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Clinical Case Seminar

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A case of familial male-limited precocious puberty in a 4-year-old boy.

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Abstract

Familial male-limited precocious puberty (FMPP), or testotoxicosis, is a rare cause of precocious puberty in males. It is caused by an activating mutation in the luteinizing hormone/chorionic gonadotropin receptor (LHCGR) gene. This causes excessive production of testosterone, with LH and FSH levels suppressed. Generally, boys present with signs of puberty, with age of onset between 2-5 years essentially with penis and testes growth, linear growth acceleration and progressive bone age advancement. Differential diagnosis is often a challenge with others causes of peripheral puberty. The goal of treatment is to decrease the effect of testosterone as well as reduce the conversion of testosterone to estrogen. The long-term aims are to prevent precocious virilization and to delay closure of the epiphyseal plates to maintain adult height potential. Little is known about the long-term effects of treatment because the disorder is so rare. However recent studies using bicalutamide and anastrozole have been promising. In this report, we present a boy with FMPP with a classic mutation in the LHCGR gene, who has been challenging to manage with off-label drugs.

Keywords: precocious puberty, testotoxicosis, Familial male-limited precocious puberty, antiandrogen, ketoconazole, letrozole

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Introduction

Familial male-limited precocious puberty (FMPP)ortestotoxicosis, is a rare genetic disorder with autosomal dominant transmission that affects men[1]. This condition causes gonadotropin-independent precociouspuberty. It is caused by a mutation in the luteinizing hormone/chorionic gonadotrophin receptor (LHCGR) gene, resulting in the receptor being constitutively activated.A mutation may occur de novo or be inherited in an autosomal dominant manner[2]. The most common mutation reported is due to a substitution A>G which leads a change from aspartate to glycine in position 578 of LHCGR. This change causes activated protein without any input from LH[2]. Clinically, early signs of puberty, growth acceleration and skeletal advancementdevelop in boys usually by 2-4 years of age[3]. Premature epiphyseal fusion can leadto reduced adult stature. Treatment goals are to decrease the effects of testosteroneand to inhibit its conversion to estrogen.

Different clinical therapeutic approaches have been used for this disorder[4]. Cyproterone acetate represents avalidoption by antagonizing androgen action at the receptor level. It can alsoinducesuppression of the

pituitary gonadotrophin secretion in patients with gonadotrophin-dependent precocious puberty[5].The main adverse effects were adrenal insufficiency and gynecomastia.However, this treatment did not decrease pubertal and bone age progression in some cases because oftestosterone aromatization to estrogen. Aromatase inhibitors have also been used for the treatment of gonadotrophin-independent precocious puberty[6].Another option for FMPP includes ketoconazole, a P450 cytochrome inhibitor. The main side-effect of ketoconazole is hepatotoxicity[7]. A study of five patients with FMPP showed that ketoconazole was well tolerated and effective in increasing adult height[8]. Recently, the association of anastrozole, a third-generation aromatase inhibitor with bicalutamide, a nonsteroidal antiandrogen, resulted in clinical improvement and a marked decrease in growth velocity in two boys with FMPP[9].In definitive there are not guidelines on the management of testotoxicosis but a combined therapy with nonsteroidal antiandrogen agents and aromatase inhibitors is a promising option.

Case Report

A 4-years and 6-months-old male child presented to our pediatric endocrinology clinic because of suspicion of precocious puberty. His parents noticed the appearance of pubic hair and enlargement of testes'volume in the previous 6 months. It was also documented a progressive acceleration of statural growth from 2-years-old from the 50th to 95th percentile. Parents denied exposure to cream or medications containing testosterone. The family history was suggestive for early puberty on paternal line. At first presentation, child's height was over the 99th percentile (+3.39 SD), above his target height (-1.13DS). The physical examination showed a herculean appearance, the presence of coffee-milk spot on right flank (3.5 x 2 cm), increased penis size, testes' volume of 6-8 cc bilaterally and dark curly pubic hair (**figure 1**). It was not referred headache or visual changes. Bone age radiograph demonstrated advanced skeletal maturation valued with Greulich& Pyle atlas (7.9 years).Laboratory evaluation revealed normal serum levels of thyroid function, serum and urinary electrolytes, ACTH, cortisol and prolactin. 17-hydroxyprogesterone (0.75 ng/dL) and human chorionic gonadotropin (hCG<0.2 U/L) were within the normal range.

