vision in his right eye and improved sexual function. He remained on levothyroxine replacement. Cosyntropin stimulation testing three months post-operatively was within normal limits and he discontinued glucocorticoid replacement.

Case 6

A 62-year-old man presented to his primary care physician with complaints of left-sided hearing loss and decreased libido with erectile dysfunction. MRI to evaluate for acoustic neuroma incidentally revealed a large, homogenously enhancing, $3.2 \times 2.3 \times 2.3$ cm tumor in the sellar region that abutted the optic chiasm. When he came to us for further care, the patient denied headache, new visual loss, and other neurologic symptoms. He noted increased nocturia (3-4 times nightly). He had a history of bilateral retinal detachments with five surgical procedures (four on the left, one on the right), which left him with impaired vision, particularly in the left eye. Laboratory testing revealed elevated FSH (25.0 mIU/L, nl 1.5-12.4 mIU/L) and prolactin (21.8 ng/mL, nl 4.0-15.2 ng/mL), an LH of 2.2 IU/L (nl 1.7-8.6 IU/L), and a testosterone of 233 ng/dL (nl 193-740 ng/dL). Other pituitary hormones were normal. He underwent transsphenoidal resection of the pituitary mass. Tumor histology confirmed the presence of adenoma, which stained positively for FSH, LH, and alpha subunit, and weakly positive for TSH, prolactin, ACTH, and HGH. The tumor was classified as an FSH-producing adenoma. One week post-operatively, the patient reported significant improvement in the visual deficits he had previously attributed to his retinal procedures. Six weeks post-operatively, laboratory testing revealed that FSH (4.7 mIU/L, nl 1.5-12.4 mIU/L), LH (3.1 mIU/mL, nl 1.7-8.6 mIU/mL), prolactin (6.0 ng/mL, nl 4.0-15.2 ng/mL), and testosterone (310 ng/dL, nl 193-740 ng/dL) were within normal limits.

Case 7

A 64-year-old man presented to a plastic surgeon for consultation regarding a neck lipoma. A CT scan was performed which incidentally demonstrated a $2.8 \times 2.5 \times 2.2$ cm pituitary macroadenoma with elevation of the optic chiasm. Laboratory testing revealed an elevated FSH (33.2 IU/L, nl 1.5-12.4 IU/L) and alpha subunit (3.2 ng/mL, nl <1.37 ng/mL) with an LH of 4.5 IU/L (nl 1.7-8.6 IU/L). His testosterone was low normal (364 ng/dL, nl 348-1197 ng/dL). Visual field testing demonstrated no deficits. He presented to our clinic after six months of conservative management, at which time he reported no vision loss, headaches, or other neurological deficits. In retrospect, he reported somewhat decreased libido, but denied erectile dysfunction, sleep disturbances, memory issues, and polyuria. He had been taking tadalafil for several years at the recommendation of his primary care doctor for symptoms of

benign prostatic hyperplasia (BPH). MRI demonstrated increase in size of the pituitary macroadenoma to $3.0 \times 2.6 \times 2.7$ cm. His FSH remained elevated (39.4 mIU/L, nl 1.5-12.4 mIU/L). Based on the growth of the tumor and potential for visual impairment, the patient underwent uncomplicated transsphenoidal resection of the lesion. The tumor stained positively for FSH and LH and was classified as FSH-producing. Six weeks post-operatively, he had levels of FSH (8.7 mIU/mL, nl 1.5-12.4 mIU/mL), LH (4.7 mIU/mL, nl 1.7-8.6 mIU/mL), prolactin (8.3 ng/mL, nl 4.0-15.2 ng/mL), and testosterone (396 ng/dL, nl 348-1197 ng/dL) that were within normal laboratory limits. Twelve weeks post-operatively, the patient reported improved libido, his endocrine testing remained stable, and an MRI of the brain showed no residual tumor.

