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Case Report

Co-occurrence of Functional Gonadotroph Adenoma and Lactotroph Adenoma: A Case Report and Literature Review

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ABSTRACT

Background/Objective: Functional gonadotroph adenomas (FGAs) are adenomas producing active gonadotropins, follicle-stimulating hormone or luteinizing hormone. Double pituitary adenomas are 2 distinct adenomas occurring in an individual. This report aimed to present an extremely rare case of an FGA, itself an uncommon disorder, co-occurring with a lactotroph adenoma.
Case Report: A 33-year-old woman presented with menorrhagia and was found to have ovarian enlargement, large uterine leiomyomas, and bitemporal hemianopsia. Initially, the levels of follicle-stimulating hormone, luteinizing hormone, estradiol, and prolactin were 73.3 mIU/mL (midcycle peak, 2.3-20.9 mIU/L), 3.74 mIU/L (midcycle peak, 8.7-76.3 mIU/L), 1071 pg/mL (midcycle peak 38-649 pg/mL), and 402 ng/mL (2-30 ng/mL), respectively. Pituitary magnetic resonance imaging demonstrated a single sellar mass (2.0 × 2.2 cm). Two months of cabergoline did not reverse visual field deficits; therefore, transsphenoidal resection was performed. Diagnosis of 2 separate adenomas, a gonadotroph and lactotroph adenoma, was confirmed on pathology.
Discussion: In this case, gonadotropins did not suppress in response to hyperprolactinemia. Although marked hyperprolactinemia has been associated with functional and clinically silent gonadotroph adenomas in prior cases, this is the first case to confirm an FGA co-occurring with a lactotroph adenoma.
Conclusion: In patients who present with elevated gonadotropin levels despite hyperprolactinemia, we suggest considering FGA. Further research is needed to clarify whether there is underdiagnosis of lactotroph adenomas co-occurring with gonadotroph adenomas.

Introduction

Gonadotroph adenomas are recognized based on transcription factor profile or immunoexpression of follicle-stimulating hormone (FSH), luteinizing hormone (LH), or α-subunit (ASU) hormone on histopathology.[1] Gonadotroph adenomas compose a substantial proportion of clinically silent pituitary adenomas, tumors expressing anterior pituitary hormones or transcription factors by immunohistochemistry (IHC) but not secreting these hormones in functional form or at clinically relevant concentrations.[2] Conversely, functional gonadotroph adenomas (FGAs) secrete active forms of 1 or both gonadotropins, FSH and LH.[3] The prevalence of FGA is not clearly defined, partially owing to ambiguous symptoms and lack of epidemiologic studies.[3] Furthermore, double pituitary adenomas are 2 co-occurring adenomas, each with unique light microscopic and IHC features.[4] Large autopsy series (n = 470 and n = 3048) indicate that double or multiple adenomas are uncommon in the general population (0.4%-0.5%), and multiple adenomas are observed in only 4%-5% of adenomas.[5,6] Owing to the rarity of FGAs and double adenomas individually, reports of double pituitary adenomas containing an FGA are sparse.[7-11] We present a rare case of the co-occurrence of a gonadotroph adenoma and lactotroph adenoma.

Abbreviations: ACTH, adrenocorticotropic hormone; ASU, α-subunit; FGA, functional gonadotroph adenoma; FSH, follicle-stimulating hormone; IHC, immunohistochemistry; LH, luteinizing hormone; MRI, magnetic resonance imaging; PRL, prolactin; TSH, thyroid-stimulating hormone.

