Treatment of Peripheral Precocious Puberty

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Abstract

There are many etiologies of peripheral precocious puberty (PPP) with diverse manifestations resulting from exposure to androgens, estrogens, or both. The clinical presentation depends on the underlying process and may be acute or gradual. The primary goals of therapy are to halt pubertal development and restore sex steroids to prepubertal values. Attenuation of linear growth velocity and rate of skeletal maturation in order to maximize height potential are additional considerations for many patients. McCune-Albright syndrome (MAS) and Familial Male-Limited Precocious Puberty (FMPP) represent rare causes of PPP that arise from activating mutations in *GNAS1* and the LH receptor gene, respectively. Several different therapeutic approaches have been investigated for both conditions with variable success. Experience to date suggests that the ideal therapy for precocious puberty secondary to MAS in girls remains elusive. In contrast, while the number of treated patients remains small, several successful therapeutic options for FMPP are available.

Introduction

Peripheral precocious puberty (PPP), or GnRH-independent precocious puberty, is defined as early pubertal maturation that is not a result of central activation of the hypothalamic-pituitary-gonadal axis. The etiology of PPP can be categorized into either genetic or acquired disorders and some vary by the gender of the child (Table 1). Congenital or genetic causes include McCune-Albright syndrome (MAS), Familial Male-Limited Precocious Puberty (FMPP), and congenital adrenal hyperplasia (CAH). Acquired causes include hormone-secreting tumors or cysts, exogenous hormone exposure, and the pseudo-precocious puberty seen in patients with profound primary hypothyroidism [1]. The treatment of PPP depends entirely on the underlying etiology. This chapter will focus on the treatment of MAS and FMPP.

McCune-Albright Syndrome in Girls

MAS is a rare disorder characterized by the triad of polyostotic fibrous dysplasia, café-au-lait macules, and precocious puberty. The café-au-lait macules characteristic of MAS are classically described as having a "coast of Maine" or jagged border, in contrast to the smooth "coast of California" configuration seen in the café-au-lait spots in children with Neurofibromatosis. Another unique feature of these lesions is that they usually follow the lines of Blaschko and do not cross the midline, although exceptions have been noted [2, 3]. The clinical manifestations of MAS are a result of constitutive activation of cells affected by a post-zygotic gain of function mutation in the *GNAS1* gene which encodes for the stimulatory subunit of the G-protein complex known as Gsα. Individual phenotypes are exceedingly heterogeneous and depend on the number and types of tissues involved. While precocious puberty is by far the most common endocrinopathy seen in MAS, many other forms of endocrine hyperfunction can occur, including hyperthyroidism, growth hormone excess, Cushing syndrome, and FGF23-mediated hypophosphatemia.

Precocious puberty in children with MAS is much more common in girls and results from estrogen secretion by autonomously functioning ovarian cysts [2]. Girls with MAS typically present with painless vaginal bleeding along with minimal breast enlargement, although breast tissue may have resolved by the time of referral. Growth parameters and bone age x-ray are usually normal at the time of initial evaluation. If MAS is suspected, initial work up should include both laboratory and radiographic studies. Laboratory investigation typically reveals elevated estradiol with suppressed random and stimulated gonadotropins. While a single suppressed LH may be sufficient in a patient with classic findings of MAS, a GnRH or GnRH analog stimulation test will provide more information about the HPG axis in equivocal situations.

Unilateral ovarian cysts are classically seen on pelvic ultrasound and may be mistaken for a neoplasm such as a Juvenile Granulosa Cell Tumor [4]. If the initial evaluation is consistent with MAS, a bone scan should be ordered to evaluate for fibrous dysplasia and screening for other endocrinopathies should be performed. Almost all clinically significant foci of fibrous dysplasia are believed to be present by the age of 5 [2]. Therefore, the majority of skeletal lesions will be identified at the first evaluation since children with MAS usually come to medical attention between 3 to 10 years of age. While genetic testing for a mutation in the GNAS gene is available, it is frequently of low yield in peripheral blood, especially in atypical cases [5]. The likelihood of detecting a mutation does, however, increase if an affected tissue is examined [6]. As such, the diagnosis rests primarily on clinical criteria.

