Gonadotropin-Independent Precocious Puberty

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**INTRODUCTION**

This manual is the second in a two-part review of precocious puberty. The first half of the review began with an overview of normal puberty and a discussion of the general clinical approach to the child who presents with one or more signs of early puberty. This was followed by clinical cases highlighting the approach to evaluation and management of patients with partial and gonadotropin-dependent forms of precocious puberty.

In this half of the review, the discussion turns to the less common forms of precocious puberty (ie, gonadotropin-independent forms). Whereas gonadotropin-dependent precocious puberty (GDPP) involves hypothalamic release of gonadotropin-releasing hormone (GnRH) in a pulsatile manner, as normally occurs in puberty, gonadotropin-independent precocious puberty (GIPP), also referred to as peripheral precocious puberty, involves early gonadal steroid production that is independent of gonadotropin stimulation. Some of the causes of GIPP are listed in Table 1. The main sources of steroid hormone excess in GIPP include the ovary, the testis, and the adrenal gland. The approach to and management of the main causes of GIPP are discussed individually according to the specific underlying diagnosis. Although there is some controversy about the normal age of onset of puberty in boys and girls, this review uses the original Marshall and Tanner definition (ie, age 8 years in girls and age 9 years in boys).

**MAJOR CAUSES: INCIDENCE, UNDERLYING DEFECT, AND KEY FEATURES**

**McCUNE-ALBRIGHT SYNDROME**

McCune-Albright syndrome (MAS) was originally described in 1937 as a triad of precocious puberty, café-au-lait spots, and lytic bone lesions occurring in girls. The cause was identified in 1991 as a constitutively activating mutation in the gene that encodes the α subunit of the stimulatory G protein (G<sub>α</sub>) (Figure 1). The gene is named GNAS1 for the guanine nucleotide α subunit. G<sub>α</sub> is involved in the action of a multitude of hormones and other mediators. Indeed, since the original description of MAS, the clinical phenotype has been expanded to include several other endocrine conditions including hyperthyroidism, acromegaly, and Cushing syndrome. Table 2 lists the known endocrine abnormalities seen in MAS along with the implicated hormonal mediator. Several nonendocrine problems have also been described in MAS. Histamines are noted to exert actions via G<sub>α</sub>, and patients with MAS have been reported to display an increased responsiveness to histamines and a higher risk for allergies. Males are at an increased risk for testicular microlithiasis.

The cutaneous hyperpigmentation in MAS follows the lines of Blaschko (ie, along dermatomes) (Figure 2). This pigmentation pattern reflects the dorsoventral outgrowth of two different populations of cells during early embryogenesis; the pattern is seen in chimeric individuals. As all cases of MAS are sporadic, it is postulated that the G<sub>α</sub> mutation is lethal and that only chimeric individuals survive. Patients with MAS display varying degrees of chimerism and therefore varying degrees of clinical severity. The presentation of MAS can range in severity from early neonatal death resulting from cardiac hypertrophy (presumably related to catecholamine and/or β-adrenergic receptor activation) to single lytic bone lesions in the absence of other endocrine problems. MAS predominantly affects females. Although the cause of the sexual dimorphism is unknown, one hypothesis is that there is an ascertainment bias; that is, more females are referred for precocious puberty and premature menarche, whereas males display more subtle signs of puberty. Data from the Italian Multicenter Study Group on MAS revealed that the age at diagnosis of MAS was significantly lower in girls than in boys. In that study, girls also displayed a significantly higher prevalence as well as an earlier onset of GIPP compared with boys.

MAS is classified as a rare disease, affecting fewer
than 200,000 people in the United States. However, a recent study suggests that the GNAS1 mutation is seen in a high percentage of patients with mono-ostotic fibrous dysplasia, implying that partial forms of this disease may be more common than the full-blown phenotype.\textsuperscript{15} This finding also suggests that MAS may be underdiagnosed.

**FAMILIAL MALE PRECOCIOUS PUBERTY**

Familial male precocious puberty (FMPP) is a gonadotropin-independent disorder that is inherited in an autosomal dominant, male-limited pattern. It is also known as testotoxicosis because of its similarity to thyrotoxicosis. The cause of FMPP was first described in 1993 as a gain-of-function mutation in a gene coding for a G protein–coupled receptor.\textsuperscript{14} The mutation in FMPP is more restricted than the G protein mutation seen in MAS. It involves a constitutively activating mutation of the gene encoding the luteinizing hormone (LH) receptor. The LH receptor also binds human chorionic gonadotropin (hCG), and so it is termed the LHCG receptor (LHCGR). The activating mutations described to date are single point mutations and are located in the transmembrane domain.

