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Case Report

Spontaneous Puberty in a Male with Heterozygous PROK2 Gene Mutation Presenting with Micropenis and Synkinesis

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Abstract:

Male idiopathic hypogonadotropic hypogonadism is characterized by absent or partial sexual maturation. The Prok2/ProkR2 genes are among the genes implicated in this condition.

Objective: Reporting a case harbouring a missense mutation in the PROK2 gene, presenting, at 7 1/2 years with micropenis and synkinesis.

History and Examination: Born at full term, with no pre/post-natal complications. On presentation his penile stretched length was 3.8 cm, (-2.5 SDS). Both testes were descended, with a testicular volume of 2ml.

Results: On follow up, the testicular volume of 4ml bilaterally, was detected at 11 1/2 years, after 3 testosterone monthly injections. The penile length increased to 5.2 cm. Puberty continued to progress spontaneously.

Genetic Analysis revealed a heterozygous missense mutation in PROK2 gene, exon 4, chromosome 3.

Conclusion: Heterozygous mutations in the PROK2 gene can present with reproductive and non-reproductive manifestations. They may progress spontaneously into puberty, in the absence of micro/cryptorchidism.

Key words: Idiopathic hypogonadotropic hypogonadism; micropenis; micro; cryptorchidism; synkinesis; PROK2 & PROKR2 gene mutations; spontaneous puberty

Introduction

Puberty results from a marked increase in Gonadotropin-Releasing Hormone (GnRH) pulsatile secretion, triggering a cascade of hormonal events which leads to the secretion of sex steroids in abundance and the appearance of secondary sexual characteristics [1]. During embryonic development, the GnRH-secreting neurons migrate along the olfactory axons to the hypothalamus. Congenital or acquired disturbance at any level of the Hypothalamic Pituitary Gonadal (HPG) axis, can result in abnormalities of the reproductive functions, known as hypogonadism. Male hypogonadism may be caused by a defect at the primary testicular level, known as hypergonadotropic hypogonadism. While hypothalamic and/or pituitary failure leads to secondary hypogonadism, known as hypogonadotropic hypogonadism [2]. Over 50 genes have been implicated in the synthesis, secretion, and function of GnRH. Defects in such genes result in a condition known as Idiopathic Hypogonadotropic Hypogonadism (IHH) [3,4,5]. The prokinectin (PROK) signalling comprises two structurally related proteins PROK1 and PROK2 and their G-protein coupled receptors PROKR1 and PROKR2.They are distributed over various tissues in the body, with PROK2 and PROKR2 abundantly found in the central nervous system and olfactory bulb. In the olfactory bulb, PROK2 and PROKR2 play a role in the bulb morphogenesis and the migration of the GnRH synthesizing neuroendocrine cells [6]. Several mutations were identified in PROK2 and PROKR2 genes accounting for the genetic transmission of Idiopathic Hypogonadotropic Hypogonadism, (IHH). Prokinectin 2 loss of function mutations can result in either anosmic IHH, known as Kallman Syndrome (KS), or normosmic idiopathic hypogonadotropic hypogonadism, (nIHH) [7]. PROKR2 and PROK2 mutations account for 7 and 3% respectively of cases of IHH in the homozygous, or compound heterozygous states. In addition, the finding of intra and inter-familial phenotypic variability among those with PROKR2 and PROK2 heterozygous mutations points towards variable penetrance or digenic/oligogenic mode of inheritance, with phenotypic features depending on the additional genetic hit [8]. Reversal of IHH with sustained release of gonadotropins after discontinuation of hormonal therapy has been seen in adult males with genetic defects including PROKR2 [9,10].

In this case report, we present the case of a boy who presented to the endocrine clinic at 7 and a half years of age with micropenis noticed since birth. He was overweight, and had synkinesis and a normal sense of smell. Genetic analysis revealed a heterozygous mutation in the PROK2 gene. On follow up, he entered spontaneously into puberty, after three

testosterone injections at 11 years of age, and he is progressing in puberty at a normal pace without any hormonal assistance.

Case Presentation

A 13 and a half years old boy of Indian origin, presented to the paediatric endocrine clinic at 7 and a half years of age for micropenis, noticed since birth.

He was a product of an emergency lower segment caesarean section for prolonged labour at full term, with Apgar Scores of 8 and 10 at one and five minutes respectively. There were no pre/post-natal complications. His birth weight was 2.3 kg. There was no history of neonatal hypoglycaemia, but he received two days of phototherapy for jaundice. The parents are non-consanguineous. They have one other normal younger boy. There is no positive family history of a similar problem.

Examination on presentation revealed a well-looking child with no dysmorphic features. His height was 135 cm, and weight 33.2 kg, both falling on the 95th centile for age and sex. His penile stretched length (PSL) was 3.8 cm, (-2.5 SDS). Both testes were descended in the scrotal sac, with a testicular volume (TV) of 2ml bilaterally. There were no signs of pubarche, no anosmia, and the rest of the systemic examination was within normal limits.

At 8 years of age, a 3-day Human Chorionic Gonadotropin test was done, which showed a baseline DHEAS: 906 ug/ml (28-852), androstenedione: 0.1ng/ml (0.05-0.5) and testosterone < 0.03 ng/ml (0.03-0.3). LH: < 0.01U/L and FSH: 0.3 IU/L. Post 3-day HCG injections, 1000 units per day, IM: DHEAS: 1051 ug/dL, androstenedione: 0.3 ng/ml, testosterone: 2.36 ng/ml, DHT: 0.37ng/ml and T/DHT: 6.3. He had a normal thyroid function test; TSH: 2.17uIU/ml and FT4: 13.69 pmol/L. His bone age was 7 years at a chronological age of 7 years and 10 months.

