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Case Report

A Rare Case of Precocious Puberty Secondary to an LH-secreting Pituitary Adenoma

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Abstract

An 8-year, 7-month-old male presented with puberty symptoms, including a 1.5-year history of facial hair with 9 months of phallic growth, body odor, and acne. Physical examination revealed phallic enlargement but only 4 mL testes bilaterally. Laboratory evaluation revealed markedly elevated LH and testosterone, but a prepubertal FSH level and minimally elevated adrenal androgens. A magnetic resonance imaging scan of the head revealed an anterior pituitary adenoma, and after the patient failed to respond to leuprolide, he was initiated on spironolactone and anastrozole to minimize pubertal progression before transsphenoidal adenomectomy. Postoperatively, the patient had rapid reduction of LH and testosterone, with subsequent cessation of pubertal progression, confirming the diagnosis of an LH-secreting pituitary adenoma despite negative immunoreactivity for LH and FSH. Functioning gonadotroph adenomas are rare and have been documented only in small case series and case reports. When active, these most commonly secrete FSH or co-secrete FSH and LH, and only very rarely result in precocious puberty. Here, we describe a rare case of an isolated LH-secreting functioning gonadotroph adenoma resulting in precocious puberty. This case reinforces the need to critically analyze departures from the typical pubertal sequence and to expand one's differential to include etiologies that can cause unbalanced secretion of gonadotropins.

Key Words: functioning gonadotroph adenoma, precocious puberty, LH-secreting pituitary adenoma, LH-secreting pituitary neuroendocrine tumor

Abbreviations: FGA, functioning gonadotroph adenoma; MRI, magnetic resonancing imaging.

Introduction

Normal male puberty results from concurrent rise in LH and FSH. LH acts on Leydig cells to stimulate testosterone and secondary sex characteristics, whereas FSH stimulates the maturation of seminiferous tubules, resulting in testicular growth. This results in a typical pubertal sequence with testicular enlargement as the earliest clinical indicator of pubertal onset [1].

Precocious puberty is defined as that which occurs before the age of 9 years in males. Although gonadotropin-dependent precocious puberty is most often idiopathic in females, it is more commonly associated with pathologic causes in males. Commonly associated intracranial lesions include hypothalamic hamartomas, hydrocephalus, neurofibromatosis type 1, and pineal tumors [1, 2]. Only rarely does precocious puberty result from a functioning gonadotroph adenoma (FGA), which are now sometimes referred to as pituitary neuroendocrine tumors [3].

FGAs can secrete LH, FSH, or both, but most commonly secrete FSH or a combination of FSH and LH. Clinically relevant FGAs are exceedingly rare, only being previously documented in small case series and case reports [4]. Although uncommon in pediatric patients, FGAs often present as mass effect and/or atypical timing or sequence of puberty [4, 5].

Here, we describe a rare case of precocious puberty secondary to an isolated LH-secreting pituitary adenoma.

Case Presentation

An 8-year, 7-month-old previously healthy male presented to a pediatric endocrinology clinic for evaluation of precocious puberty. He had a 1.5-year history of facial hair growth with 9 months of phallic growth, deepening voice, body odor, and acne. He denied headaches, changes in vision, fatigue, galactorrhea, and known exposure to exogenous androgens.

Family history was notable for a maternal aunt with precocious puberty of unknown etiology at age 6 years. Maternal menarche occurred at 11 years of age, whereas paternal pubertal onset was mildly delayed.

During the 3 months before presentation, the patient's height accelerated from the 45th to the 71st percentile (Fig. 1). A physical examination revealed Tanner stage I pubic hair and firm testes without masses measuring 4 mL in volume bilaterally. Stretched penile length at 8 years, 9 months measured 6.5 cm (mean for age, 6.3 cm), although his parents had noted subjective phallic growth [6].

