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Case Report

A Novel GnRH1 Gene Mutation in Four Omani Male Siblings, Presentation and Management

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Abstract:

Male hypogonadotropic hypogonadism results from defects in the GnRH or gonadotropins, causing sex-organ malformation, reduced or absent male secondary sexual characteristics, and infertility. Genetic mutations at the level of the hypothalamus or pituitary can result in this condition. This paper describes the clinical features and management of four Omani male siblings with hypogonadotropic hypogonadism carrying a novel mutation in the GnRH1 gene.

Case 1: 16 years old, had micro penis and bilateral undescended testes. Pubertal induction started at 12 ½ years with testosterone injections.

Case 2: 7 years old, had micro penis and bilateral retractile testes. He received HCG injections, followed by testosterone injections.

Case 3: 6 years old, had micro penis and bilateral small inguinal testes. He was given HCG injections, followed by testosterone and FSH injections.

Case 4: 3 1/2 years old, had a normal penile stretched length with bilateral undescended testes. Only the right testes was seen on ultrasound. On laparoscopic exploration, both testes were detected intra-abdominally. A repeat ultrasound did not show the testes, on either side. He received HCG injections.

Conclusion: GnRH1 gene c.85C>G (p. His 29 to ASP) is a novel mutation that can result in micro penis, undescended, or atrophic testes and infertility. Treatment with testosterone, HCG and FSH can be given depending on the clinical findings. Further follow-up is required to understand the course of this condition and the impact of early management on fertility in the future.

Key words: male-hypogonadotropic-hypogonadism; micro-penis; undescended/retractile testes; infertility; GnHRH1 gene

Introduction

The hypothalamic-pituitary-gonadal axis develops embryonically, and after a short period of activation following birth, it remains suppressed until reactivation by stimulatory influences, resulting in pulsatile gonadotropin secretion, marking the onset of puberty. Hypogonadotropic hypogonadism (HH), results from a defect in the secretion or function of gonadotropin releasing hormone (GnRH) and or gonadotropins, because of congenital or acquired causes, leading to sex-organ malformation, reduced or absent male secondary sexual characteristics, and infertility, [1].

Congenital causes of HH include genetic mutations involved in the regulation, formation, and secretion of GnRH as well as the migration of the neurons, responsible for the secretion of GnRH, from the olfactory placode to the ventromedial hypothalamus. Congenital hypogonadotropic hypogonadism (CHH), may be associated with absence of the sense of smell, known as anosmic CHH or Kallman Syndrome, or with normal sense of smell, known as normosmic CHH, [2,3]. To date, over 40 genes have been implicated in the development of CHH. Only a few cases have been reported to result from mutations in the *GnRH1* gene worldwide, and still a good number of cases remain without a molecular diagnosis, [4,5].

The aim of this paper, is to describe the clinical features of four Omani male siblings with CHH, carrying a novel mutation in the *GnRH1* gene. The clinical information was obtained from the treatment hospital computerized system, after obtaining informed consent from the parents. Genetic analysis, by whole exome sequencing (WES), was done at Invitae Labs, USA, for all the four siblings and parents.

Case Presentations:

All siblings were born at full term, through normal vaginal delivery, with no intra or post-natal complications.

Case1: A 16-year-old male, born with a birth weight of 3.2 kg, and was found to have micro penis of 1.8 cms, and bilateral impalpable testes. At

2 ½ years, he underwent laparoscopic exploration of the abdomen and pelvis and was found to have intra-abdominal bilateral atrophic testes, which were surgically removed. His systemic examination was normal, with a normal sense of smell and absent non-reproductive phenotypic defects. Investigations on presentation at 2 years of age, revealed a baseline serum total testosterone: < 0.02 nmol/L, LH < 0.1 IU/L, FSH 0.129 IU/L. Serum testosterone level post 3-day human chorionic gonadotropin (HCG) stimulation, 500 units, intra muscularly, (IM) was < 0.2 nmol/L. Thyroid function test (TFT) was normal, and he had a normal male karyotype, 46 XY.

At 10 1/2 years of age, his weight started to increase progressively, with gynecomastia. His systemic examination was normal, apart from the abnormalities mentioned above. Investigations showed baseline total testosterone 0.5 nmol/L, total testosterone post 3-day HCG injections, 1500 IU, IM was 0.61 nmol/L, serum LH < 0.1 IU/L, FSH 0.145 IU/L, Inhibin B < 15pg/ml, total FT4 0.95 ng/dL (0.93-1.7), TSH 2.9 uIU/ml (0.27-4.2).