FMPP typically presents as very early signs of puberty, most often by age 4 years, accompanied by testicular enlargement. A family history of similar changes is an important feature. Female family members who are obligate carriers of the mutation are asymptomatic, as both LH and follicle-stimulating hormone (FSH) are thought to be necessary for pubertal development.
in females. This observation is the basis for the clinical practice of screening for hCG-secreting tumors in males with sexual precocity but not in females. There have been rare reports of hCG-secreting tumors associated with precocious puberty in girls.

**ADRENAL DISORDERS**

Adrenal disorders including adenomas, carcinomas, and congenital adrenal hyperplasia (CAH) can cause isosexual precocity in boys and contrasexual precocity in girls. Adrenal tumors can produce very high levels of adrenal androgens and rapid development of acne and pubic or facial hair in addition to growth acceleration. The presentation will depend on the ratio of glucocorticoid to adrenal androgen production; high glucocorticoid production will slow the growth rate, whereas high production of androgens will accelerate growth. Sometimes, the concomitant production of excessive glucocorticoids and androgens will result in a normal growth velocity.

**CONGENITAL ADRENAL HYPERPLASIA**

CAH refers to a group of disorders of adrenal steroid synthesis. A subset of these disorders is associated with excessive androgen production resulting in virilization. The virilizing forms of CAH are caused by mutations in the genes encoding the 21-hydroxylase, 11β-hydroxylase, and 3β-hydroxysteroid dehydrogenase enzymes.

**21-Hydroxylase Deficiency**

The most common form of CAH and the one most commonly associated with sexual precocity is 21-hydroxylase deficiency. It accounts for 95% of cases of CAH and is one of the most common autosomal recessive disorders. The symptoms and signs of 21-hydroxylase deficiency depend on the degree of enzymatic deficiency and include the more severe salt wasting form, the less severe simple virilizing form, and the mild nonclassic form. The nonclassic form is high in the differential diagnosis of premature pubarche in both boys and girls. Males with 21-hydroxylase deficiency present with isosexual precocious puberty, whereas females present with contrasexual precocious puberty. Males with the nonclassic form can also present with cystic acne, advanced puberty, and advanced bone age. Postpubertal females present with the same findings in addition to irregular menses, polycystic ovary syndrome, hirsutism, and/or male pattern baldness.

**3β-Hydroxysteroid Dehydrogenase Deficiency**

3β-Hydroxysteroid dehydrogenase deficiency is caused by mutations in the HSD3B2 gene. Defects in this enzyme affect both the gonads and adrenal glands. 3β-Hydroxysteroid dehydrogenase deficiency can present as incomplete masculinization in newborn males. As in 21-hydroxylase deficiency, both boys and girls can present in childhood with signs of androgenization. Previous clinical studies examining hormonal profiles in response to adrenal stimulation testing in patients with infertility and hirsutism suggested that high percentages of patients with these disorders possessed this enzymatic defect. With the cloning of the gene, it has become apparent that many individuals

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Table 2. Endocrine Manifestations of McCune-Albright Syndrome

<table>
<thead>
<tr>
<th>Manifestation(s)</th>
<th>Hormone Involved</th>
<th>Laboratory Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precocious puberty</td>
<td>Gonadotropin-releasing hormone, luteinizing hormone,</td>
<td>Prepubertal gonadotropins, elevated gonadal</td>
</tr>
<tr>
<td></td>
<td>follicle-stimulating hormone</td>
<td>steroids</td>
</tr>
<tr>
<td>Polyostotic fibrous dysplasia,</td>
<td>Parathyroid hormone (PTH), osteocalcin</td>
<td>Low PTH, elevated calcium, low phosphorus</td>
</tr>
<tr>
<td>renal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>phosphate wasting, rickets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Café-au-lait spots</td>
<td>Melanocyte-stimulating hormone, melatonin</td>
<td>None</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Thyroid-stimulating hormone (TSH)</td>
<td>Low TSH, elevated free thyroxine</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>Growth hormone–releasing hormone</td>
<td>Elevated growth hormone, elevated insulin-like</td>
</tr>
<tr>
<td></td>
<td></td>
<td>growth factor 1</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Corticotropin-releasing hormone, adrenocorticotropic</td>
<td>Elevated cortisol</td>
</tr>
<tr>
<td></td>
<td>hormone</td>
<td></td>
</tr>
<tr>
<td>Hypertension/cardiac hypertrophy</td>
<td>Catecholamines/[β]-adrenergics</td>
<td>None</td>
</tr>
</tbody>
</table>
with hormonal profiles suggestive of 3β-hydroxysteroid dehydrogenase deficiency have no abnormalities in the HSD3B2 gene. The mechanism for the hormonal abnormalities that led to the diagnosis of mild non-classic 3β-hydroxysteroid dehydrogenase deficiency in the past remains to be determined.