The natural history of precocious puberty in girls with MAS is extremely variable and the frequency of vaginal bleeding is difficult to predict [2]. Girls with progressive disease and repeated exposure to estrogen will have growth acceleration and bone age advancement and may benefit from treatment. However, treatment of PPP in girls with MAS is challenging and its benefits have not been well established due to the rarity of patients and the heterogeneous nature of the disease.

A number of drugs have been investigated as potential pharmacologic approaches for the treatment of girls with MAS who have repeated episodes of vaginal bleeding (Table 2). GnRH analogs as primary intervention have not been successful as gonadotropins are not elevated in these patients. Cyproterone acetate (CPA) and medroxyprogesterone acetate (MPA) are two of the first agents historically used to treat precocious puberty, including in girls with MAS. CPA is a steroidal antiandrogen that works predominantly at the androgen receptor, but also has progestin and antiestrogenic activity [7]. Likewise, MPA has local antiestrogen properties.

Despite initial positive short-term reports of efficacy in controlling breast development and vaginal bleeding, long-term treatment with these agents has proven unsatisfactory as they do not appear to influence growth rate or final adult height [7, 8].

Ketoconazole has been successfully used in the short-term to treat PPP. It works through inhibition of steroid biosynthesis by blockade of cytochrome P450 enzymes. A report of 2 girls with MAS treated with ketoconazole over the course a year resulted in cessation of vaginal bleeding, reduction of estradiol levels, and decreased bone age advancement without any acute adverse events [9]. However, concerns regarding safety, including risk of adrenal insufficiency and hepatotoxicity, and lack of long-term effectiveness have limited its use. Ketoconazole has been associated with reversible liver toxicity in 1/100,000 cases and requires close monitoring of liver function [9].

Aromatase inhibitors, which were originally developed for the treatment of estrogen receptor-positive breast cancer, are relatively newer agents that have been used in the treatment of PPP in girls with MAS. Aromatase catalyzes the rate-limiting step in the conversion of testosterone to estradiol and androstendione to estrone [10]. This class of drugs binds to the cytochrome P450 portion of aromatase, thus inhibiting the conversion of androgens to estrogens [10]. Aromatase inhibitors can be classified by type (steroidal or nonsteroidal) and generation (first, second, or third) and vary with regards to potency of estrogen suppression.

Testolactone, a first generation aromatase inhibitor, was found to have minimal success in the treatment of girls with MAS. One study that followed 7 girls with MAS treated for at least 3 years showed a reduction in serum estradiol levels and frequency of vaginal bleeding. However, mean predicted adult height (PAH) was not significantly improved after treatment [11]. The positive effects seen in this study were most marked in the first year after therapy,

which is consistent with an escape effect of the drug. Another disadvantage is that this medication needs to be dosed four times daily, making compliance difficult. As such, this medication is not routinely used.

A second generation aromatase inhibitor, fadrozole, has likewise been found to be ineffective in the treatment of precocious puberty in girls with MAS. It also carries with it the concern for adrenal suppression. One study followed 16 girls with MAS treated with fadrozole and found that it did not result in a significant decrease in mean estradiol or mean ovarian volumes compared to pre-treatment values [12]. A decrease in frequency of vaginal bleeding was seen initially, but did not persist. Mean growth rate SDS was not significantly different prior to therapy and PAH was not significantly improved. A dose-dependent inhibition of adrenal steroid biosynthesis was also observed, and 3 girls ultimately required hydrocortisone replacement therapy. It appears that fadrozole is not sufficiently potent to block estrogen synthesis in the majority of girls with MAS and carries with it the concern for adrenal insufficiency.

Two third generation aromatase inhibitors, anastrozole and letrozole, have been trialed for the treatment of precocious puberty in girls with MAS. Despite early reports of efficacy, an international, multi-institutional trial investigating the utility of anastrozole found it to be ineffective [13]. This study followed 28 girls with MAS for 1 year and found no difference in frequency of vaginal bleeding or bone age advancement when compared to pretreatment values. Mean ovarian and uterine volumes were likewise unaffected. Growth velocity z-scores decreased from 1.40 ± 3.15 at study entry to 0.26 ± 2.71 during treatment, however this was not statistically significant. There were no significant adverse events reported, so while it appears to be safe, anastrozole is not recommended for treatment of precocious puberty in girls with MAS.