Diagnostic Assessment

At 8 years, 6 months of chronologic age, the patient's bone age was consistent with the 9-year standard according to the Atlas of Greulich and Pyle. However, it advanced rapidly to 13 years

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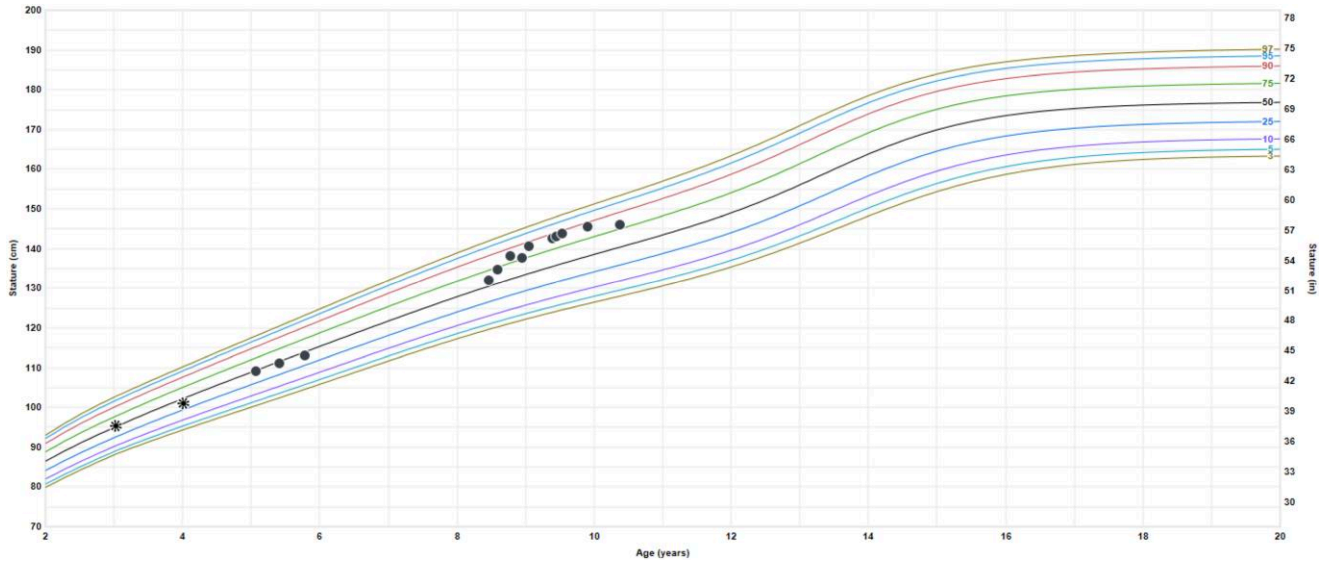

Figure 1. Patient with growth acceleration at 8 years, 6 months, with resolution following adenomectomy at 8 years, 11 months. The patient has tracked between the 80th and 88th percentile thereafter.

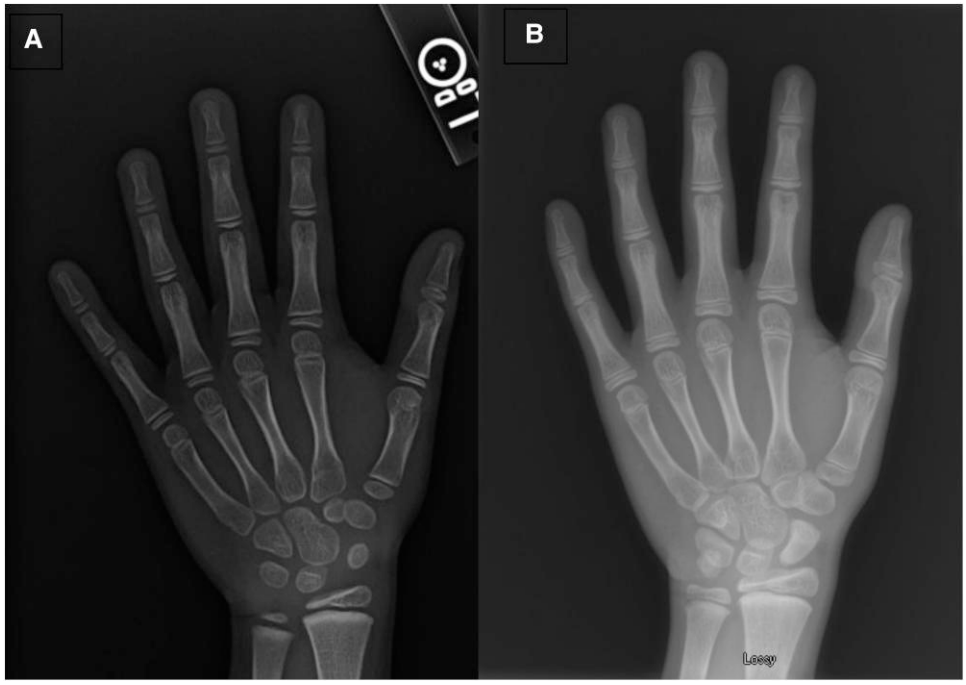

Figure 2. Patient with bone age of 9 years at 8 years, 6 months' chronologic age (A) with advancement to 13 years by 9 years' chronologic age (B).