Genetic analysis by WES was done at 12 years of age and showed a novel homozygous mutation in the *GnRH1* gene c.85C>G (p. His 29 to ASP). No other genetic mutation, related to CHH, was detected. A TFT was done and came as normal, TSH: 2.04 uIU/mL (0.27-4.2), FT4: 0.98ng/dL (0.93-1.7). Pubertal induction started at 12 ½ years with testosterone (Sustanon) injections, starting with 50 mg IM, and going up by 50 mg gradually, every 6-12 months. He has not been compliant throughout his treatment period and missed some injections, despite repeated counseling. Currently, he is on testosterone (Sustanon), 250 mg IM, monthly. His stretched penile length (SPL) was 2 cm on induction and reached up to 6.5 cms, currently.

At 15 years of age, he was started on Liraglutide injections for obesity, along with lifestyle modification, his weight was 120.5 kg and height 172 cms, BMI 40.7 kg/m2. But he was not compliant with the treatment, so the injections were discontinued after one year. His latest weight, checked at 16 years of age, was 138.8 kg (114%), and his height 174 cms (54%), with a BMI of 45 kg/m2.

Case 2: A 7-year-old male. His weight at birth was 2.9 kg, and he had a SPL of 2.6 cms and bilateral retractile testes, with a volume of around 1ml bilaterally. He was circumcised at 2 months of age. At 2 ½ years, he had revision of his circumcision, for removal of redundant skin, preceded by twice weekly HCG injections, 500IU IM, for 6 weeks, which led to the descent of his testes in the scrotal sac. This was followed by testosterone (Sustanon) injections for micro penis, 25 mg IM, every three weeks for three months and his SPL improved to 4.5 cms. At 4 years, the mother noticed that the Rt testes became retractile. He was given another course of twice weekly HCG injections 1000 IU, IM for 3 weeks, and the Rt testes descended in the scrotal sac with bilateral testicular volumes of 1.5ml. At 5 ½ years the testicular volumes were 2 ml and the PSL remained at 4.5 cms.

Investigations at 4 years of age showed basal serum testosterone <0.02 nmol/L, serum LH < 0.1 IU/L and FSH: 0.18 IU/L. Genetic analysis showed a heterozygous state of the above mutation in the *GnRH1* gene.

He is growing along the 95th centile for height and weight. His systemic examination is normal, apart from congenital cataract of the Lt eye, treated by eye patching. He has a normal sense of smell.

Case 3: A 6-year-old male. His birth weight was 3.5 kg, and the SPL was 1.6 cms with bilateral undescended testes felt in the mid-inguinal canal. At 3 ½ months of age, he received 12 HCG injections, twice weekly, 500IU IM for 6 weeks, which led to the descent of the testes in the scrotal sac without a significant increase in their size, and they were retractile, the SPL increased to 2.2 cms. At 2 years of age, he had circumcision and bilateral orchidopexy, preceded by four Testosterone (Sustanon) injections to improve the penile size, 25 mg IM, every 3 weeks for 3 months, his SPL improved to 3.4 cms.

Due to the small testicular size, < 1 ml bilaterally, he was given FSH (Fostimon) 25 units IM, twice weekly along with Testosterone (Sustanon) 25 mg IM monthly injections for 6 months. The SPL increased to 4.2 cms and the testicular volume increased to 1 ml bilaterally, well descended in the scrotal sac.

He is growing along the 90th centile for height and weight. His systemic examination is normal with a normal sense of smell. Investigations at 2 weeks of age showed total testosterone 0.23 nmol/L, LH < 0.1IU/L, FSH 0.128 IU/L, TSH 4.086 uIU/L (0.27-4.2), FT4 1.39 ng/dL (0.93-1.7), ACTH 42.05 pg/mL (7.2-63.3), Cortisol 368 nmol/L (133-537), GH 6.4 ng/ml. At 1 month of age, total serum testosterone was 1.08 nmol/L, AMH 24 ng/mL, LH <0.1 IU/L, FSH <0.1 IU/L. At 2 ½ years, LH < 0.1 IU/L, FSH < 0.1 IU/L. LH and FSH 60 minutes post GnRHa: 1.29 and 4.57IU/L, respectively. AMH 20.12 ng/mL, Inhibin B 32pg/ml. At 3 years of age, following FSH and testosterone injections: AMH and Inhibin B increased to 99 pg/mL, AMH 23 ng/ml. Testosterone 4 nmol/L.