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Case Report

A 33-year-old nulligravida woman, who provided informed consent for this case report, initially presented to the Department of Obstetrics and Gynecology following 3 months of abdominal pain and heavy menstrual bleeding requiring 1-unit blood transfusion. Gynecologic history included infertility, diagnosed at the age of 31 years following 2 years of attempted conception, and oligomenorrhea since menarche at the age of 14 years. She denied frequent headaches and galactorrhea. Abdominal magnetic resonance imaging (MRI) showed multiple heterogeneous uterine masses, largest at 13.0 × 9.7 × 10.6 cm, and bilateral ovarian enlargement (right, 6.0 × 4.2 × 5.3 cm; left, 4.8 × 4.4 × 4.4 cm) with multiple cysts. The size of the endometrium was 7 mm on pelvic ultrasound. Initial endocrinology evaluation (Table 1) showed the following: (1) serum prolactin (PRL) level, 402.1 ng/mL (2-30 ng/mL); (2) estradiol level, 1071 pg/mL (midcycle peak, 38-649 pg/mL); (3) FSH level, 60.78 mIU/L (midcycle peak, 2.3-20.9 mIU/L); (4) antimüllerian hormone level, <0.1 ng/mL (0.9-9.5 ng/mL); (5) negative urine human chorionic gonadotropin; (6) thyroid-stimulating hormone (TSH) level, 2.55 mIU/L (0.45-4.5 mIU/L); (7) free thyroxine level, 0.8 ng/dL (0.7-1.5 ng/dL); (8) insulin-like growth factor-1 level, 58 ng/mL (53-331 ng/mL, Z score = −1.8); (9) morning cortisol level, 13.2 μg/dL (>3 μg/dL); and (10) adrenocorticotropic hormone (ACTH) level, 32 pg/mL (7-63 pg/mL).

Pituitary MRI demonstrated a 2.1 × 2.0 × 2.2-cm sellar mass with suprasellar extension (Fig. 1). Visual field testing revealed bitemporal hemianopsia.

Cabergoline, 0.25 mg twice weekly, treatment was initiated, and at 2-month follow-up, the patient reported regular menses. Treatment resulted in PRL normalization, FSH reduction, and a modest decrease in the estradiol level (Table 1); however, there was no tumor volumetric response. Because visual field deficits persisted and there was concern for irreversible vision loss without intervention, she subsequently underwent transsphenoidal resection with successful gross total pituitary adenoma removal. Cabergoline was discontinued at surgery.

Immediate postoperative course was uncomplicated. Extending to 16 months postoperatively, she reported hot flashes and amenorrhea. Hormonal studies 2 months postoperatively showed estradiol, progesterone, and PRL levels of <10 pg/mL, 0.2 ng/mL (<1.7 ng/mL indicates the follicular phase), and 6.1 ng/mL, respectively. At 16 months postoperatively, the reproductive axis had not recovered (Table 1), and sex hormone replacement therapy was initiated. Neuro-ophthalmologic evaluation 6 months postoperatively revealed near-complete resolution of visual field deficits. Pituitary MRI 32.5 months postoperatively (Fig. 1) showed no definitive tumor residual.

For pathologic analysis, formalin-fixed and paraffin-embedded tissues of the pituitary tumor resection were analyzed by serial sections with hematoxylin and eosin, Wilder reticulin, and IHC stains for the pituitary hormones PRL, growth hormone, ACTH, β-TSH, β-FSH, β-LH, and ASU of the glycoproteins and transcription factors TPIT, SF1, and PIT1 using the automated Leica Bond III (Leica Biosystems) platform.

The materials received for pathologic analysis consisted of multiple tan-red, friable tissue fragments, measuring in aggregate 1.4 × 0.8 × 0.3 cm. Histologic sections revealed 2 separate adenomas composed of different cellular elements. A larger adenoma was composed of a proliferation of medium-sized cells with eosinophilic to clear cytoplasm with central small round nuclei and indistinctive nucleoli. A second and smaller adenoma was composed of smaller cells with slightly eosinophilic cytoplasm and round, hyperchromatic nuclei. Mitotic figures were not observed on either adenoma. A small rim of compressed anterior pituitary gland was present between these 2 separate adenomas. IHC stains showed diverse immunoprofiling of the 2 adenomas. The larger adenoma was immunopositive for β-FSH, β-LH, ASU, and SF1 in a widespread manner (Fig. 2). The tumor was negative for growth hormone, PRL, ACTH, β-TSH, PIT1, or TPIT. These findings were consistent with gonadotroph adenoma. The second smaller adenoma showed immunoreactivity for PRL and PIT1. The tumor was negative for all remaining pituitary hormones and transcription factors. These findings were consistent with lactotroph adenoma. Therefore, the surgical specimen revealed 2 synchronous gonadotroph and lactotroph adenomas.

