Case Report

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Luteinizing Hormone Choriogonadotropin Receptor (LHCGR) Gene Defect in a 46 XY Male Child Who was Missed as an Isolated Hypospadias

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ABSTRACT

Background: *The human Luteinizing hormone/chorionic gonadotropin receptor (LHCGR) gene belongs to the G protein–coupled receptor family. The LHCGR gene encodes a shared receptor for luteinizing hormone (LH) and chorionic gonadotropin (hCG).*

Case Summary: *A 7-year-old male (46,XY) child with hypospadias as an initial diagnosis was later found to have abnormal hormone levels (low testosterone, high LH). Genetic studies confirmed a defect in the LHCGR gene.*

Conclusion: *The LHCGR gene defect provides insights into distinct physiological roles of LH in reproduction. This case highlights the importance of considering LHCGR mutations in managing patients with disorders of sex development (DSD).*

Keywords

Disorders of sex development (DSD), Luteinizing hormone/chorionic gonadotropin (LH/hCG) receptor, Isolated hypospadias, Genetic, Hypogonadism.

Introduction

The human Luteinizing chorionic gonadotropin receptor (LHCGR) gene belongs to the G protein–coupled receptor family. The LHCGR gene encodes a shared receptor for luteinizing hormone (LH) and chorionic gonadotropin (hCG). An LHCGR gene defect can cause a range of conditions including Leydig cell hypoplasia (LCH) in males leading to disorders of sex development (DSD) [1-4].

Hypospadias and epispadias are congenital anomalies resulting in abnormal positioning of the urethral meatus which primarily affects males. Hypospadias is the second most common genital anomaly, occurring in one in 250 male births, while epispadias

is much rarer with an incidence of 0.2–4 per 100,000 male births [5-8].

In this manuscript, we describe a 7-year-old boy who was missed as an isolated hypospadias patient but later was determined to have an LHCGR gene defect.

Case Report

A 7-year-old boy, presented with poor growth of the penis. He was the product of full-term normal pregnancy, with no medication or radiation exposure. Parents were nonconsanguineous, with two siblings. No family history of infertility, abnormal genitalia or delayed puberty. He was diagnosed, in the neonatal period, as an isolated hypospadias, which was latter repaired at one year of age. Physical examination showed an obese looking child. No dysmorphic features. Weight of 45.6 Kg, and height of 119.5 cm, with a body mass index of 31.7. The phallus size of 3.5 cm, which was impeded in a suprapubic fat, both testes were down in the scrotum, (Figure 1).

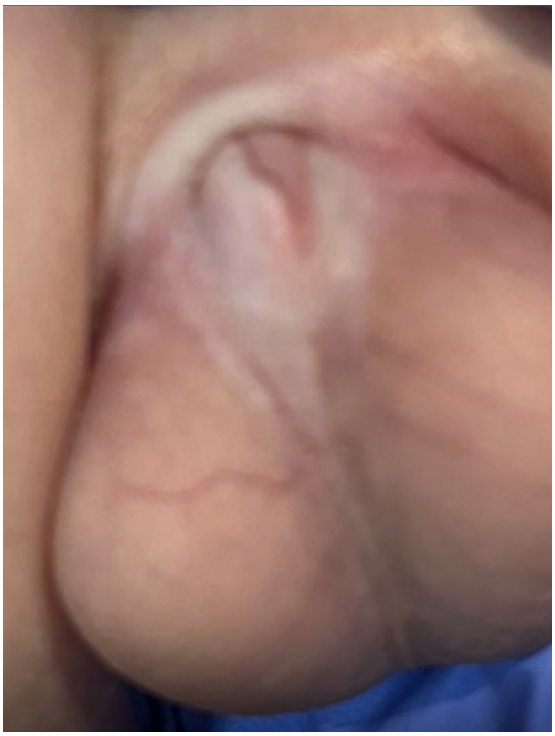

Figure 1: Genitalia of a boy with severe micropenis and bilateral descended testes.

An Ultrasound of the scrotum and testes demonstrates, right high testis in the mid- inguinal canal, measuring 1.6 cm by 0.7 cm with normal echotexture and vascularity, while left testis at a normal position, measuring 1.7 cm by 0.9 cm and normal epididymis was apparently normal. No significant hydrocele.