### 11β-Hydroxylase Deficiency

11β-Hydroxylase deficiency is caused by mutations in the CYP11B1 gene. Affected girls may present in the neonatal period with virilization of the external genitalia. If 11β-hydroxylase deficiency is not diagnosed at birth, it can present in both boys and girls with signs of androgenization. Paradoxically, although aldosterone levels are low, hypertension and hypokalemia can be seen. This results from accumulation of 11-deoxycorticosterone, which possesses mineralocorticoid properties.

### AROMATASE EXCESS SYNDROME

Increased extraglandular aromatization has been reported as the cause of familial gynecomastia. Fibroblasts from affected individuals display markedly increased aromatase activity. Affected males display gynecomastia and/or heterosexual precocity, and affected females exhibit macromastia and isosexual precocity. Symptoms become apparent at approximately age 9 years. Affected individuals exhibit advanced bone age and rapid growth.

### VAN WYK-GRUMBACH SYNDROME

The Van Wyk-Grumbach syndrome is a rare syndrome of sexual precocity associated with hypothyroidism. Patients with this form of precocious puberty are unusual in that they do not display a growth spurt. Affected individuals often have galactorrhea. Females can have multicystic ovaries. Van Wyk and Grumbach speculated that the syndrome resulted from “overlap” in the feedback regulation of thyroid-stimulating hormone (TSH), LH, and FSH, all of which share the same α subunit. More recently, authors have speculated that the markedly elevated levels of TSH are capable of exerting weak FSH activity. As in other forms of GIPP, central activation of the GnRH pulse generator can occur in later stages of this disorder.

### OVARIAN CYSTS

Ovarian cysts should be considered in the differential diagnosis of precocious puberty in girls, especially if thelarche rather than adrenarche is the first or predominant finding. Small ovarian cysts are common, especially in girls younger than age 2 years. They sometimes produce enough estrogen to induce thelarche. Small functioning ovarian cysts often have self-limiting activity, leading to breast development that is transient or that waxes and wanes. Cysts producing enough estrogen to stimulate sustained breast development or other signs of puberty may be painful and palpable on abdominal examination.

### GONADAL TUMORS

Ovarian tumors should also be considered in the differential diagnosis of precocious puberty in girls, especially if thelarche is persistent or progressive. Vaginal bleeding in a girl who is prepubertal or in early Tanner stage 2 should raise the suspicion of an ovarian tumor. Ovarian tumors are often large enough to palpate on abdominal examination at diagnosis. Abdominal pain is often present. Fortunately, only about 10% of ovarian tumors in childhood are malignant. Most ovarian tumors are granulosa cell tumors or theca cell tumors.

In boys, Leydig cell tumors are rare causes of precocious puberty. The presentation typically occurs between ages 5 and 9 years. Patients usually display gynecomastia, penile enlargement, pubic hair development, and bone age advancement. The tumors are usually unilateral and palpable, and most are benign. Sertoli cell tumors exhibit a similar presentation but are primarily seen in Peutz-Jeghers syndrome.

hCG-secreting tumors also cause precocious puberty in boys; the mechanism involves hCG binding to the LH receptor. Although both LH and FSH are known to be necessary for ovarian follicular development in girls, there has been one report of an hCG-secreting tumor in a girl with a germ cell tumor. It is thought that with
very high levels of LH or hCG, there may be enough FSH stimulation to induce follicular development.17 Mixed gonadal dysgenesis can be associated with gonadoblastomas as a rare occurrence in both phenotypic males and females. Finally, sex cord tumors are a very rare cause of feminization in both boys and girls.