Highlights

- Functional gonadotroph adenomas may be underrecognized because of ambiguous symptoms
- In women, symptoms range from ovarian hyperstimulation syndrome to irregular menses
- Double adenomas are rare but frequently missed on magnetic resonance imaging
- Hyperprolactinemia should suppress gonadotropins
- Preclinically, excess estrogen stimulates lactotroph hyperplasia and tumor growth

Clinical Relevance

There is an association between gonadotroph adenomas and profound hyperprolactinemia. We hypothesize that chronic excess estrogen stimulates lactotroph adenoma growth/development. A presumed prolactinoma lacking gonadotroph suppression or not responding volumetrically to dopamine agonism warrants broadening the differential to include a co-occurring gonadotroph adenoma.

Table 1
Hormonal Assessment Before and After Medical and Surgical Therapy

Time	PRL (ng/mL)	FSH (mIU/mL)	LH (mIU/L)	Estradiol (pg/mL)
Initial evaluation	402.1	60.78		1071
Before medical therapy, 10 d later	454.0	73.38	3.74	771
After medical therapy	3.9	10.38	0.6	658
2 mo postoperatively	6.1	10.5	1.72	<10
16 mo postoperatively	7.9	10.9	4.11	<10

Abbreviations: FSH = follicle-stimulating hormone; LH = luteinizing hormone; PRL = prolactin.
Reference ranges: for PRL, 2-30; for FSH, follicular phase, 1.1-9.6; midcycle peak, 2.3-20.9; luteal phase, 0.8-7.5; and postmenopausal, 34.4-95.8; for LH, follicular phase, <1.9-12.5; midcycle peak, 8.7-76.3; luteal phase, 0.5-16.9; and postmenopausal, 5.0-52.3; and for estradiol, follicular phase, 21-251; midcycle peak, 38-649; luteal phase, 21-312; and postmenopausal, <10-28.