Fig1. Coffee-milk spot and erection during first clinical examination

Fig 2. Patient growth chart indicating height measurements with corresponding bone age

Table 1. FSH and LH values before and after LHRH test

TEST LHRH	FSH (mIU/ml)	LH (mIU/ml)
0'	<0.3	<0.3
30'	1.07	0.88
60'	1.40	0.90

Once diagnosis reached, therapy with ketoconazole at 10 mg/kg/die was started. During clinical and biochemical follow-up, the child showed a progressive reduction in testosterone levels (from 355 ng/dl to 31 ng/dl) and partial regression of pubic hair but with persistence of erections and with progression of bone age. For this reason, we decided to add treatment with cyproterone acetate at 1 mg/Kg/die. After two months, iatrogenic adrenal insufficiency was documented. According to literature, it was decided to switch to the association of spironolactone (4 mg/kg/die) and letrozole, (2.5 mg/die). At 6.6 years-old because of growth curve acceleration and progression of bone age, althoughadequate therapy, a new GnRh test was performed which documented a central precocious puberty. For this reason, Triptorelin was started once monthly.

The patient has been tolerating treatment with progressive reduction on testosterone levels, linear growth, and regular bone-age progression. He has not presented progression of puberal signs (**Table 2**).

Finally, the bone age, after initial acceleration, remained stable at two years from starting the treatment (**Figure 2**). However, his predicted adult height has not improved at the last control probably for the initial bone ageacceleration.

Table 2. Main clinical and biochemical parameters during follow-up

	Diagnosis	After 6 months	After 12 months	After 18 months	After 24 months
Weight (kg)	**29.5**	**37.20**	**40.9**	**48**	**50.5**
Height (cm)	**120.8**	**127.5**	**131.9**	**134**	**137.3**
BMI (Kg/m2)	**20.22**	**22.88**	**23.51**	**26.73**	**26.79**
Testosterone (ng/dl)	**355**	**108**	**14.7**	**3.89**	**6.60**
Testicular volume (cc)	**6-8**	**5-6**	**5-6**	**4-5**	**6**

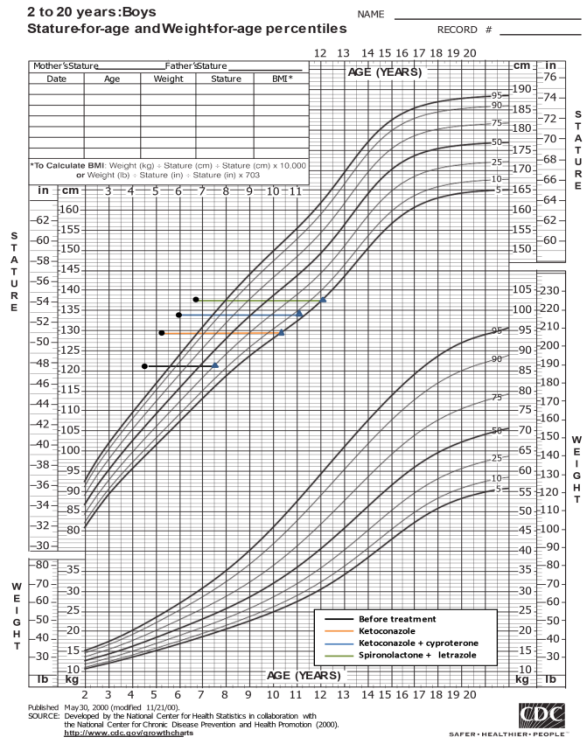
Discussion.

Precocious puberty in male is a rare condition which requires always diagnostic investigations[10]. It is rarely idiopathic and organic causes should be excluded. Laboratorytests with GnRH test lead to distinguish from central to peripheral puberty. In case of peripheral precocious puberty, after excluding neoplastic causes, congenital adrenal hyperplasia from 21-OH deficiency, rare causes such as McCune-Albright syndrome or testotoxicosis should be considered[11].