by 9 years of chronological age (Fig. 2). Initial laboratory evaluation revealed elevated LH (9 mIU/mL [9 IU/L], reference range [RR], 0.0-0.3 mIU/mL [0.0-0.3 IU/L]) and testosterone (519 ng/dL [18 nmol/L]; RR, 2-8 ng/dL [0.07-0.28 nmol/L]), prepubertal FSH (<0.1 mIU/mL [<0.1 IU/L]; RR, 0.0-2.8 mIU/mL [0.0-2.8 IU/L]), with other androgens mildly elevated for age (androstenedione, 0.36 ng/mL [1.27 nmol/L]; RR, 0.04-0.32 ng/mL [0.14-1.12 nmol/L]; 17-OHP, 155 ng/dL [4.69 nmol/L]; RR, <62 ng/dL [<1.88 nmol/L]). Both IGF-1 (541 ng/mL [70.73 nmol/L]; RR, 20-347 ng/mL [2.61-45.37 nmol/L]) and α-subunit (9 ng/mL [9 µg/L]; RR <1.2 ng/mL [<1.2 µg/L]) were elevated, whereas thyroid studies (TSH, 1.35 mIU/L; RR, 0.35-4.94 mIU/L); free T4, 0.81 ng/mL [1.74 nmol/L]; RR, 0.7-1.48 ng/mL [0.9-1.91 nmol/L]), prolactin (17.1 ng/mL [17.1 µg/L]; RR, 4.2-23 ng/mL [RR, 4.2-23 µg/L]) and β-hcg (<2 mIU/mL [<2 IU/L]; RR, <5 mIU/mL [<5 IU/L]) were within normal limits.

Concern for central precocious puberty necessitated magnetic resonance imaging (MRI) scan of the head that revealed an anterior pituitary adenoma measuring $8 \times 12 \times 10$ mm with superior and posterior displacement of his anterior pituitary. A normal posterior bright spot was present, and no compression of the optic chiasm or other surrounding structures was noted (Fig. 3).

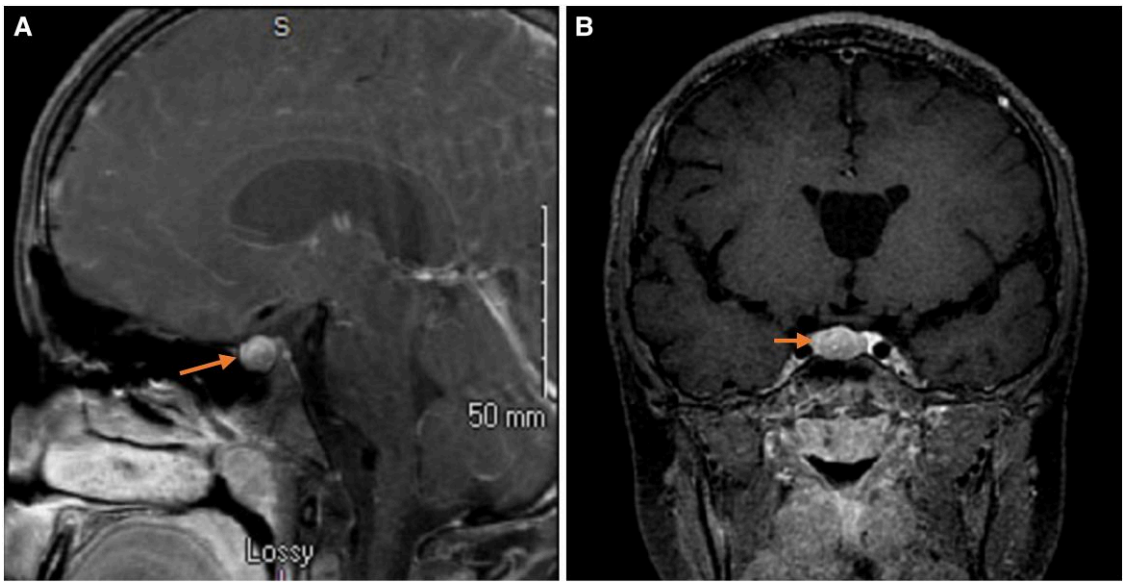

Figure 3. An 8 × 12 × 10 mm hypo-enhancing mass consistent with an anterior pituitary adenoma seen in both sagittal (A) and coronal (B) views.

