



Normosmic idiopathic hypogonadotrophic hypogonadism due to a rare KISS1R gene mutation

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Summary

Hypogonadotrophic hypogonadism is due to impaired or reduced gonadotrophin secretion from the pituitary gland. In the absence of any anatomical or functional lesions of the pituitary or hypothalamic gland, the hypogonadotrophic hypogonadism is referred to as idiopathic hypogonadotrophic hypogonadism (IHH). We present a case of a young lady born to consanguineous parents who was found to have IHH due to a rare gene mutation.

Learning points:

- The genetic basis of a majority of cases of IHH remains unknown.
- IHH can have different clinical endocrine manifestations.
- Patients can present late to the healthcare service because of unawareness and stigmata associated with the clinical features.
- Family members of affected individuals can be affected to varying degrees.

Background

Hypogonadotrophic hypogonadism is due to the impairment/deficiency of follicle-stimulating hormone and luteinizing hormone secretion from the pituitary gland. This results in the impairment of pubertal development and impaired reproductive function. In the absence of any anatomical or functional lesions of the pituitary or hypothalamic gland, the hypogonadotrophic hypogonadism is referred to as idiopathic hypogonadotrophic hypogonadism (IHH).

Normal puberty is dependent on the increased frequency and amplitude of the pulsatile secretion of gonadotrophin-releasing hormone (GnRH) from the hypothalamus during that stage of reproductive development. There is failure of this pulsatile secretion in individuals with IHH resulting in inappropriately low

gonadotrophin and sex steroid levels. Males can present with absent or incomplete puberty, cryptorchidism, small penis and infertility, while females can present with amenorrhoea, dyspareunia, partial breast development and infertility. Neonatal presentation with abnormal or underdeveloped reproductive system or external genitalia is also a feature of IHH.

Idiopathic hypogonadotrophic hypogonadism (IHH) with normal sense of smell (normosmic IHH) or with anosmia (Kallmann syndrome) is a rare genetic disorder caused by an isolated defect in the secretion of GnRH by the hypothalamus or the action of GnRH on the pituitary gonadotrophins. Loss-of-function mutations of critical components of the GnRH pathway have been implicated in the pathogenesis of idiopathic hypogonadotrophic hypogonadism (1). A few



genes that are involved in the pathogenesis of idiopathic hypogonadotrophic hypogonadism have been identified. However, this is the case in less than 30% of patients with IHH (2). These conditions can be transmitted as autosomal dominant, autosomal recessive or X-linked traits, they are 2–3 time more common in men and family members can also be affected.

The incidence of IHH is approximately 1–10 in 100 000 live births, with approximately two-thirds of cases being due to Kallmann syndrome, which has been mapped to the *ANOS1* (previously called *KALI*) and fibroblast growth factor receptor 1 (*FGFR1*) gene mutations (1, 3). Gene mutations have been identified in only 2–16% of patients with normosmic IHH of which the inactivating mutations of the GnRH receptor are the most frequent cause, especially in familial cases (4). We present a patient with IHH due to a much rarer gene mutation.

Case presentation

A 17-year-old female born to Kurdish parents was referred to the endocrine clinic in 2015 with primary amenorrhoea and poor breast development. She noticed minimal pubic hair growth when she was 16 with no axillary hair growth and no breast development. Her weight was 68.2 kg with a height of 1.64 m (50th percentile), which was within her target (mid-parental) height range of 1.59–1.76 m (body mass index of 25.5). She did not have any eating disorder nor did she take part in regular vigorous physical activity. She did not report any headache or visual disturbance. Her smell sense was intact. She was not a smoker and did not take alcohol. Her younger sister had her first period at the age 11 years with normal pubertal development, but her older brother had previously been diagnosed with hypogonadotrophic hypogonadism. Her parents are first cousins and her mother who was 36 years at the time was

having regular periods. There was no history of pubertal delay in the parents.

Investigation

The results of the baseline laboratory investigations with normal reference levels are shown in Table 1. Results demonstrated low estradiol levels in the presence of inappropriately low gonadotrophins levels, which is consistent with hypogonadotrophic hypogonadism.

An ultrasound scan revealed a small and tubular infantile uterus measuring 4.4×0.5×1.7 cm. The right ovary could not be identified but the left ovary was also small measuring 2.5×1.5×1.6 cm in size. A contrast pituitary scan revealed a pituitary gland of normal size and appearance. A bone density scan revealed a low for age value (z-score of –2.8 s.d., 0.745 g/cm²).

Genetic analysis revealed a homozygous pathogenic variant in the *KISS1R* gene (c.C969>A, p.(Tyr323Ter)).

Treatment

She was started on an estradiol patch for hormone replacement therapy and to improve her bone mineral density in 2015. She was later started on calcium and vitamin D supplements and a bisphosphonate (alendronic acid) and advised to maintain a healthy life style and weight-bearing exercises to improve bone health.

Outcome and follow-up

Patient has been attending endocrine outpatient follow-up. Her recent repeat bone density scan demonstrated marked improvement (spine z-score of –1.7 s.d., 0.838 g/cm²) when compared to the previous very low for age value.