FMPP is a rare cause of peripheral precocious puberty in male. Affected patients present with early onset puberty, accelerated growth and bone maturation. This condition can lead to premature epiphyseal fusion and altered final adult height[12]. The main goal of treatment is to minimize virilization and maintain adult height potential. Treatment efficacy is valued with clinical examination, laboratory tests and bone ages. The rarity of the condition makes it difficult to do clinical trials and there is not yet a consensus on treatment. In the last years different approaches have been proposed.

Firstly, the use of antiandrogen drug such as cyproterone acetate was used but with failure on improvement in final height[12 13]. Ketoconazole, as a solo agent or used in combination witharomatase inhibitors, has been effective by inhibiting adrenal and testicular androgen biosynthesis. It was useful in suppressing pubertal symptoms and increasing adult height such as in reducing and maintaining low testosterone levels[8 12]. However, it can causes serious side effects such as hepatotoxicity and adrenal suppression.

Spironolactone, a weak anti-androgen, in combination with aromatase-inhibitor (testolactone or letrozole) were trialed with a good success in term of skeletal-maturation, erections and aggressive behavior [14]. A major downside of this approachis the need for multiple daily doses that may limit compliance. Moreover, some studies showed central precocious puberty with spironolactone[15]. It happened in our case; in fact, it is known that the decrease in testosterone levels during therapy may cause secondary gonadotrophin-dependent precocious puberty in boys with testotoxicosis[16].



Recent studies have shown that aromatase inhibitors and antiandrogen agents were effective in reducing virilization and decreasing testosterone synthesis without side effects[17 18 19]. These treatments in combination have shown better adult height potential preservation than either alone[20].

Bicalutamide and anastrozole offer the additional advantage of a prolonged half-life that allows for convenient once-daily dosing. Long-term effects on adult height, fertility and bone age are not now available because of smaller samples and rarity of the condition but results are promising and this combination therapy should be used in the clinical practice.

In conclusion FMPP is a rare disorder that causes precocious puberty in male. No treatment guidelines have been defined because of the limited number of cases and short-term outcome. Therapeutic management, however, is complex requiring the use of off-label drugs that may lead to side effects. Close clinical-auxological and laboratory follow-up appears essential.

Conflicts of Interest

There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

References

1. Schedewie HK, Reiter EO, Beitins IZ, Seyed S, Wooten VD, Jimenez JF, et al. (1981). Testicular Leydig cell hyperplasia as a cause of familial sexual precocity. J Clin Endocrinol Metab, 52(2):271-278. doi: 10.1210/jcem-52-2-271.

2. Shenker A, Laue L, Kosugi S, Merendino JJ Jr, Minegishi T, Cutler GB Jr. (1993). A constitutively activating mutation of the lutenizing hormone receptor in familial male precocious puberty. Nature, 365:652-654. doi: 10.1038/365652a0.

3. Cooper,G.S.,Bynum,M.L.,Somers,E.C.(2021).RecentinsightsintheepidemiologyofFamilial male-limited precocious puberty. Endocrinologist, 13(2):239-244. doi: 10.4274/jcrpe.galenos.2020.2020.0067.

4.Bertelloni, S., Baroncelli, G.I., Lala, R., Cappa, M., Matarazzo, P., De Sanctis, C. & Saggese, G. (1997). Long-term outcome of male-limited gonadotropin-independent precocious puberty. Hormone Research, 48(5):235-9. doi: 10.1159/000185521.

5. Laron, Z. &Kauli, R. (2000). Experience with cyproterone acetate in the treatment of precocious puberty. Journal of Pediatric Endocrinology and Metabolism, 13 Suppl 1:805-10. doi: 10.1515/jpem.2000.13.s1.805.

6. Feuillan, P., Calis, K., Hill, S., Shawker, T., Robey, P.G. & Collins, M.T. (2007). Letrozole treatment of precocious puberty in girls with the McCune–Albright syndrome; a pilot study. Journal of Clinical Endocrinology and Metabolism, 92(6):2100-6. doi: 10.1210/jc.2006-2350.

