Familial normosmic idiopathic hypogonadotropic hypogonadism: is there a phenotypic marker for each genetic mutation? Report of three cases and review of literature

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SUMMARY

Normosmic idiopathic hypogonadotropic hypogonadism (nIHH) is familial in one-third of cases and multiple modes of inheritance have been described. Phenotypic spectrum of *GNRHR* mutations has been found to be widest without any pathognomonic phenotypic feature. However, in subjects of nIHH with *TAC3/TAC3R* mutations preservation of follicle stimulating hormone secretion is a characteristic feature and has been suggested as phenotypic marker. Despite a paucity of subjects with homozygous frame shift mutations of *GNRH*, there is remarkable similarity in the phenotypic features and neuroendocrine profile of these few subjects with *GNRH* mutations. We describe here three members of a family with nIHH and autosomal mode of inheritance with remarkably similar phenotypes.

BACKGROUND

Idiopathic hypogonadotropic hypogonadism (IHH) is a very rare genetic disorder characterised by complete or partial lack of pubertal development and infertility due to complete or partial absence of gonadotropin-releasing hormone (GnRH)-mediated release of luteinising hormone (LH) and follicle-stimulating hormone (FSH) in the setting of otherwise normal anterior pituitary anatomy and function. IHH is differentiated into normosmic IHH (40%) and Kallmann's syndrome (KS, 60%) based on the presence or absence of normal sense of smell, respectively.^{1 2} IHH is a clinically and genetically heterogeneous disease meaning thereby that clinically a case of human GnRH deficiency may present with a variety of reproductive and non-reproductive phenotypes even among the family member with identical genetic defects. Genetic heterogeneity is evident by the fact that despite numerous genetic discoveries (*KAL1*, *KISS1R*, *FGFR1*, *FGF8*, *PROK2*, *PROKR2*, *GNRHR1*, *TAC3* *TACR3* and *GNRH*) responsible for GnRH deficiency, genetic basis is still elusive in more than half of such cases. There is a growing appreciation of the fact that GnRH deficiency is not strictly a monogenic disease but rather may have a digenic/oligogenic basis. Therefore, varied phenotypes of IHH which cannot be explained by one gene defect can thus be explained by two or more gene defects occurring simultaneously in the affected individual.² Families with nIHH are few worldwide as IHH predominantly impairs infertility and thus vertical transmission of the disease. Studies of these human models of GnRH deficiency (KS and nIHH) have unearthed

much of the information regarding the ontogeny of GnRH neurons so far. With the advent of more advanced genetic studies, it is assumed that in this decade further insights into molecular physiology of the reactivation of GnRH pulse generator at puberty will be gained by the unique biological opportunity provided by these rare familial cases.

CASE PRESENTATION

In a family originating in a sub-Himalayan mountain village of northern India, two sisters of four children of non-consanguineous parents, aged 19 and 18 years (subjects III-3 and III-4, respectively) demonstrated typical signs of complete hypogonadism. There was no breast development (Tanner's stage I), no pubic hair and menarche had not occurred in either of them. Their developmental history, including their birth and successive milestones, was normal. History for eating disorder, chronic illness or head trauma was negative. Subjects III-3 and III-4 were 155 and 144 cm tall, respectively. Body proportions were normal in both. There were no craniofacial and renal abnormalities in either of them. Pelvic ultrasound revealed a small uterus and two small ovaries with no visible follicles. Their bone age was between 15 and 18 years. Both had a normal sense of smell on formal tests of olfaction. Their affected brother (subject III-5) was evaluated initially at 17 years of age and again at 18 years because of absent pubertal development. He also had a phenotype of complete hypogonadism with no facial hair, small intrascrotal testes (0.8 ml each on ultrasonography), no pubic hair (P1) and a penis 3.5 cm in length. He was 151 cm tall and weighed 36 kg. Body proportions were normal. Bone age was between 13 and 17 years (table 1).

INVESTIGATIONS

Plasma oestradiol levels were undetectable in both female subjects and male subject had very low serum testosterone. Plasma gonadotropin levels were very low in all the subjects. However, basal functions of the rest of anterior pituitary, thyroid and adrenal glands were normal. Endogenous basal LH pulsatility study in the affected male was apulsatile (table 1). MRI of hypothalamus, pituitary and olfactory bulbs revealed no abnormality. The unaffected eldest brother (subject III-2) had normal pubertal development. Both parents had timely puberty and unassisted conceptions. The family denied consanguinity.

