

CASE REPORT

MJPC Vol. 30 (3) December 2024

OFFICIAL JOURNAL



A RARE CAUSE OF PRECOCIOUS PUBERTY - TESTOTOXICOSIS

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Abstract

Background: Testotoxicosis, also known as familial male-limited precocious puberty (FMPP), is a rare cause of gonadotropin-independent precocious puberty in boys due to an activating mutation in the luteinizing hormone (LH)/choriogonadotropin receptor (LHCGR) gene. **Case report:** A 3-year 2-month-old boy presented with acne, pubic hair, phallic growth, height accelerations, and aggressiveness. At physical examination, his height was 106cm (+2.36 SDS) and weight was 16kg (+0.77 SDS). He had Tanner stage 2 pubic hair, stretched penile length was 6 cm (>2 SDS), and both testicular volumes were 5mls. Bone age was advanced at 7 years old. Testosterone level was high at 17nmol/L and the gonadotropin-releasing hormone (GnRH) stimulation test was suggestive of peripheral precocious puberty. Whole exome sequencing identified a heterozygous pathogenic variant c.1691A>G (p.Asp564Gly) in the LHCGR gene which supports the diagnosis of testotoxicosis. The child was started on both aromatase inhibitor, anastrozole, and anti-androgen, spironolactone. At 6 months of treatment, there was a halt in pubertal progression with reduced height velocity from 9cm/year to 6cm/year. **Conclusion:** Without intervention, the patient will have rapid progressive skeletal maturation and virilization which will result in compromised final adult height and psychosocial distress.

Keywords: Testotoxicosis, familial male-limited precocious puberty, bone age, aromatase inhibitor

DOI: 10.51407/mjpc.v30i3.313

Received: 25 June 2024; **Accepted revised manuscript:** 17 November 2024; **Published online:** 3 December 2024

Introduction

Testotoxicosis, also known as familial male-limited precocious puberty (FMPP), is a very rare cause of gonadotrophin-independent precocious puberty that occurs exclusively in males. Its prevalence is reported to be <1 in 1,000,000. Affected boys typically present around the age of 2-4 years old [1-4].

This disorder is caused by an activating mutation in the luteinizing hormone/chorionic gonadotropin receptor (LHCGR) gene that is located on chromosome 2p21. It can occur as a de novo mutation or be inherited in an autosomal dominant manner. LHCGR, a G- protein-coupled receptor is located on testicular Leydig cells, and under normal circumstances, it is activated by luteinizing hormone and human chorionic gonadotropin (HCG) to produce sex steroids [1-4].

In testotoxicosis, autonomous activation of the mutated LHCGR receptor resulted in excessive testosterone synthesis by Leydig cells, causing early signs of puberty, such as acne, pubic hair growth, and phallic growth in the condition of low LH levels [1-3]. Androgens are aromatised to estrogen leading to accelerated height velocity, advanced bone age, and premature epiphyseal closure which ultimately

results in shorter adult height. Behavioral issues such as masturbation and aggressiveness had been reported which caused psychosocial distress for the child and parents. [1-4]. Interestingly, female carriers are phenotypically normal and have been postulated to be due to low LH-receptor expression in prepubertal girls, and dual LH and follicular stimulating hormone (FSH) are required for estrogen biosynthesis [4,5].

Case report

We report a 3-year 2-month-old boy of Malay ethnicity presented to the paediatric endocrinology clinic with concerns about early puberty. Parents noticed the patient had acne, pubic hair, phallic growth, was tall for his age, and had aggressive behavioral changes since the age of 2 and a half years old. His parents were non-consanguineous and had no family history of precocious puberty or short