Table 1 Results of biochemical blood tests at presentation.

Biochemical test	Normal reference range	Patient's results at presentation	Repeat test results 3–4 months afterwards
Oestradiol	100–750 pmol/L	<37	<37
Follicle-stimulating hormone	1–14 U/L	5	4
Luteinizing hormone	1–9 U/L	1	1
Prolactin	<500 mU/L	163	–
Thyroid-stimulating hormone	0.3–4.2 mU/L	1.69	–
Free thyroxine	12–22 pmol/L	13.7	–
Sex hormone-binding globulin	26–110 nmol/L	42	–
Sodium	133–146 mmol/L	134	–
Potassium	3.5–5.3 mmol/L	4.3	–
Hemoglobin	115–165 g/L	129	–
Hematocrit	0.360–0.460	0.378	–



She has also been asked by the geneticist to invite her affected brother along with her parents to attend for genetic testing.

Discussion

Patients with normosmic IHH have normal smell sensation as opposed to patients with Kallmann syndrome. The mechanisms that underlie normosmic IHH involve mutations in many genes. Some of these genes encode proteins that regulate GnRH neuronal migration, regulate GnRH secretion or GnRH action. A number of these mutations have been identified only recently and their individual and/or combined roles in the regulation of reproduction are not yet completely understood (1, 2, 3, 4).

The *KISS1* gene encodes the protein called Kisspeptin-1, which interacts with the G-protein coupled receptor-54 (Kisspeptin receptor, *KISS1R*, *GPR54*), which is encoded by the *KISS1R* (*GPR54*) gene. Kisspeptin also called metastin was initially solely known to suppress tumor metastasis. Kisspeptin is distributed in both the peripheral and the central nervous system. The Kisspeptin receptors are also distributed within the central and peripheral nervous system, notably the hypothalamus and the placenta, respectively. It was not until 2003 that two groups independently reported that loss-of-function mutations of the *GPR54* gene are linked to the absence of puberty onset and hypogonadotrophic hypogonadism in humans through disruption of the Kisspeptin/Kisspeptin receptor system (5, 6).

The *GPR54/KISS1R* protein is a transmembrane receptor made up of 398 amino acids. It translates signals from the cell surface as part of the signaling pathway for the release of GnRH. The binding of Kisspeptin to these receptors in the hypothalamus stimulates the release of GnRH, which in turn stimulates gonadotrophin release. Kisspeptin may also act directly on the pituitary gland stimulating gonadotrophin release. These findings over the years have stimulated research into the use of exogenous Kisspeptin therapy to stimulate sexual maturation in children with IHH and for the treatment of male and female infertility (7).

Mutations in the *KISS1R* (*GPR54*) gene have been identified in less than 5% of patients with normosmic IHH during a screening study (8). The identification of the Kisspeptin (*KISS1*) gene mutation is even less frequent (9). Up until 2012, only 14 loss-of-function mutations

in the *KISS1R* (*GPR54*) gene had been described in the literature, and these mutations were found to have variable clinical manifestation (10, 11). The scarcity of genetic data in patients with IHH makes it difficult to genetically characterize this condition. However, more recently, another type of loss-of-function mutation of the *KISS1R* gene was newly discovered in three unrelated Kurdish families (12). This was a nonsense c.C969A (Y323X) mutation.

Our patient who is also of Kurdish origin had a similar nonsense mutation where cytosine has been substituted by adenosine at position 969 of the nucleotide sequence in the *KISS1R* gene (c.C969>A) located on the short arm of chromosome 19 (19p13.3). This results in the creation of a stop codon, which instead of translating to the usual production of tyrosine at position 323 located in the transmembrane domain of the *KISS1R* protein, translates to a premature termination (p.Tyr323Ter) at that site and incomplete production of the *KISS1R* protein. This truncated *KISS1R* protein fails to signal the release of GnRH from the hypothalamus.

Other types of gene mutations have been found in Kurdish families (12). The Kurdish population are descendants of a small number of ancestors, and there is a high prevalence of consanguinity among them, resulting in over-dominant selection of heterozygous carriers and homozygous offspring with deleterious gene mutations such as the *GPR54* gene mutation in this case. This 'founder effect' may be the reason why there is a relatively high number of cases reported in Kurdish families (13).

In conclusion, we have presented a case of normosmic IHH in a female patient from a consanguineous Kurdish family due to a homozygous nonsense mutation in the *KISS1R* gene. We hope that this case report will not only add to the existing literature but most importantly contribute to the ongoing genetic characterization of this complex condition.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent has been obtained from the patient for publication of the submitted article and any accompanying images. The signed copy of the consent form has been provided.

Author contribution statement

N Chelaghma, S O Oyibo and J Rajkanna all wrote the case report and critically revised the paper and approved the final manuscript for submission. S O Oyibo identified the case and is also the named physician for the patient. S M Park is the named genetics physician of the patient. J Trotman, G Fuller and T Eley contributed to the genetic testing and analysis performed and to the ensuing diagnosis.

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