Case Report

Access this article online
Website: www.jclpca.org
DOI: 10.4103/jclpca.jclpca_7_22
Quick Response Code:

A case of idiopathic hypogonadotropic hypogonadism with dental and orofacial defects: A key to the perception of possible molecular etiology

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ABSTRACT

Isolated deficiency of gonadotropin-releasing hormone is a heterogeneous disorder with wide genetic and clinical overlap. It mainly presents as hypogonadotropic hypogonadism (HH). HH associated with anosmia is known as Kallmann syndrome (KS), while its normosmic variant is called normosmic idiopathic HH. However, it is associated with several nonreproductive features including dental defects. Fibroblast growth factor receptor 1 gene mutation, which is seen in the autosomal dominant form of idiopathic HH (HH 2), has often been linked to the associated dental abnormalities and orofacial defects; however, no literature exists for its association with anosmin-1 (ANOS1) gene mutation which is found in the X-linked form of HH (KS). ANOS1 gene was earlier known as KAL1 (Kallmann syndrome 1) gene, and encodes for the extracellular matrix protein called anosmin. Hence, we report a case of idiopathic HH (KS) so as to delineate the possible role of ANOS1 gene in dental/orofacial development. This can help prioritize gene screening and also provide scope for further genetic studies required to prove such association.

Key words: Anosmin-1, bimanual synkinesis, fibroblast growth factor receptor 1, hypogonadotropic hypogonadism, Kallmann syndrome

INTRODUCTION

Isolated deficiency of gonadotropin-releasing hormone (GnRH) is a heterogeneous disorder with a wide range of genetic and clinical overlap. Its most important aspect is represented by hypogonadotropic hypogonadism (HH) with or without anosmia, and delayed pubertal development. However, it is associated with several nonreproductive features such as cleft lip/palate, dental defects, abnormalities of bone, renal agenesis, synkinesis, loss of hearing, and impaired balance due to cerebellar abnormality. Genetic mutations explain about 40% of HH cases in literature and the rest are uncharacterized.[1] Dental abnormalities and orofacial defects have usually been associated with fibroblast growth factor receptor 1 (FGFR1) gene mutation in HH; however, there is no literature supporting the association of anosmin-1 (ANOS1)/KAL1 gene mutation with the same. Hence, we report a case of idiopathic HH (Kallmann syndrome) so as to delineate the possible role of ANOS1 gene in dental/orofacial development, which might help prioritize the required genetic screening.

CASE REPORT

A 14-year-old male patient reported with a complaint of small-sized penis and enlargement of breast

Cite this article as: Bansal A, Verma PK, Bhakat R, Chug A, Reddy SG. A case of idiopathic hypogonadotropic hypogonadism with dental and orofacial defects: A key to the perception of possible molecular etiology. J Cleft Lip Palate Craniofac Anomal 2022;9:180-3.

Submission: 19.03.2022 **Revision:** 09.04.2022
Acceptance: 16.04.2022 **Web Publication:** 23.08.2022

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tissue. There was no history of delayed growth spurt or traumatic injury. No abnormal features could be discerned from parents. Furthermore, no significant medical or prolonged drug intake history was reported. Vitals and stature (height: 151 cm) were within the normal limits. Facial examination revealed asymmetry, with the right ear (7 cm) being greater in length than the left ear (6.5 cm), along with dental malocclusion [Figure 1] and high-arched palate [Figure 2]. Bilateral gynecomastia was evident with nonpalpable glandular tissue [Figure 3]; along with absent pubic, facial, and axillary hair. The right testis was nonpalpable, while the left testis was palpable in the scrotum, with the testicular volume of <4 ml, thus corresponding to Tanner Stage I (Sexual Maturity Rating). Stretched penile length was 5 cm [Figure 4]. Asymmetrical partial anosmia (right > left) was present, along with positive bimanual synkinesis. Blood chemistry revealed decreased levels of testosterone (20.34 ng/dL, range: 270–1070 ng/dL), luteinizing hormone (0.01 mIU/mL, range: 1.50–9.30 mIU/mL), and follicular-stimulating hormone (0.02 mIU/mL, range: 1.40–18.10 mIU/mL). GnRH analog (Leupride) stimulation test revealed minimal response indicative of GnRH deficiency. Inhibin values were significantly low (23.14 pg/mL, range: 169–216 pg/mL).