Letrozole, on the other hand, has demonstrated some short-term success in the treatment of girls with MAS. One study followed 9 girls treated with letrozole for up to 36 months and noted a significant decrease in growth velocity SDS and bone age to chronological age ratio (BA/CA) [14]. Of the 9 girls treated, 6 ceased having vaginal bleeding and 3 had a reduction in frequency of vaginal bleeding. Mean serum estradiol and ovarian volumes fell at 6 months but increased back to baseline by 12 and 24 months. The drug was tolerated well overall, although one girl developed a large ovarian cyst with torsion that required surgical intervention. Although this event may or may not have been related to the letrozole, further investigation is needed into the long-term safety and efficacy of this drug.

Another class of drugs that has been used with some success in girls with MAS is estrogen receptor modulators such as tamoxifen and fulvestrant. These drugs were also first designed for use in the treatment of breast cancer. Tamoxifen, a selective estrogen receptor modulator, was found to have positive results in a year-long multicenter trial of 25 girls with MAS and PPP [15]. After an observation period of 6 months, girls were started on tamoxifen at a dose of 20 mg once daily. Episodes of vaginal bleeding decreased from 3.42 ± 3.36 per year to 1.17 ± 1.41 per year. Growth velocity and bone maturation also significantly decreased. While there were no significant adverse events reported, uterine volumes were unexpectedly found to increase throughout the study. This raised safety concerns given the association of tamoxifen and stromal tumors. As such, periodic pelvic ultrasound examination in girls treated with tamoxifen is recommended. Long-term studies using tamoxifen in MAS have yet to be published in children.

Fulvestrant, a pure estrogen receptor blocker that is given intramuscularly, was recently found to be moderately effective in treating precocious puberty in girls with MAS in a

multicenter, international study [16]. In this trial, 30 girls were treated for 1 year at a goal dose of 4 mg/kg IM monthly. Median vaginal bleeding days significantly decreased from 12 days/year to 1 day/year and rates of bone age advancement (ΔBA/ΔCA) significantly decreased from 1.99 to 1.06. Mean growth velocity and predicted adult height remained equivalent and uterine volumes were stable. The most common adverse event was injection site reactions. It is speculated that longer treatment might improve the other growth parameters given that there was a progressive decrease in bone age advancement in the treated girls. However this has not yet been reported in the literature.

Lastly, surgical options including cystectomy or oophorectomy have been used in girls with MAS. This approach is considered sub-optimal as there is a high likelihood of cyst recurrence. These surgeries may also impact fertility in women with the potential for otherwise normal reproductive function and thus are not recommended. As in other forms of PPP, the development of secondary CPP can occur and responds to standard GnRH analog therapy.

Several challenges are faced when investigating treatment of precocious puberty in girls with MAS. The scarcity of affected patients necessitates multi-center studies which require considerable resources and a collaborative approach. Given the extreme variability between patients, girls typically serve as their own controls. It is impossible to know, however, whether periods of apparent disease quiescence are due to the intervention or simply reflect the natural history of the condition. Lastly, concurrent endocrinopathies such as subclinical hyperthyroidism and/or growth hormone excess along with bony deformities render it difficult to derive accurate information regarding the relationship between linear growth rates and degree of skeletal maturation and precocious puberty in girls with MAS.

McCune-Albright Syndrome in Boys

MAS in boys is exceptionally rare. PPP in boys with MAS occurs less frequently and later in life when compared to girls [17]. When it occurs, it is typically associated with penile growth and bilateral testicular enlargement secondary to Leydig cell hyperplasia. Labs in boys with MAS reveal elevated testosterone with suppressed gonadotropins. Even in the absence of precocious puberty, testicular pathology can be seen in boys with MAS, most commonly unilateral or bilateral macroorchidism [2]. One study evaluated 54 males with MAS and found that 44% had macroorchidism, including 13 of 26 children [18]. Only 21% presented with precocious puberty, which is in contrast to the high numbers of girls with MAS who initially present with signs of precocious puberty. However, 81% of the males had abnormalities on testicular ultrasound, the most common of which were hyperechoic or hypoechoic lesions. Other ultrasound findings included microlithiasis, heterogeneity, and focal calcifications. Conservative management of testicular lesions with observation and serial imaging is recommended as cancer is rare. This study showed that contrary to conventional thinking, MAS-associated gonadal involvement is not significantly more common in females than males when testicular ultrasounds are performed.

