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Original Article

Internal Medicine Section

Clinicohormonal Parameters as a Primary Step to Differentiate Normosmic Idiopathic Hypogonadotropic Hypogonadism and Kallmann Syndrome in a Tertiary Care Hospital in Eastern India

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ABSTRACT

Introduction: Idiopathic hypogonadotropic hypogonadism is a rare gonadal dysgenesis in which puberty does not take place naturally. It occurs due to insufficient pulsatile secretion of Gonadotrophin-Releasing Hormone (GnRH) and the resulting Follicle-Stimulating Hormone (FSH) and Luteinising Hormone (LH) deficiency leads to absence of or delayed sexual maturation. Kallmann syndrome is an uncommon genetic disorder characterised by hypogonadotropic hypogonadism associated with anosmia or hyposmia. When anosmia is absent, the same is referred as normosmic Idiopathic Hypogonadotropic hypogonadism (nIHH).

Aim: To find out the significant differences between Kallmann syndrome and nIHH based on clinical features and biochemical assessment as a primary measure to initiate the treatment early.

Materials and Methods: This hospital based cross-sectional observational cohort study was conducted in Department of Endocrinology, Nilratan Sircar Medical College and Hospital, Kolkata, India. The study was done on 55 cases of IHH presenting to the department with delayed secondary sexual characteristics.

Results: Out of these 55 cases, 45 (81.8%) were of nIHH and only 10 (18.2%) cases were of Kallmann Syndrome. It was found that both the conditions show male predominance. Smell abnormalities were present only in Kallmann group. The level of serum testosterone was significantly higher ($p<0.05$) in nIHH subjects (mean-35.59 ng/dL) than patients with Kallmann Syndrome (mean-14.90 ng/dL). Patients with Kallmann syndrome showed significantly reduced pubic and axillary hair development and absence of gonadal development.

Conclusion: Absence of puberty with anosmia/hyposmia with low serum FSH and LH, drastically reduced serum testosterone, are factors that point towards the diagnosis of Kallmann syndrome even in absence of genetic study, which is helpful for initiation of hormone replacement therapy for treatment.

Keywords: Anosmia, Gonadal dysgenesis, Puberty

INTRODUCTION

The IHH is a disorder characterised by absence or incomplete sexual maturation by the age of 18, in conjunction with low levels of circulating gonadotropins and testosterone and no other abnormalities of the hypothalamo-pituitary axis [1]. In the presence of anosmia, IHH is called as the Kallmann syndrome, whereas in the presence of a normal sense of smell, it is termed nIHH. It has a prevalence of approximately 1-10:100000 live births, of which 1/4,000-1/10,000 seen in male and 1/40,000 seen in females [2]. Among IHH, approximately 1/3rd and 2/3rd of cases are of normosmic and Kallmann syndrome, respectively [3].

The hypothalamic GnRH pulse generator is the Central Nervous System (CNS) control for pubertal development. GnRH secretion is inhibited by inhibitory neurotransmitters, like Gamma Aminobutyric Acid (GABA) and opioid peptides. After the age of eight or nine years, there is gradual decrease of inhibitory neurotransmitter and increase in excitatory neurotransmitters like glutamate and kisspeptin, which enhance GnRH secretion. GnRH secretion in puberty is increased by attention of transsynaptic and glial inputs to the GnRH neuronal network [4]. Kisspeptin correlates metabolic and environmental factors for regulation of the hypothalamic-pituitary-gonadal axis by modulation of GnRH, LH, and FSH secretion and steroid feedback mechanism [5]. The pulsatile release of GnRH from GnRH-containing neurons with frequency and amplitude modulation is the key determinant of system activation with progression into and through puberty.

A defect involving the GnRH pulse generator or gonadotrophs without an anatomic lesion causes selective deficiency of gonadotropins, producing IHH. Characteristic features are low concentrations of gonadal sex steroids (testosterone in boys; estradiol in girls) and gonadotropins, pulsatile LH secretion is often virtually absent, and the LH response to GnRH or GnRH agonist administration is deficient in the severe form. The testes are small and may be hard to find [6].