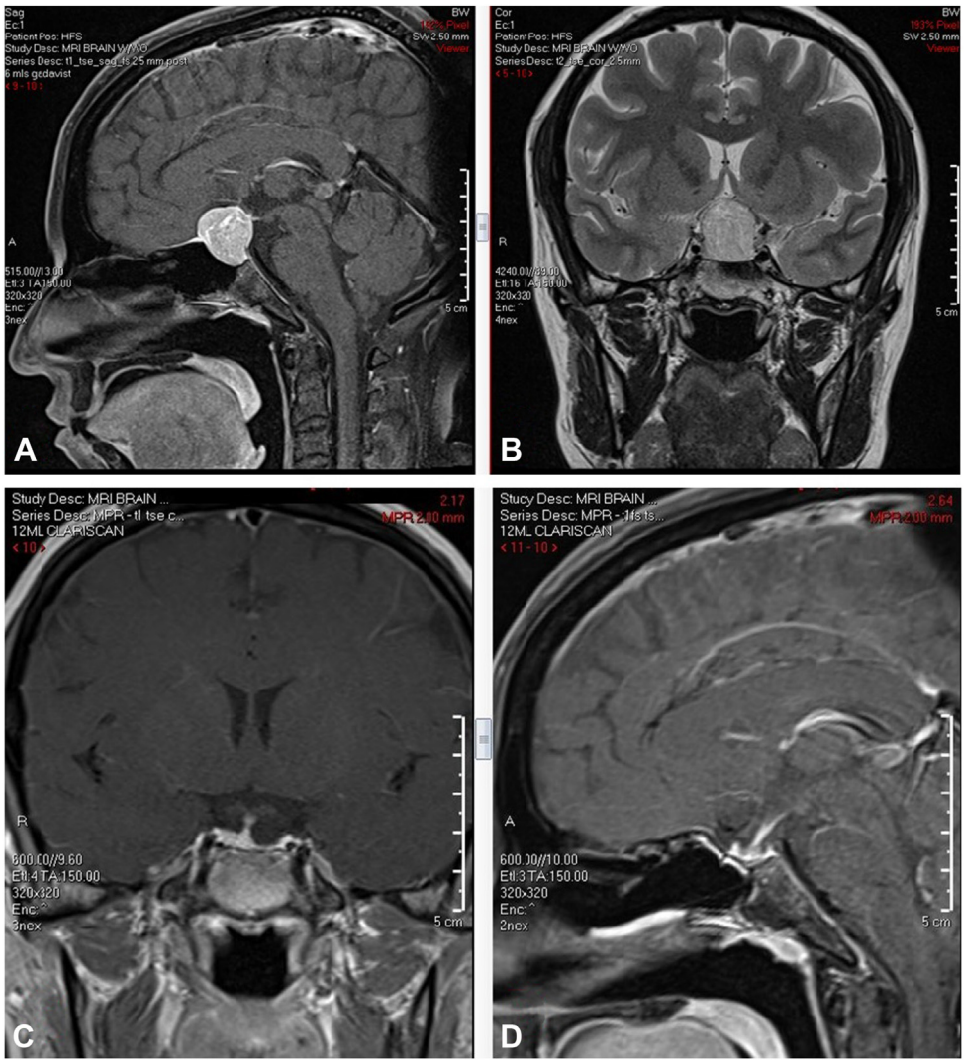

Fig. 1. Preoperative and postoperative pituitary magnetic resonance imaging (MRI). Preoperative postcontrast T1 sagittal (*A*) and T2 coronal (*B*) pituitary MRI demonstrating a 2.1 × 2.0 × 2.2-cm sellar mass with suprasellar extension compressing the optic chiasm without evidence of cavernous sinus invasion. Postoperative T1 coronal (*C*) and T1 sagittal (*D*) MRI showing no definitive mass residual or recurrence.

Review of previously resected uterine leiomyomas with additional IHC staining showed no PRL expression.

To ensure a comprehensive literature search, the first and last authors conducted a literature review from March 2022 to July 2022 for pathology-confirmed double lactotroph and gonadotroph adenomas using the U.S. National Library of Medicine Medical Subject Headings terms “prolactinoma” AND “gonadotrophs” + “gonadotrophs” AND “lactotrophs,” which yielded 2 of 43 and 0 of 25 relevant manuscripts, respectively. The terms “Lactotroph adenoma” AND “gonadotroph adenoma” + “gonadotrophs” AND “double adenoma” were also used, yielding 2 of 43 and 1 of 1 relevant manuscript, respectively, which were all duplicates.

Discussion

In this report, we describe a 33-year-old woman who presented with polymenorrhagia and abdominal pain and was found to have ovarian enlargement, large uterine leiomyomas, and bitemporal hemianopsia. The FSH and estradiol levels were elevated despite a profoundly elevated PRL level. This was unexpected given modest hyperprolactinemia suppresses gonadotropins, largely via inhibiting gonadotropin-releasing hormone pulsatility.[12] The patient also had evidence of mild ovarian hyperstimulation syndrome, a condition of excess gonadotropin-mediated ovarian stimulation typically encountered as an adverse effect of artificial reproductive technology but also previously reported in several cases of FGA.[13] Ovarian hyperstimulation syndrome symptoms include enlarged/cystic ovaries, abdominal pain/bloating, nausea/vomiting, and diarrhea in mild cases.[13] These clinical features, along with an elevated estradiol level, indicate that the gonadotroph adenoma was functional.

Additionally, cabergoline caused FSH and LH level reductions and a more modest decrease in the estradiol level. Dopamine 2 receptors are expressed in gonadotroph and other cell-type adenomas, and they are potential mediators whereby dopamine agonists reduce hormonal secretion and tumor cell proliferation/volume.[14,15] Thus, direct tumor effect by cabergoline may have caused the observed gonadotropin reduction preoperatively.

Following surgery, hypogonadotropic hypogonadism was evident. This could be tumor-mediated or due to surgical iatrogenic damage. Excess gonadotropin production could mask tumor−related damage to normal gonadotrophs. The patient reported regular menses following brief cabergoline treatment, potentially indicating preserved gonadotroph function; however,