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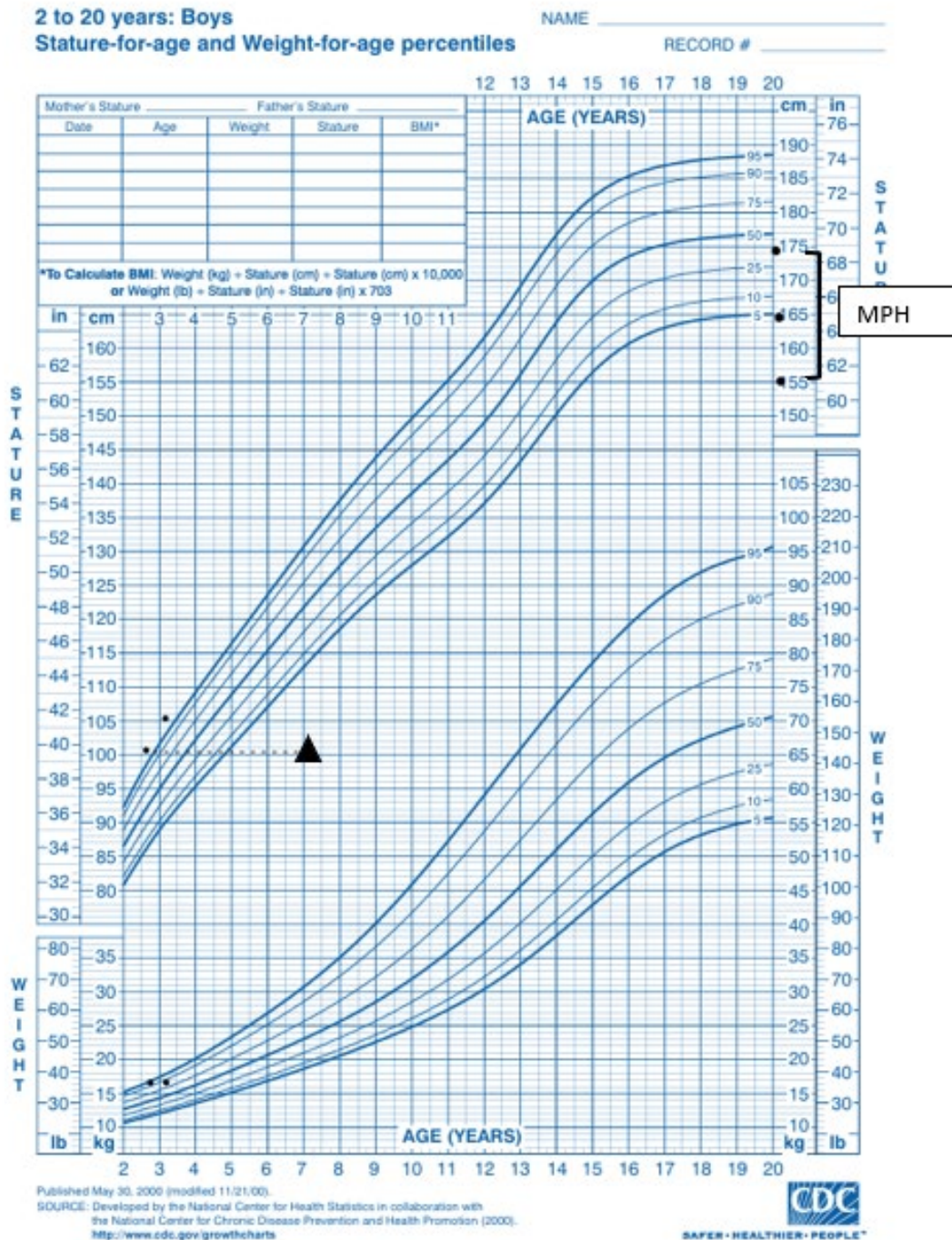


Figure 2. The growth chart showed bone age (black triangle) was significantly advanced for chronological age.