**Syndromes Associated with Gonadal Tumors**

Several inherited syndromes are associated with a high incidence of gonadal tumors in addition to tumors of other organs. Most of these syndromes fall into a category of conditions termed familial lentiginosis syndromes. These syndromes cover a wide phenotypic spectrum ranging from syndromes associated with skin lentigines only to syndromes that predispose individuals to development of hamartomas, hyperplasias, and other neoplasms. Three of these syndromes have been reported to include gonadal tumors as part of their pathophysiology. These include the Carney complex, Peutz-Jeghers syndrome,28 and Cowden syndrome. Table 3 lists the familial lentiginosis syndromes associated with gonadal tumors along with the main distinguishing features and the molecular defects.

**GLUCOCORTICOID RECEPTOR GENE MUTATIONS**

Inactivating mutations of the glucocorticoid receptor gene cause compensatory elevations of adrenocorticotropic hormone (ACTH) and cortisol. There is a concomitant overproduction of adrenal androgens and mineralocorticoids. The adrenal androgen excess can lead to precocious puberty.29 Treatment involves high doses of synthetic glucocorticoids without mineralocorticoid properties, such as dexamethasone.29

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**McCUNE-ALBRIGHT SYNDROME**

**CASE I PRESENTAION**

A 30-month-old girl is referred by her general pediatrician to an endocrinologist for evaluation of vaginal bleeding.

**History**

The child’s history is notable for a fall that occurred approximately 1 month ago, when the girl had been playing at home and fell off the sofa. The following day, the mother noticed the child was limping and subsequently brought her to her pediatrician, who ordered films of the ankle and knee. An astute radiologist noted fibrous dysplasia of the tibia. A skeletal survey was performed, and the patient was diagnosed with polyostotic fibrous dysplasia, prompting endocrinology referral. Within 1 week, and before she was seen in the endocrinology clinic, the patient experienced menarche. Birth history is unremarkable. The patient has a history of a birth mark on her flank, which was first noted at approximately 10 days of age. No acne has been noted. The mother reports no observed growth spurt but says she has periodically noted enlargement of the child’s breasts. This development appears to wax and wane. There is no history of bone fractures. The patient is allergic to penicillins and cephalosporins. The mother also reports that the child experienced an anaphylactic reaction to cashews at age 2 years. Review of systems is remarkable for photophobia. Family history is noncontributory. However, the child’s mother is 5 ft 4 in and father is 5 ft 10 in, for a calculated midparental height (MPH) of 5 ft 4.5 in, which is at the 50th percentile.

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**Table 3. Familial Lentiginosis Syndromes Associated with Gonadal Tumors**

<table>
<thead>
<tr>
<th>Syndrome/Disease</th>
<th>Inheritance</th>
<th>Features</th>
<th>Gonadal Tumors</th>
<th>Molecular Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>Autosomal dominant</td>
<td>Mucocutaneous pigmentation, gastrointestinal hamartomatous polyps</td>
<td>Females: small, benign ovarian tumors Males: Sertoli cell testicular tumors</td>
<td>Germline mutations in the STK11/LKB1 gene (19p13.3) that codes a multifunctional serine threonine protein kinase</td>
</tr>
<tr>
<td>Carney complex (multiple neoplasia syndrome)</td>
<td>Autosomal dominant</td>
<td>Spotty skin pigmentation, cardiac and other myxomas, endocrine tumors, psammomatous melanocytic schwannomas</td>
<td>Males: large-cell, calcifying Sertoli cell testicular tumors</td>
<td>Missense mutations and microdeletions at PRKAR1A gene on chromosome 17q22-q24; a further chromosome 2p16 gene is unknown</td>
</tr>
<tr>
<td>Cowden disease</td>
<td>Autosomal dominant</td>
<td>Hamartomas, breast cancer, thyroid tumors, increased risk of early cancers</td>
<td>Males: Testicular hamartomas, possible testicular seminoma</td>
<td>Abnormalities in PTEN gene on chromosome 10q22-23</td>
</tr>
</tbody>
</table>

PRKAR1A = protein kinase A regulatory subunit α.
Physical Examination

Pulse and blood pressure are normal. Height is 95 cm (3 ft 1.4 in), which is at the 90th percentile. Weight is 16 kg, which is at the 75th percentile. Physical examination generally reveals no dysmorphic features. Findings on examination of the head, ears, eyes, nose, and throat are within normal limits. Examination of the teeth reveals the presence of the 2-year molars. The neck is without thyromegaly and without thyroid nodules. The lungs are clear, and the heart examination is normal. Genital examination reveals that the child is at Turner stage 2 for breast development and Turner stage 1 for pubic hair. There is no clitoromegaly. A linear café-au-lait spot is noted on her flank, which follows a dermatome distribution and exhibits respect for the midline.