Laboratory investigation revealed: LH 0.3 mIU/ml (0.02–0.3), low FSH 0.4 mIU/ml (0.2–3), low testosterone 2.5 ng/dl (5-11), DHT 5 ng/dl (3-17), androstenedione 30 ng/dl (40–170).

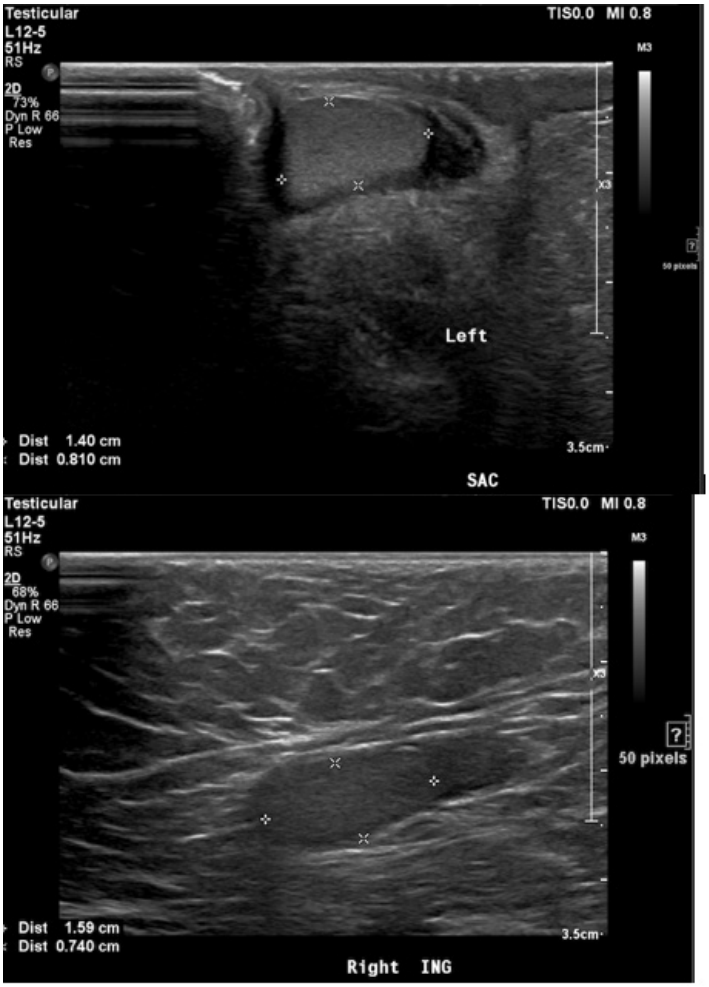

Figure 2: An Ultrasound of both testes.

Genetic study: arr[GRCh37] 2p16.3(48977120_49210746)x1, confirmed mutation in LHCGR gene.

Discussion

This is the first report of a patient with LHCGR gene defect from Saudi Arabia. It is a genetic mutation in the gene responsible for the luteinizing hormone / choriogonadotropin receptor leading to a range of disorders by interfering with the response to LH and human choriogonadotropin (HCG) in males. These mutations can lead to Ledying cell hypoplasia (LCH), a form of 46XY DSD, where Ledying cell hypoplasia and testosterone, are impaired. In females, LHCGR gene defects, typically result in female infertility, characterized by delayed or absent menustration and lack of ovulation. Other conditions associated with LHCGR gene defects include familial male limited precocious puberty and empty follicle syndrome [1-4].

Disorders of sex development (DSD), are secondary to abnormal development of sex chromosome, as well as atypical growth of gonads and genital anatomy. Specifically, DSDs result from insufficient virilization of the genitalia in a 46XY fetus due tob disorders of gonadal development, abnormal androgen. Synthesis

or disorders of androgen action or secondary to defective masculinization of the external genitalia in a 46,XY fetus, represents a broad phenotypic expression of DSD [9].

Beyond minor variations in gonadal function and external appearance, hypospadias is an important and known abnormality associated with DSD [5-8,10-12]. Several mutations have been described, associated with two main conditions: low testosterone, which correlates with abnormalities, and decreased responsiveness of the mutated receptor to hormone stimulation [13-18].

Conclusion

This case report illustrates the value of genetic study in patients with disorders of sex development (DSD). The LHCGR mutation was revealed to provide important insights into distinct physiological roles in reproduction and sexual differentiation. This also highlights the importance of considering such mutations in managing patients with DSD.

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