Genetic analysis revealed the above mutation in the *GnRH1* gene, in a homozygous form.

Case 4: A 3 1/2-year-old male. His birth weight was 3.1 kg, and he had a SPL of 3.4 cms, with bilateral impalpable testes at birth. Ultrasound of the abdomen, at one month of age, showed the right testes (1.8 x 1.2 x 0.8cms), while the left testes could not be visualized. On laparoscopic exploration, both testes, proven by biopsy, were found intra-abdominally with absent vas deferens. The right testes were partially encapsulated, 0.7x 0.5 x 0.3 cms, while the left testes looked irregular and partially encapsulated, 1x 0.6 x 0.5 cms. A male pattern urethra was seen, with normal size and normally placed verumontanum.

At 1 year and 8 months, an ultrasound of the abdomen and pelvis did not show the testes in the scrotum, inguinal canal, iliac fossa, or retro peritoneal. He was given HCG injections 500 IU twice weekly, IM for 2 months. The SPL increased to 4.8 cms, but on a repeat ultrasound at 2 years and 2 months, the testes were still not visualized. He was referred to pediatric surgery and a repeat laparoscopic exploration of the abdomen and pelvis was scheduled.

Genetic analysis: Heterozygous for the above mutation in the *GnRH1* gene.

He is growing along the 90th centile, for height and weight. The systemic examination is normal. Investigations at 1 1/2 years of age showed a baseline total testosterone 0.17 nmol/L (0.1-1.12). Post three-day HCG stimulation (500 IU): total testosterone, 2.56 nmol/L Baseline Inhibin B 153 pg /ml (30-150). LH: < 0.1 IU/L, FSH, 0.129 IU/L, karyotype 46XY.

The following table summarizes the sex hormones concentration in the serum for the four siblings at different ages.

Case 1	Investigations	Age	Serum concentration
	Baseline total testosterone Post 3day HCG	2 years	<0.02nmol/L <0.2nmol/L
	LH		<0.1IU/L
	FSH		0.13IU/L
	Baseline total testosterone Post 3day HCG	10 ½ years	0.5nmol/L 0.61nmol/L
	LH		< 0.1U/L

	FSH		0.15IU/L
	Inhibin B		< 15pg/ml
Case 2	Baseline total testosterone	4 years	<0.02nmol/L
	LH		<0.1IU/L
	FSH		0.18IU/L
Case 3	Baseline total testosterone	2 weeks	0.23nmol/L
	LH		<0.1IU/L
	FSH		0.13IU/L
	Baseline total testosterone	1 month	1.08nmol/L
	LH		<0.1IU/L
	FSH		<0.1IU/L
	AMH		24ng/mL
	LH	2 ½ years	<0.1IU/L
	FSH		<0.1IU/L
	60 minutes post GnRHa LH FSH		 1.29IU/L 4.57IUL
	AMH		20.12ng/ml
	Inhibin B		32pg/ml
	Following FSH & testosterons injections AMH Inhibin B	3years	 23ng/ml 99pg/ml
Case 4	Baseline total testosterone Post 3day HCG	1 ½ years	0.17nmol/L 2.56nmol/L
	LH FSH		<0.1IU/L 0.13IU/L
	Inhibin B		153pg/ml

Table 1: Sex hormone serum concentration for the four siblings, at different ages.

The parents are first degree cousins and carriers of the above mutation. The mother aborted twice between the first and second children. She has autoimmune hypothyroidism and is on replacement therapy with thyroxin. There is a positive history of infertility and repeated abortions among other members of the family.

Discussion:

In a newborn male, a surge in the LH and FSH secretion, enhanced by GnRH secretion, is observed in the first week of life, peaking at around 3 months of age. This is accompanied by a surge in the testosterone level, which follows a similar trend, falling to a low concentration at 6 months of age, and remaining low till the onset of puberty. The GnRH secretion promotes the secretion of Inhibin B and anti mullerian hormone, (AMH) from the testicular Sertoli cells, which are believed to enhance the proliferation of the Sertoli cells, affecting positively their function during puberty, and promoting fertility later [6,7].