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Table 1 Clinical, hormonal and radiological profile of the three affected siblings

Age (years)	19	18	18
Sense of smell	Normal	Normal	Normal
Breasts	I	I	
Pubic hair	Few thin strands	P1	P1
External genitalia	Infantile	Infantile	
Penis length			3.5 cm
Testicular volume			0.7/0.8 ml
LH (mIU/ml)	0.4	0.9	0.2
FSH (mIU/ml)	0.8	0.6	0.4
Estradiol (pg/ml)	6.0	2.2	
Testosterone			25(ng/dl)
Prolactin (ng/ml)	7.0	5.0	3.0
TSH (μ IU/ml)	3.2	2.1	3.0
Bone age (years)	15–18	15–18	13–17
MRI head	Normal	Normal	Normal
LH pulsatility			Apulsatile

FSH, follicle stimulating hormone; LH, leuteinising hormone; PRL, prolactin; TSH, thyroid stimulating hormone.

DIFFERENTIAL DIAGNOSIS

A diagnosis of nIHH was made based on the absence of spontaneous puberty by age 18 and hypogonadal sex steroid levels (testosterone ≤ 100 ng/dl; oestradiol ≤ 20 pg/ml) in the setting of inappropriately low gonadotropin levels and no evidence of a mass lesion on the imaging of hypothalamic pituitary region. Additional evidence for a diagnosis of IHH was provided by normal basal levels of TSH, PRL and basal adrenal functions. Inheritance was classified as autosomal recessive as all affected individuals were members of the same generation and included two women (figure 1).

TREATMENT AND OUTCOME

Subjects III-3 and III-4 were put on continuous low-dose (0.3 mg) conjugated equine oestrogen (CEE) and calcium supplementation. The dose of CEE was increased to 0.625 mg daily after 3 months and cyclical progestin was added for first 14 days of every month after 6 months. The breast growth started and withdrawal bleeding was experienced by both sisters after addition of cyclical progestin. The dose of premarin was finally increased to 1.2 mg daily and progestin was curtailed to duration of 7 days a month only. Subject III was put on long acting parenteral testosterone preparation started with a dose of

50 mg. The dose of testosterone was increased by 50 mg every 3–4 weeks to a maximum of 200 mg to be given every 2 weeks.

OUTCOME AND FOLLOW-UP

All subjects are on regular observation and follow-up.

DISCUSSION

Supreme neuroendocrine control of the reproductive axis in non-primate mammals, monkeys and humans rests with a group of neurons called GnRH neurons, approximately 1500 in number and dispersed in hypothalamus. GnRH neurons are extra-central nervous system (CNS) in origin, nasal placode to be precise. Once specified, they begin a migratory journey along a platform provided by olfactory tract to their final destination in hypothalamus. On reaching the hypothalamus, they network with each other and median eminence by sending axonal processes. This network is the hypothalamic pacemaker of reproductive axis as it synthesises and then releases in a pulsatile manner the master neurohormone of the reproductive axis, that is, GnRH. GnRH then travels via hypothalamic-hypophyseal portal circulation to reach anterior pituitary, where it binds to GnRH receptor 1 on gonadotrops to stimulate the synthesis and secretion of FSH and LH. FSH and LH in turn travel through systemic circulation to the gonads, stimulating steroidogenesis and gametogenesis in both genders, thus bringing about pubertal changes and sexual maturity to reproduce. Clinical syndrome of IHH can thus occur by genetic defects affecting the aforementioned cascade at three crucial steps; (1) extra-CNS origin, specification, proliferation and migration of GnRH neurons to hypothalamus, (2) the synchronised synthesis and release of GnRH in hypothalamus and (3) by resistance to GnRH action at pituitary. A number of genes are involved and important for these crucial steps. nIHH is caused by mutations of genes affecting synthesis, secretion or action of hypothalamic GnRH. Genetic defects of *GNRHR1*, *KISS1R*, *TAC3/TAC3R* and *GNRH* are implicated for nIHH without non-reproductive phenotypes and are inheritable by the autosomal-recessive mode, as seen in the index family. Mutations of *FGFR1* have been shown to cause both KS and nIHH. Only one-third cases of nIHH have an inheritable basis and autosomal-recessive mode of inheritance accounts for 30% of these familial cases. *GNRHR* mutations are responsible for 40% cases of nIHH with autosomal-recessive inheritance.³ Since 1997, numerous loss-of-function mutations of *GNRHR* have been described. Phenotypic spectrum for *GNRHR* mutations is probably the widest with complete hypogonadism on one end and a partial gonadotropic deficiency called fertile eunuch in man on the other. Phenotypic heterogeneity has been