Laboratory evaluations revealed testosterone level was significantly high at 17nmol/L (normal prepubertal level: <0.3nmol/L) with baseline luteinizing hormone (LH) <0.3 u/L and follicular stimulating hormone (FSH) < 0.3u/L. Testosterone level was not proportionate with clinical findings of the testicular size. A Gonadotropin-releasing hormone (GnRH) stimulation test excluded central precocious puberty (peak LH 1.44u/L and FSH 3.02

u/L). Thyroid function tests (FT4: 13.77 pmol/L; TSH: 1.71 mIU/L) and adrenal hormone levels (dehydroepiandrosterone sulfate (DHEAS): 0.46umol/L; 17-hydroxyprogesterone: 3.42 nmol/L; cortisol: 400nmol/L) were within normal ranges. Synacthen test excluded virilising congenital adrenal hyperplasia. Alpha-feto protein AFP (2.95ng/ml) and beta-HCG (1.2mIU/ml) were negative (table 1). Testicular ultrasound showed no sonographic

Table 1. Laboratory result

Test	Result	Reference level
Testosterone	17nmol/L	< 0.3nmol/L
GnRH stimulation test		
Basal LH	<0.3u/L	
Peak stimulated LH	1.44u/L	
Basal FSH	<0.3 u/L	
Peak stimulated FSH	3.02u/L	
TSH	1.71mIU/L	0.4-4mIU/L
FT4	13.77pmol/L	10-21pmol/L
DHEAs	0.46 umol/L	0.01-0.53
Synacthen test		
basal 17-OHP	1.41nmol/L	< 6.06nmol/L
stimulated 17-OHP	6.91nmol/L	
basal cortisol	251nmol/L	
stimulated cortisol	765nmol/L	
Beta-HcG	1.2mIU/ml	0-5mIU/ml
AFP	2.95ng/ml	0-10ng/ml

evidence of testicular lesion. Whole exome sequencing identified a heterozygous pathogenic variant c.1691A>G (p. Asp564Gly) in the LHCGR gene which supports the diagnosis of testotoxicosis.

Following genetic confirmation of the diagnosis, the patient was started on aromatase inhibitor, anastrozole 1mg daily, and anti-androgen, spironolactone 25mg (2mg/kg) BD. He has been tolerating the treatment well and at review following 6 months of treatment, there was a halt in pubertal progression with reduced height velocity from 9cm/year to 6cm/year. His parents were satisfied with the improvement of his behavior and temperament after starting treatment.

Discussion

Testotoxicosis typically presents by 2-4 years of age as we observed in this patient. High testosterone levels resulted in virilization, muscular build, rapid growth, and aggressive behavior. However, a relatively small, and moderate increase in testicular volume was less than expected for the degree of sexual development. It may be explained by the lack of physiological stimulus from FSH on seminiferous tubules [6]. Laboratory evaluations revealed raised testosterone levels with low stimulated LH and FSH levels suggestive of gonadotrophin-independent precocious puberty. The differential diagnosis for this patient included virilizing congenital adrenal hyperplasia, HCG-secreting tumour, adrenal tumour, Leydig cell tumour, and McCune Albright syndrome. Genetic analysis is important to confirm the diagnosis of testotoxicosis, an extremely uncommon condition, and to guide further treatment directions.

The therapeutic goal of the management for testotoxicosis is to alleviate the physical and psychological consequences of excess androgen and preserved adult height potential. These goals are achieved by using a combination therapy of anti-androgen agents to block testosterone action and aromatase inhibitors to block the synthesis of estrogen.

In the past, a steroidogenesis inhibitor, ketoconazole, had been used to treat testotoxicosis and was reported to show improvement in final adult height. However, due to its side effects of hepatotoxicity and adrenal insufficiency, it is no longer being recommended as currently there are other treatment modalities with better safety profiles [3,4].

Spironolactone, a weak anti-androgen, acts by interfering with testosterone biosynthesis and inhibits dihydrotestosterone binding to its receptor. It is administered twice daily, at a dose of 2-5.7 mg/kg daily, and is a readily available medicine. However, it may result in metabolic acidosis, and hyperkalemia, particularly in the event of gastrointestinal illness [3,4]. Bicalutamide, a newer and more potent selective antiandrogen, acts by directly binding to androgen receptors and increasing receptor degradation. It was used for the treatment of prostate cancer in adult men. Bicalutamide is administered at a dose of 2 mg/kg once daily for the treatment of testotoxicosis. Gynecomastia is a common side effect [7,8].