- What is the differential diagnosis for this patient’s clinical presentation?

The triad of features that define MAS include precocious puberty, café-au-lait spots, and lytic bone lesions. Technically, the case patient does not meet the definition of true precocious puberty, because she does not have pubic hair. However, she does have premature thelarche, café-au-lait spots, and polyostotic fibrous dysplasia. The fact that her height is at the 90th percentile when she should be at the 50th percentile suggests hormonal excess. With these findings, the only other disease entity to be considered high in the differential diagnosis is neurofibromatosis (NF). Patients with NF can exhibit precocious puberty in addition to multiple café-au-lait spots and lytic bone lesions. The characteristics of the hyperpigmented skin lesions are an important consideration in distinguishing MAS from NF. The café-au-lait spots in NF tend to be multiple and oval and to possess smooth edges. In contrast, the hyperpigmented spots in MAS are generally larger lesions that follow dermatome distributions and exhibit irregular borders; there is no minimum number of skin lesions required to diagnose MAS. Given the presence of hyperpigmentation in this case, other lentiginosis syndromes also may be considered (Table 3).

- What is the approach to the evaluation in this case?

As in any child with true precocious puberty, the biochemical tests should include basal estradiol in girls, testosterone in boys, LH, FSH, free thyroxine (FT$_4$), and TSH. Basal LH levels below 0.3 IU/L are consistent with GIPP. In MAS, estradiol levels in girls (and testosterone levels in boys) are elevated in the presence of prepubertal levels of LH. In MAS, hyperthyroidism should be ruled out, as TSH signals via G$_{α}$. Additional testing that is not part of the general evaluation for precocious puberty includes a test for insulin-like growth factor 1 (IGF1). Patients with MAS are at risk for growth hormone (GH) excess because growth hormone–releasing hormone (GH-RH) signals via G$_{α}$.

Bone age assessment is helpful in determining the growth potential and can also be important for establishing or confirming the diagnosis of MAS. Measurement of uterine and ovarian volumes via pelvic ultrasonography has been found to be a sensitive and specific test for differentiating between early premature thelarche and early GDPP, which can present similarly.$^{30}$ The presence of masses or cysts suggests a cause for GIPP, whereas pubertal/maturational changes in the ovaries (increased size with mature follicles) suggests GDPP.

Few radiographic studies other than plain film radiography are required in a typical case of polyostotic disease. Bone films reveal fibrous dysplasia as an intramedullary lesion, sometimes with a thinned, slightly bulged cortex. The lesions have a heterogeneous density, yielding a so-called ground-glass appearance. An angular deformity in the bone can be present at the level of the lesion. Periosteal reaction is absent except when a pathologic fracture is present. Computed tomography (CT) can be helpful in differentiating among eosinophilic granuloma, osteomyelitis, and unicameral bone cyst.

CASE 1 CONTINUED

Results on initial biochemical studies are: estradiol, 32 pg/mL; LH < 0.1 IU/L (normal, 0.0–1.6 IU/L); FSH < 0.3 IU/L (normal, 0.0–2.8 IU/L); FT$_4$, 1.2 ng/dL (normal, 0.8–1.7 ng/dL); and TSH, 1.6 µU/mL (normal, 0.3–4.5 µU/mL). IGF1 level is 190 ng/mL (normal for age, 17–248 ng/mL).

Bone age is assessed at 4 years 2 months (at a chronologic age of 30 months). Pelvic ultrasonography shows a uterus with a more mature configuration than would be expected for a 30-month-old, with an endometrial stripe noted. The ovaries, while not enlarged, contain prominent follicular cysts bilaterally. The largest cyst measures 7 mm on the right side. There is no dominant ovarian cyst or adenexal mass.

Review of films from the skeletal survey performed prior to referral shows intramedullary lesions in the radius and tibia, with thinned, slightly bulging cortical tissue. There is also a lesion in a metacarpal bone with a heterogeneous density, yielding a ground-glass appearance. Periosteal reaction is absent.