Figure 1 Pedigree analysis: female members are represented by circles and male members are represented by squares. Affected members are represented by solid symbols.

described among family members with identical *GNRHR* mutations.^{3–4} Review of literature for genotype/phenotype correlations refutes the presence of any characteristic phenotypic feature in subjects of nIHH with *GNRHR* mutations.^{3–12} Inactivating mutations in *KISS1R* account for 5% cases of nIHH with autosomal-recessive inheritance. Kisspeptin through its receptor is thought to be the upstream gatekeeper of GnRH release and the modulator of GnRH action on gonadotrope in pituitary. The reported phenotypes of subjects with *KISS1R* mutations varied from incomplete puberty to deep hypogonadism with micropallus and cryptorchidism in man.¹³ *TAC3/TAC3R* genetic defects have been reported in 5% cases of nIHH inherited by the autosomal-recessive mode.^{14–15} Phenotypic features with biallelic *TAC3/TAC3R* mutations are consistent with severe hypogonadism with associated micropallus and bilateral cryptorchidism. A characteristic finding in the neuroendocrine profile of patients with these mutations is a preserved FSH concentration and a high serum FSH/LH ratio, a feature that authors have suggested as a phenotypic marker for identifying *TAC3/TAC3R* mutations.¹⁵ *GNRH* gene was an obvious candidate for nIHH, and in *hpg* mouse model hypogonadotropic hypogonadism was linked to homozygous deletions in the *Gnrh1* gene. However, despite efforts of several teams world over, the defects in this gene remained elusive till recently. In 2009, two teams independently reported three cases of nIHH with homozygous frame shift mutations in *GNRH*, thus implicating this gene in human isolated GnRH deficiency. Bouligand *et al*¹⁶ reported two siblings with nIHH of autosomal-recessive inheritance. Both siblings displayed phenotypic features of severe hypogonadism with infantile genitalia and absent secondary sexual characteristics. Serum gonadotropins were almost undetectable and basal LH secretion was apulsatile in the affected women. Chan *et al*¹⁷ reported a sporadic case of nIHH with homozygous frame shift mutation of *GNRH* independently in the same year. Phenotypic features bore remarkable resemblance to the cases reported by the other team. Subject had deep hypogonadism with micropallus, bilateral cryptorchidism and almost undetectable serum gonadotropins and sex steroids.

Although only three cases of *GNRH* homozygous frame shift mutations have been reported so far, the phenotypic details are remarkably similar, a feature not seen with other genetic defects responsible for nIHH. Interestingly, reproductive phenotype and neuroendocrine profile of index cases were remarkably similar, a feature not seen consistently with mutations of genes other than *GNRH*. Could there be a phenotypic marker for *GNRH* mutations in patients with nIHH? Drawing any conclusion based on our limited clinical data and review of the literature is premature but further neuroendocrine and genetic studies of these subjects, in particular the familial cases, might give us the answer in this decade.

Learning points

- ▶ Idiopathic hypogonadotropic hypogonadism (IHH) is a rare genetic disease with few affected families worldwide.
- ▶ Human models of IHH have helped us understand the ontogeny of gonadotropin-releasing hormone (GnRH) neurons so far, and with advanced genetic studies of these rare cases further insight into the pubertal reactivation of GnRH pulse generator is likely to be gained in the near future.
- ▶ IHH is a clinically heterogeneous disease and so far phenotypic marker has been established only for subjects with *TAC3/TAC3R* mutations.

Competing interests None.

Patient consent Obtained.

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