Micro penis and undescended testes are the most common presenting signs in patients with congenital hypogonadotropic hypogonadism, with delayed puberty later. Undescended testes has been reported in 50-30% of individuals with CHH, contrasting with 1-3% in full term, normal newborn males [8]. Micro penis is found in 20-40 % of Kallmann Syndrome patients, in contrast to 0.015% of normal males [9]. Our cases presented different degrees of severity of genital malformation. Case 1 was the first among the siblings to present to the endocrine clinic at 2 years of age. He had the most severe clinical presentation, with micro penis and bilateral intra-abdominal atrophic testes, which were surgically removed. 8 years later, his sibling, case 3, was referred to the pediatric endocrine clinic right after birth, with micro penis and bilateral undescended testes, felt in the inguinal canal. Later, the parents brought case 2 for consultation and checkup. This sibling had the mildest clinical manifestation at birth, with a SPL of 2.6 cms and bilateral retractile testes. The youngest sibling was referred at 21 days of age. He had a normal SPL of 3.4 cms, however, his testes were impalpable. Two small testes could be seen on laparoscopic exploration. However, they could not be seen on subsequent ultrasounds.

Around 75% of CHH patients never attain puberty, while 25% have partial GnRH deficiency, leading to partial testicular volume increase with some degree of virilization, which halts subsequently [10].

CHH is a heterogenous condition in phenotypic manifestations. Up to date, over 40 underlying causative genes have been discovered. However, in over 50% of cases, genetic etiology is not identified. It is more common in the males with a male to female ratio of 3-5: 1, [11]. The genes involved can be transmitted in autosomal dominant, autosomal recessive, X-linked and/or bigenic or oligogenic forms. In addition to variable penetrance which can contribute to the variable phenotypic manifestation. The *GnRH1* gene is one of the genes implicated in CHH with an autosomal recessive inheritance. Mutations in this gene affect the gene product 'PreproGnRH', involved in the secretion and homeostasis of GnRH, [12,13]. In the four siblings described the cases with the heterozygous mutation (cases 2 and 4), had a better PSL at birth, compared to the homozygous cases. However, the genotypic state did not seem to correlate with the testicular size as cases 1 and 4 had atrophic testes; this could be the result of the variable penetrance known in such conditions. Bi/oligogenic inheritance could also contribute, but this was excluded on genetic analysis.

Testosterone replacement therapy (TRT) is given to CHH males around the age of puberty for pubertal induction. It is also given in short courses prepuberty, to improve the SPL. TRT was given to case 1 to induce puberty, at 12 ½ years and his SPL improved from 2 cms to 6.5 cms. Currently, he is on 250 mg, IM monthly injections of testosterone. He is not compliant with the medication, despite regular counselling. Testosterone in short courses were given to his two siblings, cases 2 and 3, to improve the SPL, with good results. In case 2, the SPL increased from 2.6 to 4.5 cms and in case 3, from 2.2 to 3.4 cms and further on to 4.2 cms after receiving FSH and testosterone injections. HCG injections may be used, IM or SC, to push retractile /low lying undescended testes

into the scrotal sac, it can also improve the testicular size, [14,15,16] This was applied in cases 2 and 3 and the testes descended in the scrotal sacs. In addition, gonadotropin weekly injections +/- testosterone can be an alternative method to induce puberty in males with CHH, it has the advantage, over testosterone alone, of increasing the testicular size, as well as promoting the appearance of secondary sexual characteristics, [17,18,19].

Early post-natal treatment of CHH males with FSH and LH [20,21], or priming with FSH in childhood, or prior to pubertal induction, was found to be effective in increasing serum testosterone, gonadotropins, Inhibin B, and AMH as well as enhancing testicular enlargement, through Sertoli cell proliferation, [22]. This was attempted in case 3 and the testicular size improved to 1 ml bilaterally, with an increase in serum AMH, Inhibin B and testosterone concentrations. However, long term results are still needed to assess their impact on adult fertility.

Post puberty, treatment protocols with GnRH or gonadotropins: HCG and recombinant FSH, should be considered to induce and support spermatogenesis, once fertility is a concern, [23 24].

Conclusion:

GNRH1 gene c.85C>G (p. His 29 to ASP) is a novel mutation that can result in micro penis, undescended, retractile or atrophic testes and infertility. Treatment with testosterone, HCG and/or FSH was given depending on the clinical findings. Further follow-up is required to understand the course of this condition and the impact of the treatment given on fertility in the future

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