Discussion

Multiple reports have demonstrated that FGA are infrequent and difficult to diagnose preoperatively, often presenting in late stages as a macroadenoma exerting mass effect.^{24, 36, 37} Our case series confirms these observations, as each of our seven patients had a macroadenoma, and six of the seven presented with symptoms attributable to mass effect (vision loss and/or headache). It is likely that FGA are more common than previously reported, and are underdiagnosed as a result of non-specific presentation.^{1, 2, 11, 38} In many cases, particularly in men, the symptoms related to endocrinopathy of the pituitary-gonadal axis can be attributed to mass effect caused by a slowly enlarging tumor or to associated hyperprolactinemia. Morbidity is higher in patients with FGA than in patients with typical null-cell adenomas of similar radiographic dimensions, however, secondary to concomitant endocrinopathies.^{1, 8, 9, 12, 20}

Diagnosis of FGA is further complicated because many clinically non-functioning adenomas stain positively for FSH and/or LH.^{2, 8} Much confusion has arisen as a result of the conflation of the terms “gonadotroph adenoma” and “silent gonadotroph adenoma.” Because many adenomas stain positively for FSH/LH regardless of functional status, they are often incorrectly categorized as functioning gonadotroph adenomas in cases where they are actually silent, and vice versa. This report of seven cases over a 17-year period cannot be considered an exhaustive review of all patients undergoing pituitary tumor resection. Rather, it represents a report of several patients currently under our care with pathologically confirmed FGA. Review of the literature provided the diagnostic criteria used in this analysis: a diagnosis of FGA can be made only when there are either elevated levels of FSH/LH or non-suppressed FSH/LH in the presence of elevated gonadal steroids, and clinical symptoms of FGA as noted above.^{2, 5, 9, 24, 35, 39} In six of the seven patients in this series, excess serum levels of FSH led to diagnosis of FGA. In the remaining case, both FSH and LH appeared within normal limits, but additional testing revealed elevated gonadal steroids, which should have suppressed gonadotropin levels. Hormonal excess along the hypothalamic-pituitary-gonadal axis should, therefore, be considered a strong indicator for FGA in patients harboring a pituitary adenoma. Early detection and surgical intervention for FGA has the potential to preempt unnecessary and potentially damaging treatment for comorbidities (e.g., ovarian cysts) and improve or restore sexual and reproductive function.

Both female patients presented with clinical symptoms attributable to a gonadotroph adenoma—in one case, infertility, ovarian cysts, and menstrual irregularity; in the other, ovarian hyperstimulation and polycystic ovaries prompting unilateral salpingo-oophorectomy. Subsequent imaging revealed pituitary adenoma; nevertheless, the diagnosis of FGA was elusive. In one case, both LH and FSH were within normal limits (in the setting of elevated gonadal steroids); in the other, FSH was only mildly elevated. Pathologic examination of tumor tissue supported the diagnosis underlying each patient's symptoms.

Because menstrual irregularity frequently motivates a thorough endocrine workup, it is often more difficult to diagnose FGA in men compared to women.²⁴ Symptoms in men such as testicular hypertrophy and sexual dysfunction often escape notice, or are attributed to alternative causes, such as aging, prostate dysfunction, or cardiovascular illness. Four of the five male patients in this series presented with the sequelae of a slowly enlarging tumor, and none was found to have symptoms specific to hormonal excess. In some instances, as in Case 7, the symptoms common to FGA among men (e.g., sexual dysfunction and erectile dysfunction) may be masked or treated effectively by use of tadalafil or other common medications for BPH and ED, delaying diagnosis and treatment of FGA. All five men had evidence of FSH excess on initial biochemical evaluation, and tissue diagnosis proved confirmatory in all.

Resection of FGA is typically successful in ameliorating symptoms from both mass effect and gonadotrophic excess.^{4, 6, 27} Among the seven, those with the largest lesions experienced peri-operative complications with need for further treatment. Patient 2, one of the two patients who underwent reoperation for lesional resection, had neither gross total resection nor a definitive pathological diagnosis during the first operation. Patient 3, who also had a reoperation, never entered endocrinological remission from the symptoms of FGA, and was known to have residual tumor after the first operation. Patients 4 through 7 underwent tumor resection within the last year and will need continued supervision for possible recurrence of tumor or endocrinopathies.

Limitations

Limitations of this study include the lack of a thorough testicular exam in all male patients upon presentation, which could have aided in a conclusive diagnosis of FGA through detection of testicular hypertrophy. This study is additionally limited by its retrospective design and relatively short follow-up time on several patients, as well as by the aforementioned difficulties in conclusive diagnosis of FGA itself. For example, the patients in cases five and six may have been experiencing beta subunit secretion alone, as they remained hypogonadal.

