Gonadotropin independent sexual precocity in a Pakistani male infant from an activating mutation in LHCGR gene

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Abstract

A male child, aged seven months, visited the out patients clinic of the National Institute of Child Health, Karachi, in May 2020 with the features of iso-sexual puberty. After ruling out the more common causes of early puberty, like congenital adrenal hyperplasia and tumours secreting chorionic gonadotropin hormone, hormonal assessment indicated raised testosterone independent of gonadotropin. The volume of the testicles was symmetric and testicular ultrasonography revealed no mass. Genetic analysis for the LHCGR gene was performed for confirmation which revealed activating heterozygous missense pathogenic mutation in c.1732G>T (p.Asp578Tyr). This is the first reported case of testotoxicosis (FMPP) from Pakistan which was genetically confirmed.

Keywords: Testosterone, Puberty, Gonadotrophins, Mutation, Genetic.

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Introduction

Testotoxicosis or familial male limited precocious puberty (FMPP), is an uncommon cause of isosexual early puberty by autonomous testosterone secretion. Testicular Leydig cells have these 11 exons, 10 introns, and seven transmembrane helices (TMH) genetic makeup of luteinizing hormone/choriogonadotropin receptor (LHCGR) genes from the family of the G protein-coupled receptor expressed on the short arm of chromosome 2 (2p21),1 whose constitutive activating mutations can culminate in this type of unusual precocity. The mutations which drive these changes are usually allocated to exon 11.2-4

The raised testosterone levels lead to early-onset progression of puberty typically earlier than their fourth birthday and is apparent as virilisation, increased muscle mass, accelerated growth, and advancement in the bone age.2,5,6 Hormonal assessment may reveal testosterone levels similar to that of an adult male or sometimes even higher despite the suppressed gonadotropins luteinising hormone (LH) and follicular-stimulating hormone (FSH).2,7

Treatment is based around reducing the effects of androgens and slowing down advancing bone age (BA), for which various options such as medroxyprogesterone, ketoconazole, cyproterone, and aromatase inhibitors (AIs) come to use.5,3 Recently, newer drugs are under study which combine the effects of both AIs and anti-androgens, like Bicalutamide.5,6,8

After crossing the usual age of puberty and maturation of the hypothalamic-pituitary-testicular axis, the affected adults may have gonadotropin profiles ranging from normal fertility to reduced sperm count.1,2,9

This case educates its readers about the importance of identification and diagnosis of this rare genetic mutation in a timely manner to minimize its impact on the child’s life.

Case Report

A seven-month-old male child from Balochistan was referred to the paediatric endocrinology OPD at the National Institute of Child Health, Karachi, in May 2020 with pubic hair growth, enlarged penis, husky cry, and aggressive behaviour. The parents were aware of growing genitals by the time he was just four months age. According to the parents, he had never been subjected to external androgens. The parents were healthy and consanguinely married. The family reported having never come across a case of such an early puberty before.

On physical examination, the child’s height was recorded as 92cm, he weighed 18kg, and the penile stretch length was 4.5cm. Pubic hair growth corresponded to Tanner’s stage 210 (Figure 1). Ultrasonographic examination revealed the right testicular size of 1.2 x 0.8cm, left testis was 0.9 x1.0cm, and testicular volume was 3ml symmetrically and bilaterally. His bone age was calculated by the Greulich-Pyle11 method which came out to be 3.4
years (BA/CA: 4.85) (Bone Age/Chronological Age). No dysmorphic features like gynecomastia, abdominal masses, or café au lait spots were notable over his body.

Multiple follow-up hormonal profiles for Follicle-stimulating hormone (FSH), luteinising hormone (LH), total testosterone, free thyroxine (FT4), thyroid-stimulating hormone (TSH), cortisol, 17-alpha-hydroxyprogesterone, androstenedione and dehydroepiandrosterone sulphate were done, which revealed very high testosterone levels. The hormone levels are given in Table 1. Surprisingly, gonadotropin-releasing hormone (GnRH) stimulation showed age appropriate reading.

Radiologic investigations, including MRI of the brain and pituitary with contrast, MRI of the neck and chest, and CT of the abdomen with contrast, came out normal. Ultrasonography of the inguinoscrotal region and prostate showed no abnormalities and both the testes were visualised in the scrotal sac and no masses were seen. First, a genetic analysis of CYP21 was done which revealed no mutation. Thereafter, upon suspicion of the LH receptor mutation for testotoxicosis, analysis for the LHCGR gene was sent to Radboudumc Genome, which identified an activating heterozygous pathogenic mutation in c.1732G>T (p.Asp578Tyr).

A combination treatment of Anastrozole 1mg twice a day, Spironolactone 25mg half a tablet twice per day, and Bicalutamide 50mg once a day per os was initiated.

The patient is being followed-up with radiology and hormonal analysis at the OPD regularly.

Discussion

Gonadotropin-independent early puberty in males constitutes a group of heterogeneous disorders including the hCG- or androgen-producing tumours, McCune-Albright syndrome, several types of congenital adrenal hyperplasia, and, finally, true familial male precocious puberty.5, 7

Recent demographic data available on various web sites is very limited to know the exact figures regarding how commonly encountered is precocious puberty in Pakistan or the sub-continent. Certain studies from the US have shown that it is more frequently seen in girls than boys with the ratio of 0.2% in girls and less than 0.05% in boys; it usually has a more serious cause in boys. About 10% of white girls and 23% of black girls started puberty at the age of seven.11

We present the first genetically confirmed case of testotoxicosis from Pakistan, since genetic analysis is not available here and is very expensive if undertaken from a foreign facility. The parents were financially stable and could afford the cost for genetic analysis.