The PSL increased to 4.2 cm post HCG. The TV remained at 2 ml bilaterally.

He received 3 doses of Testosterone (Sustanon), 25 mg, IM, monthly, as he was psychologically upset about the small penile size. Genetic analysis for hypogonadotropic hypogonadism was done at MedGenome, Bangalore, India, after counselling the parents and obtaining a written informed consent.

His PSL increased to 5.2 cm and TV increased to 4 ml bil at 11 and a half years of age. His height was 150 cm and weight: 48kg, both at the 95th centile for age and sex. Investigations showed LH: 2.88mIU/L, FSH: 2.63mIU/L and testosterone: 2.78 ng/ml. Next Generation Sequencing for targeted genes of the hypogonadotropic hypogonadism and sex development disorder came positive for a heterozygous missense mutation in the PROK2 gene in exon 4 on chromosome 3, c.301 C>T (p. ARG 101Trp). Another blood sample was sent to CentoGene in Germany for Whole Exome Sequencing (WES).

His PSL increased to 5.8 cm and TV increased to 6 ml bilaterally at 12 and a half years of age. He was last seen at 13 and a half years of age; his PSL increased to 6.7 cm and TV increased to 8 ml bilaterally. His height was 175 cm, and weight: 74 kg, both above the 95th centile for age and sex. The WES confirmed the previous heterozygous missense mutation in the PROK2 gene with no other related genetic abnormality.

Discussion

Male IHH is a disorder characterized by absent or incomplete sexual maturation, pubertal delay and impaired fertility in conjunction with abnormal gonadotropins production, secretion or action and low male sex hormones in the absence of other abnormalities of the hypothalamic-pituitary axis, [11].

Our case was first seen at 7years and 6 months of age with small penile length. Investigations revealed low baseline testosterone, LH and FSH, as expected at this age. The testosterone level increased after 3 days of HCG injection and so did the penile length, which indicate functioning androgenic receptors and responsive testicular tissue. At 11 years, he received 3 testosterone injections, IM, to improve his penile length which was 4.2 cm. Subsequently, he went spontaneously into puberty with an increase in the serum testosterone, LH and FSH to pubertal levels, as well as an increase in the penile length and testicular volumes, which are good predictors of spontaneous puberty [12]. Hypogonadotropic hypogonadism in males manifests a complexity of genetic and phenotypic features. There have been asymptomatic family members of patients with IHH, harbouring the same PROK2/PROKR2 gene mutations.This could be explained by the influence of epigenetic factors and the fact that such mutations can have variable penetrance, in addition to the involvement of other genes, some of which might not have yet been discovered, resulting in digenic/oligogenic mode of inheritance. Furthermore, reversal of IHH with reactivation of the HPG axis in adulthood, has been described in a sub-group of patients with normalisation of steroidogenesis and gametogenesis [13]. Studies have shown a 10-20% life-time reversal rate of male IHH. Several genes were associated with reversal of hypogonadism, among which PROKR2 had been described. In addition, a subset of the patients who reversed went back to their hypogonadotropic state after some time in future [3,14]. A recent study, looking into the factors which increase the likelihood of reversal in adulthood in males with IHH, had highlighted that reversal is more likely to occur in the absence of undescended testes and micropenis and the presence of a larger mean testicular volume and higher serum FSH concentration, consistent with the Pasqualini Syndrome, (Fertile eunuch subtype of congenital HH), known to have better fertility outcome [15].

Genetic analysis of our case revealed a known missense mutation in the PROK2 gene. This mutation has been detected by Dode et al, (unpublished data) with no functional consequences described, [7].

Although there have been a few reports of synkinesis in hypogonadotropic hypogonadism patients harbouring heterozygous mutations in the PROK2/PROKR2 genes, it is described more frequently in patients with ANOS1, also known as KAL1 mutations (16,17). As described in the literature, those with homozygous mutations in the PROKR2 and PROK2, do not have the extra olfactory and nonreproductive manifestations such as the bimanual synkinesis, renal agenesis, dental agenesis and cleft lip or palate, yet they have more severe reproductive manifestations such as cryptorchidism, micropenis, small testicular volume, lower serum testosterone levels and lower post stimulation LH levels, as compared to those who have heterozygous mutations [18]. Our patient harbouring a missense heterozygous mutation, had reproductive manifestation in the form of micropenis with no micro or cryptorchidism and good serum testosterone response to 3-day HCG injections. This could explain why he had gone into spontaneous puberty after stimulation with testosterone. In addition, he had non-reproductive manifestations in the form of involuntary lip smacking and arm movement, which are more common in the heterozygous state of the PROK2/PROKR2 mutations, as described above.

Beside their role in the reproductive system, the prokinetin 2 protein plays a role in regulating important biological body functions such as circadian rhythms, mood regulation, angiogenesis, neurogenesis, muscle contractility, haematopoiesis, immune response, pain perception, food intake, energy balance and insulin sensitivity [19,20]. Further follow up of patients with mutations in the PROK2 gene is warranted to exclude development of other manifestations of PROK2 gene defects.

Conclusion and Limitations

Heterozygous mutations in the PROK2 gene can present with both reproductive and non-reproductive manifestations, and they may progress spontaneously into puberty, in the absence of micro/cryptorchidism. Further follow up is warranted to exclude reverting to a hypogonadotropic

state or the development of other abnormalities of PROK2 gene defects in nonreproductive body tissue.

Specific genetic events like copy number variants, translocations and repeat expansions may not have been reliably detected with targeted Clinical Exome Sequencing (CES), thus, additional variants could not have been confidently detected.

The author, a senior consultant paediatric endocrinologist, is the main care giver to the reported case, responsible for diagnosing and managing the case as well as writing the manuscript and forwarding it for publication.

Conflict of Interest

No conflict of interest to be declared

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