Major complications are uncommon during surgery for all types of pituitary adenoma, but they vary based on tumor size and location.⁴⁰ Some studies have demonstrated that patients with larger or more invasive tumors are more likely to develop peri-operative hypopituitarism.⁴¹⁻⁴³ Because FGA often present as macroadenomas, complications linked to large tumor size should be considered during peri-operative care. In this case series, three patients (Patients 1, 2, and 5) developed pituitary insufficiency (one in the thyroid axis only, two panhypopituitary). Nevertheless, in comparison to transsphenoidal surgery for other

types of pituitary adenoma—including ACTH-, GH-, and prolactin-secreting—transsphenoidal surgery for FGA is highly similar and likely poses no additional risk based on subjective surgical experience when controlling for complicating variables such as tumor size, invasion, and recurrence, and remains the standard of care.

Conclusion

FGA can pose both a diagnostic and therapeutic challenge. The tumor is often diagnosed as a macroadenoma in the setting of a patient presenting with non-specific symptoms, and is associated with significant morbidity. FGA should be considered in the differential diagnosis of patients harboring pituitary adenomas with reproductive dysfunction. Transsphenoidal resection is the initial treatment of choice. Resection can reduce endocrine dysfunction, resolve headaches, improve visual impairment, sexual and reproductive function, and provide tissue for detailed analysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Immunohistological characteristics of seven cases of functional gonadotroph adenomas.
Hematoxylin and eosin staining (a-g). Immunohistochemical staining for FSH-beta subunit
(h-n), and LH (o-u).

Figure 2.
Pre- (left) and post-operative (right) T1 gadolinium-enhanced, coronal MRI showing resection of FGA and decompression of optic chiasm (Case 4).

Table 1

Presenting symptoms of patients with functional gonadotroph adenomas.

Case	Sex	Age	BMI [*]	FMH [#]	Headache	Vision Impaired	Hypopit.	Sexual Dysfunction	Infertility	Menstrual Irregularities	Galactorrhea
1	Male	45	30.9	No	No	Yes	No	No			No
2	Female	35	19.1	No	Yes	No	No	No	No	No	No
3	Male	52	24.2	No	Yes	Yes	No	No			No
4	Female	32	24.0	No	Yes	Yes	No	Yes	Yes	Yes	No
5	Male	71	24.1	No	No	Yes	Yes	Yes			No
6	Male	62	32.5	No	No	Yes	No	Yes			No
7	Male	64	31.6	No	No	No	No	No			No

^{*} BMI = body mass index.

[#] FMH = relevant family medical history

Table 2

Endocrine test results for patients with functional gonadotroph adenomas.

Patient	Pre-Operative FSH	Pre-Operative LH	Pre-Operative Prolactin	Pre-Operative Estradiol	Pre-Operative Testosterone	Post-Operative FSH	Post-Operative LH	Post-Operative Prolactin	Post-Operative Estradiol	Post-Operative Testosterone
1	27.8 *	4.5	10.8		253.9	1.8	0.3	3.3		442.4
2	17.3 *	<0.1 *	122.9 *	130		8.3	1.3	13.3	21	
3	159.1 *	4.2	6.5		830.0	139.6 *	2.6	7.2		502
4	9.4	0.04 *	45.9 *	458 *		13.2 *	11.7	8.7	153	
5	125.3 *	2.5	8.7		48.0 *	7.1	2.9	5.6		358.3
6	25.0 *	2.2	21.8 *		233	4.7	3.1	6.0		310.0
7	39.4 *	4.5	9.5		457	8.7	4.7	8.3		396.0

* abnormal result

Table 3

Peri-operative characteristics and care of patients with functional gonadotroph adenomas.

Patient	Pre-Operative MRI Max Dimension	Pre-Operative MRI Volume *	Suprasellar Extension	Abdominal Fat Graft	Hospital Days	Permanent Diabetes Insipidus	Transient Diabetes Insipidus	Radiation	Path FSH	Path LH
1	4.5	30.38	Yes	Yes	4	Yes	No	Yes	Yes	Yes
2	2.9	7.61	Yes	Yes	2	No	Yes	No	Yes	No
3	2.9	6.96	Yes	No	19	No	No	No	Yes	No
4	1.3	0.65	No	No	3	No	No	No	Yes	Yes
5	2.4	4.05	Yes	No	2	No	No	No	Yes	Yes
6	3.2	8.464	Yes	No	3	No	No	No	Yes	Yes
7	3.0	10.53	Yes	Yes	3	No	No	No	Yes	Yes

* by ABC/2 method (cm^3)