Anastrozole, a potent 3rd generation aromatase inhibitor, is administered at a dose of 1mg daily and acts by disrupting the conversion of estrogen from androgens. Treatment with anastrozole showed no significant changes in blood counts, liver profiles, or

lipid profiles [9]. However, there were cases reported vertebral endplate changes in idiopathic short-stature boys treated with letrozole, another 3rd generation aromatase inhibitor, which had much stronger aromatase blockade than anastrozole [10].

A study by Leschek et al showed promising results by using both spironolactone combined with aromatase inhibitors (testolactone /anastrozole) for 28 boys with FMPP diagnosed at 4.9 ± 1.5 years of age. The treatment duration was 6.9 ± 1.8 years (range, 2.7–10.3). They reported adult height modestly below sex-adjusted midparental height and within the range for adult males in the general population (-0.4 SD) [3].

The BATT study (Bicalutamide and Anastrozole Treatment of testotoxicosis), a multicentre study involving 14 boys with FMPP, found that combination therapy using bicalutamide and anastrozole effectively reduced growth rate by -1.6cm/year , delayed bone maturation from baseline by 2.3 years and reduced child aggression scale. The drugs were well tolerated with no serious adverse events reported and gynecomastia was the commonly observed side effect [7].

Various case reports had also demonstrated impressive clinical results following the combination therapy of bicalutamide and anastrozole which included reduced bone-age advancement in the face of continued linear growth, improved final adult height potential, and halted progression of virilization without any serious side effects [8,9,11].

Some patients with FMPP can progress into central precocious puberty (CPP) secondary to prolonged exposure of the hypothalamus to high levels of sex steroids. Our patient needed to be monitored for evidence of CPP by monitoring testicular size and gonadotropin levels. Gonadotrophin-releasing hormone analog may be needed if CPP develops.

Literature research revealed 6 cases of men with FMPP who developed testicular malignancy at the age of 14-35 years old. Therefore, monthly self-examination of the scrotum and annual ultrasound follow-up from age 12 to 40 years old is suggested to allow early detection of malignancy [12].

For our patient, parents were keen to start treatment after disclosing genetic analysis results and discussing the treatment modalities. We opted for spironolactone because it is readily available and we are well acquainted with its safety profile. Anastrozole was not available in our hospital drug formulary and measures needed to be taken to procure it for our patient. We plan to periodically monitor blood

counts, electrolytes, blood sugar, lipid profiles and perform spine imaging if symptoms occur to check for potential treatment side effects.

Conclusion

This case study highlights a young boy diagnosed with a rare form of precocious puberty. Testotoxicosis should be considered after other more common causes of precocious puberty have been ruled out. Given the rarity of testotoxicosis, there are no consensus guidelines on the management of testotoxicosis. From the cases reported in the literature, a combination of an aromatase inhibitor and anti-androgen appears to be an appropriate treatment regimen for this patient.