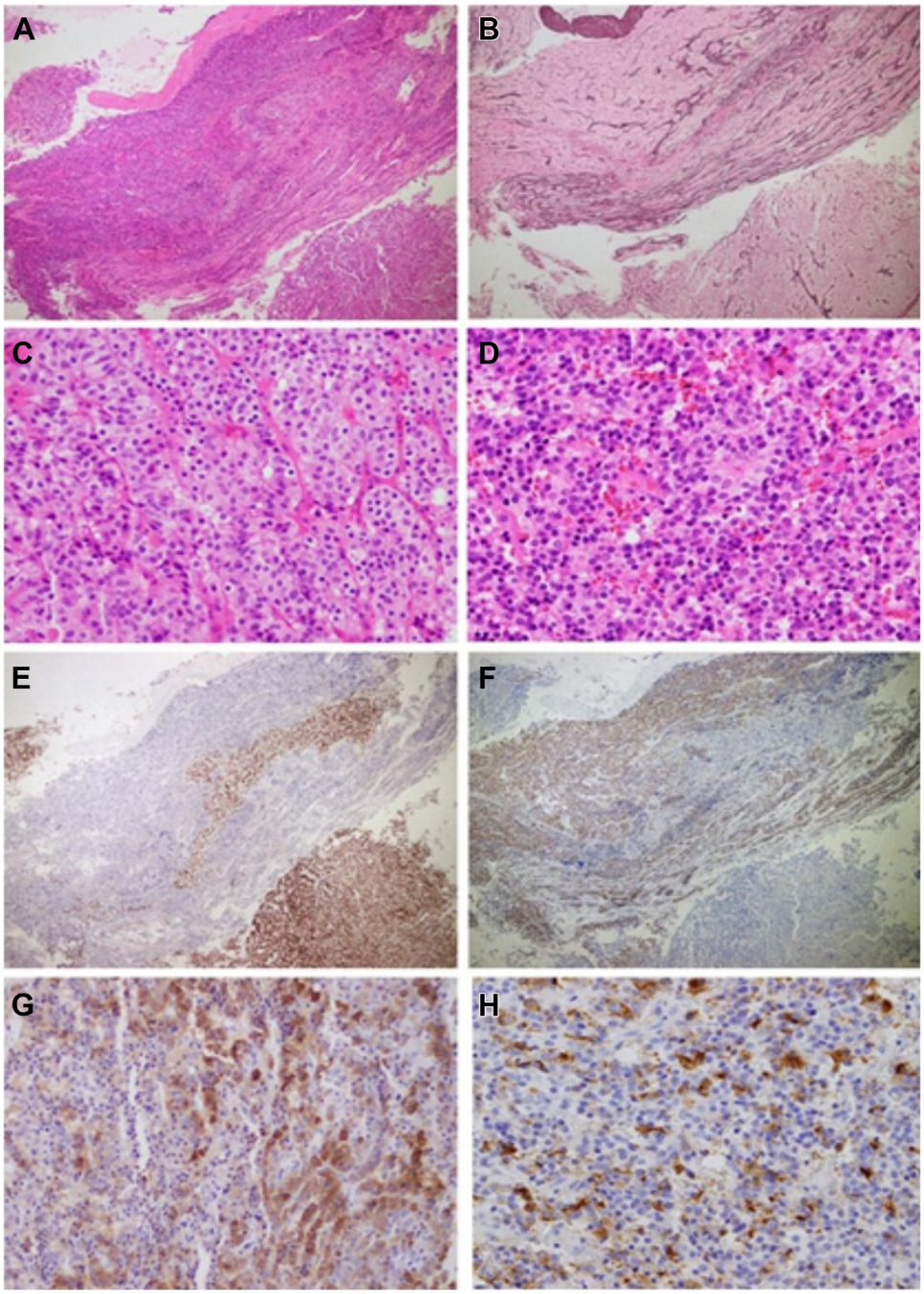

Fig. 2. Histopathology of the pituitary adenomas. Two separate adenomas were present on the surgical specimen that were separated by tongues of compressed pituitary gland (*A*, hematoxylin and eosin; *B*, Wilder reticulin). The larger tumor was composed of medium-sized cells with eosinophilic to clear cytoplasm and central nuclei with homogeneous chromatin pattern (*C*). The tumor cells expressed SF1 (*E*) and β-follicle-stimulating hormone (*G*). The tumor was also immunoreactive for β-luteinizing hormone and α-subunit of glycoproteins (not shown). The second adenoma was composed of smaller eosinophilic cells with central hyperchromatic nuclei (*D*). The tumor cells expressed PIT1 (*F*) and prolactin (*H*). (*A*, *C*, *D*) Hematoxylin and eosin. (*B*) Wilder reticulin (B). (*C-F*) Immunohistochemistry for SF1 (*E*), PTI1 (*F*), β-follicle-stimulating hormone (*G*), and prolactin (*H*). Original magnifications: ×10 (*A*, *B*, *E*, *F*) and ×40 (*C*, *D*, *G*, *H*).

we cannot rule out dysfunctional uterine bleeding from persistent estrogen elevation.