X-ray wrist and pelvis estimated bone age to be 12–14 years which were equivalent to the chronological age. Ultrasound of the kidney, urinary bladder, and scrotum (USG KUB) revealed right ureterocele and small right kidney (4.2 cm × 3.6 cm) suggestive of renal dysplasia, along with normal left kidney (9.2 cm × 3.5 cm). Furthermore, the right testis was absent in the scrotum. The right renal dysplasia was confirmed in magnetic resonance imaging (MRI) abdomen and pelvis, along with absent right seminal vesicle. The right kidney could not be visualized in dimercaptosuccinic acid scan. A micturating cystourethrogram showed no vesicoureteral reflux. MRI brain depicted partial empty sella. The above positive clinical features and investigations were consistent with HH 1 with partial anosmia or Kallmann syndrome (KS) as shown in Table 1, but the diagnosis could not be confirmed as genetic study could not be undertaken due to financial constraints of the family. The patient responded well to hormone replacement therapy (HRT).

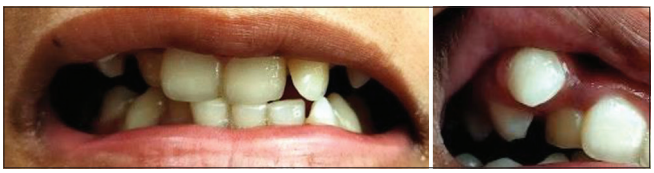

Figure 1: Dental malocclusion associated with the case

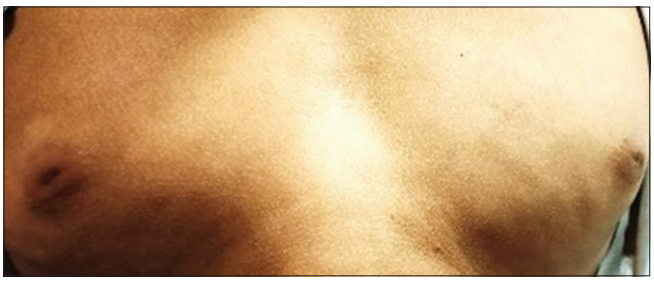

Figure 3: Evident bilateral gynecomastia with nonpalpable glandular tissue

DISCUSSION

Isolated GnRH deficiency (IGD) includes a wide spectrum of disorders. It shows male predominance, with an incidence of 1:30,000 in males and 1:125,000 in females.[2] IGD mainly presents as HH, which has 25 phenotypic variants as per Online Mendelian Inheritance in Man (OMIM) database search [Table 1].

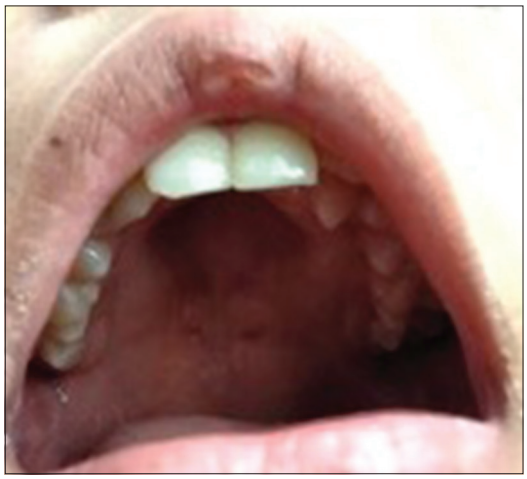

Figure 2: Associated high-arched palate

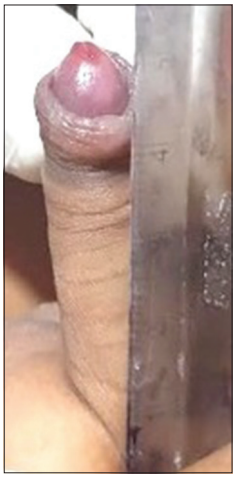

Figure 4: Stretched penile length which was found to be 5 cm

Table 1: Phenotypic series of hypogonadotropic hypogonadism along with its characteristic features as per OMIM database search