- What is the most likely diagnosis?

The prepubertal levels of LH and FSH in the
presence of pubertal levels of estradiol confirm the presence of GIPP. Because the Bayley Pinneau tables do not apply to bone age less than 6 years, these cannot be used. For children with a bone age less than 6 years, one can plot the patient’s height using the bone age in place of the chronologic age on the x-axis. Plotting the case patient’s height at her bone age places her at the 10th percentile, which can be roughly extrapolated to yield a target adult height at the 10th percentile. According to the calculated MPH, she should be at the 50th percentile. This discrepancy is a further indication of excessive hormonal exposure. Combined with the patient’s radiographic studies, the clinical findings thus far are consistent with the diagnosis of MAS. Although it may possible to confirm the diagnosis by sequencing the GNAS1 gene, testing can be misleading. Because patients are chimeric, peripheral blood mononuclear cells may not carry the mutation. Thus, the diagnosis of MAS is often made on clinical grounds.

• How should this patient be treated?

Treatment of MAS depends upon the severity of disease and which organs are involved. The main management concern generally is to reduce the excessive gonadal steroid exposure in order to preserve adult height. Aromatase inhibitors have been shown to be inapplicable in this regard; those used in the pediatric setting have included testolactone, fadrozole, letrozole, and anastrozole. (Note that the use of aromatase inhibitors to slow bone age is not approved by the U.S. Food and Drug Administration.) Testolactone, a nonselective steroidal aromatase inhibitor, has been shown to be effective in reducing estradiol levels and delaying advancement of bone age in girls with MAS.31 Patient compliance with testolactone can be an issue because of its relatively low potency and the need for frequent dosing. Although they are not as well validated as testolactone in MAS or in other disorders of puberty, new-generation aromatase inhibitors (ie, anastrozole, exemestane, and letrozole) show promise in delaying bone age progression in precocious puberty.32,33 Finally, in a multicenter study of MAS patients, tamoxifen (an estrogen receptor antagonist) was shown to delay bone age advancement and decrease vaginal bleeding.34

Hyperthyroidism resulting from hyperfunctioning thyroid nodules is usually amenable to thyroid synthesis blockade. Thyroidectomy is sometimes necessary when multiple hyperfunctioning nodules are present and/or there is a poor response to antithyroid medications. Allergies to antithyroid medications have necessitated thyroidectomy in the author’s patient population. Ovarian cysts should be monitored by periodic pelvic ultrasonography; large cysts may require surgical resection. Bony lesions that cause significant or progressive deformity or that jeopardize the integrity of the bone may require surgical treatment. Bisphosphonates have been used in an effort to reduce the progression of lytic bone lesions in MAS, with mixed results.35,36 Bisphosphonate treatment has been shown to improve bone pain in MAS.36 Patients with lytic bone lesions should be referred to orthopedic physicians, and restriction in contact sports may be necessary. Finally, at our institution, we have observed that a high percentage of patients with MAS have experienced anaphylaxis or anaphylactoid reactions. Our group has reported on an increased prevalence of allergic phenomena and enhanced histamine responsiveness in patients with MAS compared with age-matched sex-matched controls.9 It is our institution’s practice to prescribe epinephrine pens to all patients with a suspected or confirmed diagnosis of MAS.

Because of the autonomously functioning Gsα protein, MAS patients are at an ongoing risk for the development of hyperfunctioning thyroid nodules, the development of new bone cysts and fractures, and rapid acceleration of puberty. As in other forms of sexual precocity, advancement of the bone age will eventually be associated with activation of the GnRH pulse generator, an additional pituitary stimulus for pubertal development. Patients with MAS are also at an increased risk for acromegaly and Cushing’s disease, as GH-RH, corticotropin-releasing hormone, and ACTH function through Gsα. Frequent growth monitoring (every 4–6 months) will aid in early detection of these potential problems. GH-producing and ACTH-producing pituitary tumors may be amenable to resection via a transsphenoidal approach.

CASE 1 CONCLUSION

The patient initially is treated with testolactone and 1 year later is switched to letrozole (2.5 mg/day) because of the convenience of once-daily dosing. Both medications are well-tolerated. The patient’s bone age remains stalled at 4 years 2 months for the next 2 years. During this time, she undergoes annual thyroid function tests and IGF1 measurements as well as periodic pelvic ultrasonography, skeletal surveys, and bone scans.