The treatment of PPP in boys with MAS has not been extensively studied in the literature due to the rarity of patients. Combination therapy with an androgen receptor blocker and an aromatase inhibitor is typically used [2]. The drugs used to treat FMPP, which will be discussed in the next section, should theoretically work in this patient population as well. A single report noted normalization of growth velocity, regression of genital changes, and stabilization of testicular volume in a 4.6 year old boy with PPP and MAS treated with bicalutamide and anastrazole [19]. This was the first reported use of bicalutamide, a nonsteroidal antiandrogen, in a boy with MAS.

Familial Male-Limited Precocious Puberty

FMPP, or testotoxicosis, is a rare genetic disorder caused by a mutation in the gene encoding the LH receptor that results in constitutive activation. The mutation can occur *de novo* or it can be inherited in an autosomal dominant fashion. The phenotype is limited to males. Boys present with early pubertal development, typically before the age of 4, with rapid growth, tall stature, an enlarged penis, minimal testicular enlargement, and pubic hair [20]. Labs reveal elevated testosterone with suppressed gonadotropins. If left untreated a short adult height will result due to early closure of the epiphyses. Given the rarity of FMPP, extensive treatment data in this disorder is lacking. Drugs that have been used to date are listed in Table 3.

As in MAS, CPA and MPA have been used in boys with FMPP for their antiandrogen properties. A Brazilian study reported limited success in 5 boys with FMPP treated with CPA at a dose of 70 mg/m^2 for a mean period of 5 years [21]. One patient also received MPA in combination therapy and two patients were ultimately started on an aromatase inhibitor as well. Compared to pretreatment values, growth velocity decreased significantly during treatment. The BA/CA ratio likewise significantly decreased. Despite these improvements, there was limited efficacy with regards to normal adult height attainment. The same study also evaluated 5 boys treated with ketoconazole at a dose of 10 mg/kg for a mean duration of 8 years. The results were nearly identical to the CPA-treated group, except the boys on ketoconazole had significantly lower testosterone levels compared to the group treated with CPA.

Ketoconazole has been effective in the treatment of boys with FMPP due to its ability to inhibit adrenal and testicular androgen biosynthesis, although there are a number of safety concerns. The primary safety concerns are hepatotoxicity and adrenal suppression. Mild adverse effects include gynecomastia, nausea, and diarrhea. Ketoconazole is metabolized in the

liver and reports ranging from mild transaminitis to severe liver damage have been described. The prevalence of mild, asymptomatic, reversible elevation in the transaminases in adults receiving an average of 200 mg daily ranges from 5-17%, with hepatitis developing in 2.9% [22]. In children with FMPP, there has been one reported case of severe liver damage in a child receiving high dose therapy (1,200 mg/day) with reversal of the liver disease after dose reduction [23].

Ketoconazole can be used as a solo agent or used in combination with other drugs such as aromatase inhibitors. It is typically dosed three times daily in the range of 10-20 mg/kg/day. A study using it alone found that it was well-tolerated and effective in suppressing pubertal symptoms and increasing adult height [22]. This French study followed 5 boys with FMPP who were treated with ketoconazole for 5-10 years until adult height was reached. The median dose during the course of therapy was 16.2 mg/kg/day. Safety was monitored through routine testing of liver enzymes, cortisol, and ACTH. Growth velocity decreased significantly with improvement in the BA/CA ratio. Testosterone levels significantly decreased and remained low during treatment. PAH significantly increased and final median adult height was -0.3 SDS (-1.7 to +1.1 SDS). One patient experienced a mild transaminitis that self-resolved. Another patient was found to have an elevated ACTH level to 347 pg/mL with a normal cortisol, and required hydrocortisone treatment during stress for a period of 6 months until it normalized. Despite this complication, the authors concluded that ketoconazole should be a first line therapy in boys with FMPP due to their favorable results.