This patient presented at a much earlier age than most boys with the same complaints.2-4,6-8 After a thorough clinical examination to establish precocious puberty and excluding the external source of androgen exposure, it had to be ascertained whether it was GnRH-dependent Central precocious puberty (CPP) or GnRH-independent (PPP). When the pre-pubertal response was elicited in the levels of LH and FSH to gonadotropin administration, further hormonal evaluation and radiological examination of the adrenals and testes for congenital adrenal hyperplasia, hCG- or androgen-secreting tumours, and McCune-Albright syndrome was performed. Treatment was started after excluding the potential causes of sexual precocity and upon genetic confirmation of Familial Male-limited Precocious Puberty (FMPP).

The Lutropin-choriogonadotropin hormone receptor (LHCGR) is a member of the superfamily, guanine nucleotide-binding protein-coupled receptors (GPCRs),

Table-1: Hormone profile.

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<tbody>
<tr>
<td>1. FT4</td>
<td>1.07 ng/dl</td>
</tr>
<tr>
<td>2. TSH</td>
<td>1.6 mIU/ml</td>
</tr>
<tr>
<td>3. 17-OHP</td>
<td>2.84 ng/dl</td>
</tr>
<tr>
<td>4. Cortisol</td>
<td>15.20 μg/dL</td>
</tr>
<tr>
<td>5. Serum aldosterone</td>
<td>10.50 ng/dl</td>
</tr>
<tr>
<td>6. Serum FSH</td>
<td>0.30 mIU/ml</td>
</tr>
<tr>
<td>7. Serum LH</td>
<td>0.30 mIU/ml</td>
</tr>
<tr>
<td>8. Serum testosterone</td>
<td>1116 ng/dl</td>
</tr>
</tbody>
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belonging to the glycoprotein hormone receptors (GPHRs), a subfamily of the family GPCRs, whose distinguishing feature is a large N-terminal extracellular domain consisting of several leucine-rich repeats (LRR).1 This glycoprotein hormone receptor family has been named the LRR-containing GPCR (LGR) family.1,2

The LHCG gene consists of 11 exons, and has been assigned to 2 p 21.1

In males, chorionic gonadotropin is responsible for cells in the testes called Leydig cells, which produce androgens under the influence of the luteinising hormone. Androgens (testosterone) are the hormones that are accountable for influencing male sexual development and reproduction (promoting masculinity, pubertal androgenisation, libido, and virility).1

Activating mutations of the LHCG receptor lead to autonomic hyperplasia and hyperfunction of Leydig cells due to the unwarranted stimulation of adenyl cyclase and the cAMP signalling pathway bringing about gonadotropin-independent male-limited precocious puberty.3,9

Histological findings of the testes reveal the typical picture of puberty which includes Leydig cell hyperplasia and Sertoli cell in early stages of meiosis.8

Medical intervention is needed to allow individuals to reach their optimum adult height and for combating the detrimental effects of high androgens; however, due to the rarity of such cases and limited research in the field, there is no consensus over the best treatment modality. Medroxyprogesterone Acetate and Cyproterone Acetate are used for their anti-androgenic properties to slow down the bone age advancement.5

Ketoconazole uses its inhibitory action on P450 enzymes to suppress adrenal and testicular androgen production, but due to its safety concerns of causing hepatotoxicity, adrenal suppression and some other mild unpleasant effects such as gynaecomastia and upset stomach, monitoring is needed through regular assessment of liver enzymes, cortisol, and the ACTH.5,6 Ketoconazole suppresses testosterone levels and slows down growth velocity.5

Spironolactone, a weak antiandrogen agent in combination with Testolactone, a first-generation steroidal AI, decrease the growth velocity significantly but requires multiple daily doses.5

Another treatment modality is Anastrozole or Letrozole, third-generation AIs in combination with Bicalutamide, which is a strong nonsteroidal agent that stops the androgens from reaching its receptor and causes the receptor’s degeneration resulting in decreasing the growth rate5,6 but the downslope is the cost of Bicalutamide, gynaecomastia, and breast pain.5,6 With the use of AIs, most patients reach an appropriate adult height.9 GnRH analogues are almost always routinely required in most cases along with the anti-androgen agents since FMPP usually triggers the activation of the hypothalamic-pituitary-gonadal axis or central precocious puberty (CPP).5

Despite suppressed LH and FSH levels, intra-testicular testosterone production can lead to spontaneous fertility in patients.8 Follow-ups include clinical assessment and ultrasonic scanning of the testes periodically so as not to disregard the possible elevated risk of testicular malignancy such as precancerous lesions (GCNIS) and Leydig cell adenoma, although no links have been reported between precocious puberty and the development of such lesions.4,7,8 It is also important to keep a watch for CPP.5 Adults usually attain good height outcomes with normal to slightly decreased fertility.2,8

**Conclusion**

Isosexual precocious puberty is a rare genetic disorder which can be quite surprising for the family just like in the above mentioned case. Fortunately, with the correct diagnosis, management and in light of the current literature, family can be reassured that adults usually seem to attain good height and fertility outcomes on long-term follow-up.

**Consent:** Consent for publishing the case was provided by the parents.

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**Conflict of Interest:** None.

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**References**