Treatment

Leuprolide (30 mg every 3 months) was started following initial evaluation in an attempt to slow pubertal progression. However, at 8 years, 9 months, LH (9.8 mIU/mL [9.8 IU/L]; RR, 0.0-0.3 mIU/mL [0.0-0.3 IU/mL]) and testosterone (758 ng/dL [26.28 nmol/L]; RR 2-8 ng/dL [0.07–0.28 nmol/L]), remained up-trending with concurrent elevation of estradiol (44 pg/mL [161.54 pmol/L]; RR 0-13 pg/mL [0.0-47.73 pmol/L]). Anastrozole (1 mg daily) and spironolactone (2.5 mg/kg twice per day) were then started to minimize height acceleration and pubertal symptoms while pursuing transsphenoidal adenomectomy, with suppression of estradiol (<10 pg/mL [<36.7 pmol/L]) and modest decrease in testosterone (571 ng/dL [19.8 nmol/L]) 5 weeks after initiation. The patient had subsequent improvement in acne and reduction in height velocity from 20 cm/y between 8 years, 6 months, and 8 years, 9 months, to 9 cm/y between 8 years, 9 months, and 9 years (Fig. 1).

The patient's adenoma was resected successfully at 8 years, 11 months without evidence of residual tumor during surgery or on MRI in the immediate postoperative period. Pathology was positive for steroidogenic factor 1, but negative for LH, FSH, and TSH immunoreactivity.

Outcome and Follow-up

One week postoperatively, the patient showed reduction of LH (0.4 mIU/mL [0.4 IU/L]), testosterone (16 ng/dL [0.55 nmol/L]), and α-subunit (0.4 ng/mL [0.4 µg/L]; RR, <1.2 ng/mL [<1.2 µg/L]). Both LH (0.3 mIU/mL [0.3 IU/L]) and testosterone (5 ng/dL [0.17 nmol/L]) demonstrated further reduction to prepubertal levels 5 weeks postoperatively with associated reduction of IGF-1 (382 ng/mL [49.94 nmol/L]; RR, 20-347 ng/mL [RR, 2.61-45.37 nmol/L]). Clinically, the patient experienced stabilization of facial hair and penile growth and body odor and acne resolved. The patient's height velocity stabilized and consistently tracked between the 80th and 88th percentile thereafter (Fig. 1). A follow-up MRI scan at 9 years, 6 months, showed no evidence of residual or recurrent tumor.

The patient entered central puberty at 9 years, 4 months, of age with elevation of LH (0.8 mIU/mL [0.8 IU/L]), FSH (3.3 mIU/mL [3.3 IU/L]), and testosterone (98 ng/dL [3.40 nmol/L]). To optimize height, leuprolide (30 mg every 3 months) was initiated with successful suppression of LH (0.4 mIU/mL [0.4 IU/L]) and testosterone (8 ng/dL [0.28 nmol/L]) 15 weeks after initial leuprolide administration. Bone age advancement slowed and remained 13 years at 9 years, 11 months' chronologic age, with associated reduction of growth velocity (Fig. 1).

Discussion

We report a case of precocious puberty in a male patient secondary to an LH-secreting pituitary adenoma. In this case, digression from the typical pubertal timing and sequence raised concern for an underlying pathologic cause. Minimal testicular enlargement with advanced signs of androgen production was initially concerning for peripheral precocious puberty, with exogenous androgen exposure, familial male-limited precocious puberty, Leydig cell tumor, human chorionic gonadotropin–secreting tumor, and adrenal etiologies high on the differential. However, elevated LH instead indicated gonadotropin-dependent precocious puberty. With a known association of gonadotropin-dependent precocious puberty with central nervous system lesions in males and the disproportionate elevation of LH compared with FSH, the patient appropriately underwent further evaluation with head imaging, revealing a pituitary adenoma as the likely cause of his symptoms.