Phenotype/ OMIM number	Location on chromosome	Inheritance pattern	Gene/ locus	Characteristic feature
HH 1 (KS)/308700	Xp22.31	X-linked recessive	ANOS1	Delayed puberty, partial or complete anosmia, unilateral renal agenesis, bimanual synkinesis
HH 2/147950	8p11.23	Autosomal dominant	FGFR1	Cleft palate/lip
HH 3/244200	20p12.3	Autosomal dominant	PROKR2	Variable olfactory and reproductive dysfunction
HH 4/610628	3p13	Autosomal dominant	PROK2	Variable olfactory and reproductive dysfunction
HH 5/612370	8q12.2	Autosomal dominant	CHD7	Mild form of CHARGE syndrome
HH 6/612702	10q24.32	Autosomal dominant	FGF8	Microsomia, primary amenorrhea
HH 7/146110	4q13.2	Autosomal recessive	GNRHR	Variable reproductive dysfunction
HH 8/614837	19p13.3	Autosomal recessive	KISS1R	Variable reproductive dysfunction
HH 9/614838	9q34.3	Autosomal dominant	NSMF	Increases severity of HH
HH 10/614839	12q13.3	Autosomal recessive	TAC3	Variable reproductive dysfunction
HH 11/614840	4q24	Autosomal recessive	TACR3	Microphallus
HH 12/614841	8p21.2	Autosomal recessive	GNRH1	Long extremeties
HH 13/614842	1q32.1	Autosomal recessive	KISS1	Variable reproductive dysfunction
HH 14/614858	10q26.12	Autosomal dominant	WDR11	Hyposmia
HH 15/614880	2q14.3	Autosomal dominant	HS6ST1	Reduced activity
HH 16/614897	7q21.11	Autosomal dominant	SEMA3A	Cryptochidism, reduced testicular volume, hyosmia/anosmia
HH 17/615266	5q31.3	Autosomal dominant	SPRY4	Low bone mass, hearing loss and abnormal dentiton
HH 18/615267	3p14.3	Autosomal dominant, autosomal recessive, digenic dominant	IL17RD	Anosmic, absent puberty, congenital hearing loss
HH 19/615269	12q21.33	Autosomal dominant	DUSP6	Abnormal dentition, low bone mass and hearing loss
HH 20/615270	8p21.3	Autosomal dominant	FGF17	Low bone mass
HH 21/615271	20p12.1	Autosomal dominant	FLRT3	Anosmia, low bone mass and hearing loss
HH 22/616030	7q31.32	Autosomal recessive	FEZF1	Anosmia
HH 23/228300	19q13.33	Autosomal recessive	LHB	Eunuchoid habitus
HH 24/229070	11p14.1	Autosomal recessive	FSHB	Amenorrhoea
HH 25/618841	4q27	Autosomal dominant	NDNF	Cryptochidism, micropenis

KS: Kallmann syndrome, CHARGE: Coloboma, heart defects, atresia choanae, growth retardation, genital and ear abnormalities, FGF: Fibroblast growth factor, FGFR1: FGF receptor 1, ANOS1: Anosmin-1, GnRH1: Gonadotropin-releasing hormone, LHB: Luteinizing hormone beta, FSHB: Follicle stimulating hormone subunit beta, IL17RD: Interleukin 17 receptor D, HH: Hypogonadotropic hypogonadism, OMIM: Online mendelian inheritance in man

HH associated with partial or complete anosmia is known as KS, while its normosmic variant is called normosmic idiopathic HH.[3] Constitutional delay of puberty, hypothalamic amenorrhea, and adult-onset HH are milder and common diseases associated with IGD.[1]

Along with reduced sense of olfaction, KS presents with decreased levels of sex hormones along with unilateral renal agenesis, delayed puberty, micropenis, ectopic testis, and bimanual synkinesis.[4] Till date, 15 genes have been found responsible for isolated HH, such as FGFR1, KAL1, NELF, FGF8, PROKR8, PROK2, WDR11, CHD7, KISS1R, KISS1, SEMA3A, TAC3, TACR3, GNRHR, and GNRH1.[5] Several genes act as "overlap genes" which are involved in both neuroendocrine and neurodevelopmental pathogenetic pathway, and thus play as "second hits" explaining their variable expressions and incomplete mode of penetrance.[1]

KAL1 (Kallmann syndrome 1) gene, which is now known as ANOS1 gene has been identified for X-linked form of HH, i.e., KS, while FGFR1 gene has been associated with its autosomal dominant form, i.e., HH 2.[6] Heterozygous mutations in FGFR1 account for 10% of HH two patients, and they occasionally feature characteristic dental agenesis/malocclusion, midline defects such as cleft lip and palate, and high-arched palate.[6] Massin N *et al.* also identified heterozygous missense mutation in FGFR1 or KISS1R responsible for such orofacial defects.[7] However, no literature exists for its association with ANOS1 gene mutation.

ANOS1 gene encodes the extracellular matrix protein called anosmin. It is implicated in fibroblast growth factor (FGF) signaling and enhancement of FGF8 functions and hence is required for the formation of the neural crest cells of cranium by modulating growth factors.[8] Thus, its mutation can cause imbalance in embryonic development including the development of dentition and morphology of craniofacial region, equivalent to our case report. However, ANOS1/KAL1 gene mutation has not been ascribed to the dental and orofacial features in the X-linked form of HH, i.e., KS till date.

Chan *et al*. presented the first case of genetic testing of such disorders in preimplantation phase.[9] Management of such genetic disorders requires frequent family counseling due to their risk of transmission, and medically assisted management with HRT for better prognosis.[10]

KS is a genetic disorder presenting mainly with HH along with partial or complete anosmia. It has a wide and variable clinical spectrum along with different genetic patterns. FGFR1 gene mutation has often been linked to its associated dental and orofacial defects. However, this is the first case report giving an insight toward the possible role of ANOS1 gene toward such development. This can help us prioritize particular gene screening and also provides scope for further genetic studies required to prove such association.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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