FAMILIAL MALE PRECOCCIOUS PUBERTY

CASE 2 PRESENTATION

A 16-month-old boy is referred for evaluation of
precocious puberty. His parents have noted increased pubic hair, deep voice, acne, and enlargement of the phallicus and scrotum.

The child was born at term without complication. His general health is good, apart from recurrent urinary tract infections, and his growth has been at the 95th percentile for height since he was 12 months old. His family history is notable for an older half-brother (different father) and 2 maternal uncles who went through puberty at a very early age and are now very short adults.

Physical examination reveals normal vital signs. Review of the growth curve shows the boy to be well above the 95th percentile for height and weight. There is no axillary hair. Pubic hair is assessed at Tanner stage 2. Testicular volume is 8 mL bilaterally. Skin examination reveals mild acne.

Results on initial biochemical testing are: testosterone, 254 ng/dL; LH < 0.1 IU/L; FSH < 0.3 IU/L; and dehydroepiandrosterone sulphate (DHEA-S), 58 µg/dL (normal, 3–85 µg/dL). Bone age is assessed at 6 years.

- **What is the differential diagnosis in this case?**
- **What is the approach to the evaluation of this patient?**

The differential diagnosis includes FMPP and familial testicular tumors. Adrenal tumors and CAH might be considered. However, the normal DHEA-S level and the enlarged testes argue against an adrenal source of androgen. The fact that multiple family members experienced early-onset puberty virtually excludes MAS from the differential, as this mutation does not occur in the germline. The most striking finding is that, although familial, the precocious puberty in this case appears to affect only boys. The fact that the mother is not affected suggests a male-limited pattern of expression, which would support the diagnosis of FMPP. Most inherited forms of testicular tumors are autosomal dominant. The fact that the testes are bilaterally and symmetrically enlarged also argues against testicular tumors.

In FMPP, serum testosterone levels are pubertal and may increase further with hCG stimulation. Both basal and GnRH-stimulated levels of LH and FSH are low. Molecular diagnosis of disorders caused by mutation of the LH receptor can be achieved by direct sequencing of the LHCGR gene.

A baseline bone age assessment is essential. Once the bone age reaches 6 years, the child’s PAH can be determined using the bone age and the Bayley Pinneau tables.

- **How should this patient be treated?**

Because of the activation mutation of the LH receptor, testosterone production cannot be suppressed by GnRH agonists. Aromatase inhibitors are beneficial in slowing the progression of bone maturation in precocious puberty in both boys and girls. Antiandrogens such as flutamide have also been used effectively. Spironolactone possesses androgen antagonistic properties and has been used effectively in FMPP. However, once the patient’s bone age reaches the pubertal range, these treatments place him at increased risk for developing GDPP. If this occurs, treatment with a GnRH analog would be indicated.

Lifelong monitoring for testicular cancer is important, as a constitutively activating mutation of the LH receptor may predispose the patient to the development of testicular neoplasia.

### CASE 2 CONCLUSION

The patient initially is treated with both spironolactone (100 mg/day) and testolactone (40 mg/kg/day divided into 4 doses). He ultimately develops GDPP (central precocious puberty), and a GnRH analog is added to his therapeutic regimen. Despite this treatment, his bone age continues to progress and is 11 years at chronologic age 4 years. At this point, he is switched to letrozole, a more selective aromatase inhibitor.

### CONGENITAL ADRENAL HYPERPLASIA

### CASE 3 PRESENTATION

A 6-year-old boy is referred for evaluation of early pubic hair development. His parents also report acne and occasional body odor and note that their son is much taller than his kindergarten classmates. He also masturbates frequently, for which the parents consulted his primary pediatrician about 6 months earlier. Neonatal history is significant for failure to regain his birth weight before age 2 weeks. There is no family history of early puberty or of any heritable diseases and no family history of neonatal deaths.

Physical examination is positive for normal vital signs with tall stature. Genital examination reveals pubertal testes with Tanner stage 3 pubic hair. The phallicus is slightly enlarged.