In our literature review, FGA co-occurring with lactotroph adenoma was not previously reported although our search generated 3 silent gonadotroph and lactotroph double adenoma cases (Table 2). Roberts et al[7] presented 2 such cases; the first case was a 43-year-old woman who presented with amenorrhea and galactorrhea and had an elevated PRL level. Cabergoline treatment yielded a biochemical response without tumor size reduction.[7] The second case was a 56-year-old woman who presented with headaches.[7] Although the PRL level was not elevated, pathology reported an FSH/ASU staining—positive adenoma slightly intermingling with a PRL staining—positive adenoma.[7] Coiré et al[11] described a 43-year-old man experiencing headaches, with an extremely elevated PRL level of 5088 ng/mL, FSH level of 2.9 mIU/mL, and low total testosterone and free testosterone levels. Cabergoline treatment resulted in partial volumetric and biochemical response, with the PRL level decreasing to 274 ng/mL.[11] Similar to our case

Table 2
Comparison of Previous Cases

Study	PMID	Age (y)	Symptoms	Pituitary tumor size (cm)	PRL (ng/mL)	FSH (mIU/mL)	LH (mIU/mL)	E2 (pg/mL)	Neuropathology immunostaining
Roberts et al[7]	27209585	43	Amenorrhea, galactorrhea	-	139	-	-	-	FSH/ASU and PRL
Roberts et al[7]	27209585	56	Headaches	-	14	-	-	-	FSH/ASU and PRL
Coiré et al[11]	20058099	43	Headaches	-	5,088	2.9	-	-	FSH and PRL

Abbreviations: ASU = α-subunit; E2 = estradiol; FSH = follicle-stimulating hormone; LH = luteinizing hormone; PRL = prolactin.

presentation, in all of these prior cases, the presence of 2 adenomas was not recognized by imaging or intraoperatively, and the tumors responded biochemically to cabergoline.

We hypothesize that in our patient, without a known family history or clinical features suggesting multiple endocrine neoplasia type 1 or other predisposing condition, prolonged and profound estrogen level elevation from the FGA could have contributed to prolactinoma development or growth. Estrogen stimulates PRL gene expression and secretion under normal physiology. Thus, the PRL levels increase in the periovulatory phase and pregnancy.[16] In preclinical studies, consistent evidence indicates that high-dose estrogen induces prolactinomas. Estrogen stimulates cell-type transdifferentiation to lactotroph,[17] a longer duration of estrogen stimulates greater lactotroph hyperplasia, and estrogen induces proangiogenic growth factor expression, which may promote tumor growth.[17-19] Furthermore, estrogen likely directly stimulates lactotroph proliferation.[18] Thus, several potential mechanisms exist whereby excess estrogen could stimulate lactotroph adenoma development or enlargement.

In humans, excessive PRL level elevations (>200 ng/mL) accompany gonadotroph adenomas in several cases.[8-10] Although these cases report negative PRL IHC staining, it is plausible that either estrogen stimulated normal lactotroph proliferation/PRL secretion or a small prolactinoma was missed in surgical resection or histopathology evaluation. It is also noteworthy that a meta-analysis describes gonadotroph adenomas as one of the most common silent adenomas associated with profound hyperprolactinemia.[20] This raises the possibility of FGA being underrecognized.

Conclusion

This case highlights the extremely rare co-occurrence of an FGA with a lactotroph adenoma. Because of the rarity and ambiguous symptoms, FGA is a diagnostic challenge. This case suggests a need to consider FGA in cases of presumed prolactinomas that do not demonstrate gonadotroph suppression despite an elevated PRL level. More research is needed to understand whether FGAs, and possibly co-occurring lactotroph hyperplasia or lactotroph adenomas, are underrecognized.

Disclosure

The authors have no multiplicity of interest to disclose

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