References

- [1] Shenker A, Laue L, Kosugi S, Merendino JJ Jr, Minegishi T, Cutler GB Jr. A constitutively activating mutation of the luteinizing hormone receptor in familial male precocious puberty. *Nature*. 1993;365(6447):652–654
- [2] Gurnurkar S, DiLillo E, Carakushansky M. A Case of Familial Male-limited Precocious Puberty with a Novel Mutation. *J Clin Res Pediatr Endocrinol*. 2021 Jun 2;13(2):239-244. doi: 10.4274/jcrpe.galenos.2020.2020.0067. Epub 2020 Aug 6. PMID: 32757547; PMCID: PMC8186329.
- [3] Leschek EW, Flor AC, Bryant JC, Jones JV, Barnes KM, Cutler GB Jr. Effect of Antiandrogen, Aromatase Inhibitor, and Gonadotropin-releasing Hormone Analog on Adult Height in Familial Male Precocious Puberty. *J Pediatr*. 2017 Nov;190:229-235. doi: 10.1016/j.jpeds.2017.07.047. PMID: 29144249; PMCID: PMC5726420.
- [4] A. Daussac, P. Barat, N. Servant, M. Yacoub, S. Missonier, F Lavran, L. Gaspari, C. Sultan & F. Paris (2019): Testotoxicosis without Testicular Mass: Revealed by Peripheral Precocious Puberty and Confirmed by Somatic LHCGR Gene Mutation, *Endocrine Research*, DOI: 10.1080/07435800.2019.1645163
- [5] Lane LC, Flowers J, Johnstone H, Cheetham T. Adult height in patients with familial male-limited precocious puberty and the role of an aromatase inhibitor in patient management. *J Pediatr Endocrinol Metab*. 2018 Apr 25;31(5):551-560. doi: 10.1515/jpem-2017-0363. PMID: 29654692.
- [6] Bertelloni S, Baroncelli GI, Lala R, Cappa M, Matarazzo P, De Sanctis C, Saggese G. Long-term outcome of male-limited gonadotropin-independent precocious puberty. *Horm Res*.

- 1997;48(5):235-9. doi: 10.1159/000185521. PMID: 9362394.
- [7] Reiter EO, Mauras N, McCormick K, Kulshreshtha B, Amrhein J, De Luca F, O'Brien S, Armstrong J, Melezinkova H. Bicalutamide plus anastrozole for the treatment of gonadotropin-independent precocious puberty in boys with testotoxicosis: a phase II, open-label pilot study (BATT). *J Pediatr Endocrinol Metab.* 2010 Oct;23(10):999-1009. doi: 10.1515/jpem.2010.161. PMID: 21158211
- [8] Lenz AM, Shulman D, Eugster EA, Rahhal S, Fuqua JS, Pescovitz OH, Lewis KA. Bicalutamide and third-generation aromatase inhibitors in testotoxicosis. *Pediatrics.* 2010 Sep;126(3):e728-33. doi: 10.1542/peds.2010-0596. Epub 2010 Aug 16. PMID: 20713483; PMCID: PMC4096839.
- [9] Kreher NC, Pescovitz OH, Delameter P, Tiulpakov A, Hochberg Z. Treatment of familial male-limited precocious puberty with bicalutamide and anastrozole. *J Pediatr.* 2006 Sep;149(3):416-20. doi: 10.1016/j.jpeds.2006.04.027. PMID: 16939760.
- [10] Hero M, Toiviainen-Salo S, Wickman S, Mäkitie O, Dunkel L. Vertebral morphology in aromatase inhibitor-treated males with idiopathic short stature or constitutional delay of puberty. *J Bone Miner Res.* 2010 Jul;25(7):1536-43. doi: 10.1002/jbmr.56. PMID: 20200972.
- [11] Yuan X, Chen R, Zhang Y, Yang X, Lin X. Long-Term Treatment With Letrozole in a Boy With Familial Male-Limited Precocious Puberty. *Front Endocrinol (Lausanne).* 2022 Jul 14;13:906852. doi: 10.3389/fendo.2022.906852. PMID: 35909557; PMCID: PMC9329579.
- [12] Kooij CD, Mavinkurve-Groothuis AMC, Kremer Hovinga ICL, Looijenga LHJ, Rinne T, Giltay JC, de Kort LMO, Klijn AJ, de Krijger RR, Verrijn Stuart AA. Familial Male-limited Precocious Puberty (FMPP) and Testicular Germ Cell Tumors. *J Clin Endocrinol Metab.* 2022 Nov 23;107(11):3035-3044. doi: 10.1210/clinem/dgac516. PMID: 36071555; PMCID: PMC9681611.