In this case, isolated hypersecretion of LH-stimulated testosterone production by Leydig cells, causing development of secondary sex characteristics. He did not experience the testicular enlargement that typically heralds the onset of puberty because FSH, which stimulates proliferation of the seminiferous tubules, remained prepubertal. Although surgical pathology was negative for LH, his presentation remained consistent with a LH-secreting adenoma resulting from positive steroidogenic factor 1 staining, a transcription factor

that exhibits strong nuclear staining in gonadotroph adenomas, and postoperative reduction of LH, testosterone, and α-subunit, with halting of pubertal progression [5]. In personal communication with our pathologist, histology may have stained negative for LH because of inadequate antibody recognition during the staining process, or rapid production and secretion without storage of LH by neoplastic cells.

On presentation, the patient had elevated IGF-1 levels that decreased to age-appropriate levels following adenomectomy. Surgical pathology was not stained for Pit-1 because of unavailability of stain; therefore, production of GH by the adenoma cannot be definitively ruled out. However, elevated IGF-1 levels were considered appropriate for the patient's pubertal status and therefore likely resulted from stimulation of GH release by testosterone and estrogen, similar to that which occurs during normal puberty [7].

Shortly following surgical resection, the patient entered central puberty at early-normal timing. This likely resulted from activation of the hypothalamic-pituitary-gonadal axis secondary to previous sex steroid exposure.

FGAs as a source of precocious puberty is very rare, with only 3 previously described cases in male pediatric patients in the English literature, none of which secreted LH alone. First, a 4-year-old male with an LH- and prolactin-secreting pituitary adenoma presented with growth acceleration, pubic hair, adult male testicular and phallic size, galactorrhea, and visual field deficits. Elevated LH, testosterone, estradiol, and prolactin failed to respond to bromocriptine and cyproterone acetate [8]. Similarly, a 7-year-old male with an LH-, prolactin-, and FSH-secreting adenoma presented with phallic enlargement (9.5 cm), 4 to 5 mL testicular volume, and visual field defects. LH, FSH, prolactin and testosterone were elevated, and medical treatment with bromocriptine and buserelin failed to improve biochemistry, clinical symptoms, or tumor burden [2]. Last, an 8-year, 8-month-old male presented with tall stature, acne, Tanner 3-4 pubic hair and enlarged testes measuring 6 and 10 mL. LH was elevated, whereas FSH remained undetectable, with later elevation in prolactin. Pubertal suppression was not achieved following treatment with leuprolide or histrelin implant [9]. All 3 patients required surgical resection following inadequate response to medical therapy, similar to our patient. The first 2 had subsequent normalization of biochemistry and regression of presenting symptoms, although the last patient continued to have elevated LH and prolactin despite 2 surgical resections. Although 2 of these cases similarly demonstrated LH secretion in the absence of FSH, our patient did not have concurrent prolactin secretion, which in part resulted in a more limited set of presenting symptoms.

FGAs in adults are similarly infrequent and tend to secrete FSH or co-secrete FSH and LH. A report of 7 FGAs identified at 1 institution over a 17-year period included 5 adenomas with co-secretion of FSH and LH and 2 with isolated-FSH production [10]. Isolated LH-secreting adenomas are rare, with very few cases in the literature. Zhang et al reported 7 cases that required surgical resection following attempted medical therapy with TRH, LH-releasing hormone, L-dopa, metyrapone, cabergoline, somatostatin, oral contraceptives, and leuprolide [4].

As demonstrated by the present and previous cases, multiple medical treatment modalities have been attempted and are rarely successful; surgical resection remains the most promising treatment for FGAs [5]. Unfortunately, long-term outcomes of FGAs remain unclear because many reported cases do not include long-term follow-up. However, recurrence following surgical resection has been reported, necessitating long-term follow-up with clinical surveillance, hormone levels, and imaging [5].

In conclusion, FGAs are exceedingly rare in pediatric patients. However, the differential diagnosis should include FGAs when there is evidence of gonadotropin-dependent precocious puberty, especially if there are departures from the typical sequence of development raising concern for nonconcurrent secretion of gonadotropins.

Learning Points

- Functioning gonadotroph adenomas (FGAs) are rare in children, although often present as mass effect or precocious puberty when present
- Surgical resection remains first-line treatment for FGAs
- Males with central precocious puberty require further evaluation with head imaging given association with central nervous system lesions

Contributors

M.C. was involved in the diagnosis and medical management of the patient, as well as the oversight of the conception and writing of the manuscript. A.A. was responsible for surgical intervention. S.S. was responsible for immunohistochemical staining and review of surgical pathology. A.U. was involved in the diagnosis and care of the patient and contributed substantially to the conception and writing of the manuscript. All authors reviewed and approved the final draft.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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