Bone age is assessed at 11 years. Results of biochemical testing are: LH, 0.1 IU/L (normal, 1–12 IU/L); FSH, 1.2 IU (normal, 1–12 IU/L); 17-hydroxyprogesterone (17-OHP), 12,500 ng/dL (normal, 40–330 ng/dL); DHEAS, 166 µg/dL (normal, 3–85 µg/dL); androstenedione, 2.8 ng/dL (normal, 0.1–0.5 ng/dL); and testosterone, 38 ng/dL (normal < 30 ng/dL). Plasma
renin level is normal. Molecular genetic testing reveals a val281-to-leu mutation genotype, a variant of the CYP21B gene mutation that has been shown to account for up to 80% of cases of the nonclassic form of CAH.\textsuperscript{39}

- **Is genetic testing necessary to make a diagnosis of CAH? How are other potential adrenal causes of precocious puberty ruled out?**

Diagnosis of CAH secondary to 21-hydroxylase deficiency is often possible based on a random 17-OHP measurement. An elevated baseline 17-OHP level should be confirmed with a high-dose ACTH-stimulation test. Molecular genetic testing is available for 21-hydroxylase deficiency and is especially important to perform when future pregnancies are anticipated. Defining the molecular defect in the proband will be useful in determining whether the fetus in future pregnancies is affected.

An excellent laboratory screening test for adrenal adenoma and carcinoma is a DHEAS level. DHEAS levels tend to be in the 1000 µg/dL range in adrenal cancer. A baseline bone age is necessary to determine whether PAH is compromised. Suspected adrenal masses are usually best visualized by abdominal CT.

- **How should patients with a CAH diagnosis be treated?**

Treatment of CAH is based on the 3 endocrine problems associated with the diagnosis: insufficient production of glucocorticoid and mineralocorticoid and overproduction of adrenal androgens. Lifelong glucocorticoid replacement therapy is the mainstay of treatment for the classic and symptomatic nonclassic forms of CAH. Although glucocorticoid insufficiency is universal, there is a spectrum of severity of salt wasting, such that even patients with no clinical signs of salt wasting may have subtle mineralocorticoid deficiency. A very sensitive test for subclinical mineralocorticoid deficiency is a plasma renin level.

Treatment is not geared toward complete normalization of 17-OHP and, thus, glucocorticoid dosing should not be excessive. Excessive glucocorticoid administration can cause cushingoid features, including growth retardation and inhibition of epiphyseal maturation. Hydrocortisone is a better option for infants and children with CAH because its lower potency allows for a greater ability to be titrated compared with prednisone or dexamethasone. Successful treatment of CAH depends on achieving the delicate balance of suppressing adrenal androgen secretion while maintaining normal growth. However, CAH can be associated with adult short stature even when good adrenal hormonal control is maintained throughout childhood and puberty. A recent study suggests that GH therapy in conjunction with GnRH analogs may improve final height prediction in pubertal children with CAH exhibiting advanced bone ages.\textsuperscript{40}

Successfully treated male patients with CAH may have normal pubertal development, normal testicular function, and normal spermatogenesis and fertility. However, in some, testicular nodules, testicular atrophy, azoospermia, and the suppression of gonadotropin secretion have been reported.\textsuperscript{41} Testicular nodules and even larger tumors caused by expanding adrenal rests are another frequently reported complication in postpuberal boys with classic CAH and inadequate hormonal control.\textsuperscript{42,43} Regular testicular examination and periodic testicular ultrasonography are recommended for early detection of testicular lesions.

**CASE 3 CONCLUSION**

The patient is started on hydrocortisone. Because his renin level is normal, no mineralocorticoid is required. By the next clinic visit, his pubic hair has regressed slightly to Tanner stage 2. His growth velocity slows to 5.5 cm/year. The patient is followed every 4 to 6 months for assessment of growth velocity, pubertal status, testicular evaluation, 17-OHP and androstenedione levels, and bone age.

**CONCLUSION**

One of the key steps in the evaluation of precocious puberty is distinguishing GIPP from GDPP. The differential diagnosis of precocious puberty—GIPP in particular—can be complex and challenging. Arriving at the correct diagnosis is of great importance, as the management differs dramatically for each condition. Management of precocious puberty involves not only attempting to preserve adult height but also managing associated endocrine and nonendocrine conditions. Several conditions associated with precocious puberty are associated with malignancy or with the potential for malignancy. The complexity of some of these conditions emphasizes the importance of early recognition of sexual precocity and referral to specialists.

**REFERENCES**