Another successful therapeutic regimen in boys with FMPP is the combination of spironolactone, an antiandrogen that works at the receptor, along with testolactone, an aromatase inhibitor. Aromatase inhibitors are used in combination therapies in FMPP due to the critical

role that estrogen plays in epiphyseal fusion. One study followed 10 boys with FMPP treated with spironolactone twice daily and testolactone 3-4 times daily for six years [24]. A GnRH analog was also added as necessary for central precocious puberty (CPP). Growth velocity decreased significantly after 1 year of treatment and was maintained during the next 5 years. PAH increased progressively after the first year of treatment from 106.7 ± 14.7 cm at baseline to 173.6 ± 10.1 cm after 6 years. There were no significant adverse effects. The subjects were not followed until adult height attainment, but these results led the authors to conclude that this combination of therapy was successful in normalizing growth. A major downside of this approach, however, is the need for multiple daily doses of medication that may limit compliance.

Finally, recent reports have shown modest success using the combination of bicalutamide and a third-generation aromatase inhibitor in boys with FMPP. Bicalutamide is a potent nonsteroidal antiandrogen that binds to and inhibits the androgen receptor and increases the receptor's degradation [25]. This drug was initially developed for the treatment of prostate cancer. Conveniently, it can be dosed once daily at a dose of 2 mg/kg, though it is fairly expensive. The most common adverse effects are gynecomastia and breast pain [25]. The BATT study (Bicalutamide and Anastrozole Treatment of Testotoxicosis), a multicenter, international trial of 13 boys with FMPP treated with bicalutamide and anastrozole for 12 months found decreased growth rates from baseline in 9 of the 13 patients, however this was not statistically significant [26]. In contrast, the BA/CA ratio decreased significantly from 2.1 ± 0.6 to 1.0 ± 0.4. Pubic hair and Tanner stage remained largely unchanged and mean testicular volume minimally increased. Almost half of the patients experienced gynecomastia and 12.5% reported breast tenderness. The extension phase of this study following the children until adult height has not yet been published, however promising results were seen a small case series of 2

boys treated with the same regimen who were followed for almost 5 years. In this study, bone age advancement stabilized and PAH increased [25].

Lastly, FMPP is often complicated by the activation of the hypothalamic-pituitary-gonadal axis, or CPP, and GnRH analogs are frequently necessary as adjuvant therapy. Although it has not been rigorously studied, usual clinical care includes monitoring boys with FMPP for secondary CPP and initiating treatment once central puberty commences for optimal adult height outcome.

Conclusion

There are a number of causes of PPP in children and treatment depends on the etiology. There is a lack of sufficient treatment data in children with genetic causes of PPP due to the rarity of patients with MAS and FMPP. Despite trials of a number of therapies in MAS, treatment remains challenging and a gold-standard therapeutic regimen does not yet exist. However, a number of successful treatment options are available for boys with FMPP. Further prospective studies involving more patients will hopefully illuminate optimal therapeutic strategies for the treatment of children with both of these rare forms of precocious puberty.

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Table 1. Differential Diagnosis of Peripheral Precocious Puberty

Girls	**Boys**
Ovarian tumor	Familial Male-Limited Precocious Puberty
Ovarian cyst	Leydig cell tumor
Aromatase excess	HCG-secreting tumor
	Familial glucocorticoid resistance
Both Sexes	
McCune-Albright syndrome	
Adrenal tumor	
Exogenous sex steroid exposure	
Primary hypothyroidism	
Congenital adrenal hyperplasia	
Peutz-Jeghers Syndrome	
Endocrine disrupting chemicals	

Table 2. Treatment Options for MAS

Drug Name	**Mechanism of Action**
Ketoconazole	Inhibits P450 enzymes
Medroxyprogesterone	Antiandrogen
Cyproterone acetate	Antiandrogen
Testolactone	First-generation AI
Fadrozole	Second-generation AI
Anastrozole	Third-generation AI
Letrozole	Third-generation AI
Tamoxifen	Selective Estrogen Receptor blocker
Fulvestrant	Pure Estrogen Receptor blocker

Table 3. Treatment Options for FMPP

Drug Name	**Mechanism of Action**
Cyproterone acetate	Antiandrogen
Medroxyprogesterone acetate	Antiandrogen
Ketoconazole	Inhibits P450 enzymes
Spironolactone	Weak antiandrogen agent
Testolactone	First-generation AI
Anastrozole	Third-generation AI
Letrozole	Third-generation AI
Bicalutamide	Potent nonsteroidal antiandrogen agent