7. Holland, F.J., Fishman, L., Bailey, J.D. & Fazekas, A.T. (1985). Ketoconazole in the management of precocious puberty not responsive to LHRH analogue therapy. New England Journal of Medicine, 312(16):1023-8. doi: 10.1056/NEJM198504183121604.

8. Soriano-Guillen, L., Lahlou, N., Chauvet, G., Roger, M., Chaussain, J.L. &Carel, J.C. (2005). Adult height after ketoconazole treatment in patients with familial male-limited precocious puberty. Journal of Clinical Endocrinology and Metabolism, 90(1):147-51. doi: 10.1210/jc.2004-1438.

9. Kreher, N.C., Pescovitz, O.H., Delameter, P., Tiulpakov, A. &Hochberg, Z. (2006). Treatment of familial male-limited precocious puberty with bicalutamide and anastrozole. Journal of Pediatrics, 149(3):416-20. doi: 10.1016/j.jpeds.2006.04.027.

10. Latronico, Ana Claudia; Brito, Vinicius Nahime; Carel, Jean-Claude. (2016). Causes, diagnosis, and treatment of central precocious puberty. The Lancet Diabetes & Endocrinology, 4(3):265-274. doi: 10.1016/S2213-8587(15)00380-0.

11. Haddad NG, Eugster EA. (2019). Peripheral precocious puberty including congenital adrenal hyperplasia: causes, consequences, management and outcomes. Best Pract Res Clin Endocrinol Metab, 33(3):101273. doi:

10.1016/j.beem.2019.04.007.
12. Schoelwer M, Eugster EA. (2016). Treatment of peripheral precocious puberty. Endocr Dev, 29:230-9. doi: 10.1159/000438895.
13. Almeida MQ, Brito VN, Lins TS, Guerra-Junior G, de Castro M, Antonini SR, Arnhold IJ, Mendonca BB, Latronico AC. (2008). Long-term treatment of familial male-limited precocious puberty (testotoxicosis) with cyproterone acetate or ketoconazole. Clin Endocrinol (Oxf), 69(1):93-98. doi:10.1111/j.1365-2265.2007.03160.x
14. Laue L, Kenigsbery D, Pescovitz OH, Hench KD, Barnes KM, Loriaux DL, Cutler GB Jr. (1989). Treatment of familial male precocious puberty with spironolactone and testosterone. N Engl J Med, 320(8):496-502. doi: 10.1056/NEJM198902233200805.
15. Leschek EW, Jones J, Barnes KM, Hill SC, Cutler GB Jr. (1999). Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. *J ClinEndocrinolMetab*, 175-8. doi: 10.1210/jcem.84.1.5413.
16. Boepple, P.A., Frisch, L.S., Wierman, M.E., Hoffman, W.H. & Crowley, W.F. Jr (1992). The natural history of autonomous gonadal function, adrenarche, and central puberty in gonadotropin-independent precocious puberty. Journal of Clinical Endocrinology and Metabolism, 75(6):1550-5. doi: 10.1210/jcem.75.6.1464663.
17. Mitre N, Lteif A. (2009). Treatment of Familial Male-Limited Precocious Puberty (Testotoxicosis) With Anastrozole and Bicalutamide in a Boy with a Novel Mutation in the Luteinizing Hormone Receptor. J Pediatr Endocrinol Metab, 22(12):1163-7. doi: 10.1515/jpem.2009.22.12.1163.
18. Lenz AM, Shulman D, Eugster EA, Rahhal S, Fuqua JS, Pescovitz OH, Lewis KA. (2010). Bicalutamide and third-generation aromatase inhibitors in testotoxicosis. Pediatrics, 126(3):e728-33. doi: 10.1542/peds.2010-0596.
19. Kreher NC, Pescovitz OH, Delameter P, Tiulpakov A, Hochberg Z. (2006). Treatment of familial male-limited precocious puberty with bicalutamide and anastrozole. J Pediatr, 149(3):416-20. doi: 10.1016/j.jpeds.2006.04.027.
20. Lane LC, Flowers J, Johnstone H, Cheetham T. (2018). Adult height in patients with familial male-limited precocious puberty and the role of an aromatase inhibitor in patient management. J Pediatr Endocrinol Metab, 31(5):551-560. doi: 10.1515/jpem-2017-0363.

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