In normal embryonic development, the olfactory neurons and GnRH neurons migrate together from nasal olfactory epithelium to the basal hypothalamus. A fault in this migratory process can result in hyposmic or anosmic type of hypogonadism. Aplasia or hypoplasia of the olfactory bulbs and tracts lead to inability to perceive olfactory stimuli [7]. Maestre de San Juan A was probably the first who reported the association of absence of olfactory structures and presence of small testes in the year of 1856 [8]. In 1944, an American medical geneticist, Kallmann, identified it as a clinical entity after a study on the occurrence of hypogonadism associated with anosmia in three affected families [9]. He showed the association of the anosmia and the hypogonadism in all the affected individuals. Therefore, he established it as a hereditary syndrome called Kallmann syndrome. The classical Kallmann syndrome is characterised by isolated gonadotropin deficiency, anosmia, and X-linked inheritance. This disorder is due to mutations in anosmin 1 encoded by the KAL1 gene resulting in failure of GnRH neurons to migrate to the hypothalamus. Mutations in genes such as FGFR1, FGF8, PROKR2 and PROK2 have also been shown both in KS and in nIHH, reinforcing the hypothesis of a pathophysiological overlap between these diseases. The majority of cases of HH are sporadic but gene mutations or deletions can be detected in about 20% of cases of KS and in over 50% of cases of nIHH [10].

The nIHH is a rare disease, characterised by frank hypogonadism with low or inappropriately normal gonadotropin levels in the absence of any anatomic abnormality of their hypothalamo-pituitary-gonadal axis resulting into absent pubertal development in both males and females [1].

The IHH generally requires lifelong therapy, however, cases of spontaneous reversal later in life have been reported in about 10% of patients with either absent or partial puberty [11]. IHH is a heterogeneous disease characterised not only by alteration of hypothalamo-pituitary-gonadal axis and/or olfactory structures but also by many developmental anomalies such as midline defects, hearing loss, renal anomalies, cryptorchidism. Only a few studies reported the prevalence of clinical features in Kallmann Syndrome patients, showing a large variability, and only rarely a comparison between KS and nIHH was made [12,13]. Thus, present study was conducted with the objective to find out the significant differences between Kallmann syndrome and nIHH based on clinical features and biochemical assessment as a primary measure to initiate the treatment early.

MATERIALS AND METHODS

This was a hospital based cross-sectional observational cohort study conducted in Department of Endocrinology, Nilratan Sircar Medical College and Hospital, Kolkata, India during January 2018 to June 2019.The study was approved by Institutional Ethical Committee of Nilratan Sircar Medical College and Hospital, Kolkata registered with Central Drug Standard Control Organiser (ECR/609/Inst/WB/2014/RR-17). Written consent was taken from every patient included in this study.

Inclusion and Exclusion criteria: All patients of within 20 years of age presented in OPD with absent or underdeveloped secondary sexual characteristics were included in this study. Patients above the age of 20 years and not willing to participate in the study were excluded from the study. Patients with absent or delayed puberty with decreased LH, FSH, testosterone levels and other normal hormonal level mentioned below were included in the study. Clinical examinations were done on following headings:

i. Height

ii. Weight

iii. Body Mass Index (BMI)

iv. Arm span

v. Stretched Penile length-micropenis/normal

vi. Testicular volume and consistency-Right/Left

vii. Scrotum-underdeveloped rugae/normal

viii. Gynecomastia-disc diameter-Right/Left

ix. Pubic hair, Axillary hair-Tanner Staging

x. Beard and moustache-absent/sparse/normal

xi. Upper segment lower segment ratio

Investigations done were:

- Serum cortisol (Basal) level, serum prolactin level
- Serum IGF1(Insulin like Growth Factor 1)
- Serum Testosterone, Serum LH and FSH level
- Thyroid function test, Fasting and postprandial blood glucose test

STATISTICAL ANALYSIS

A proforma was designed for recording the details of the patient including history, clinical examination and biochemical reports. The statistical software SPSS 21.0 was used for the analysis of the data. The p-value of less than 0.05 was accepted as indicating statistical significance.

RESULTS

The present study included 55 patients who presented with absent or delayed puberty. Both the conditions showed male (89.10%) predominance. In present study, no female patient was affected by Kallmann syndrome. However, only six (13.3%) female patients among the 45 cases of nIHH were found [Table/Fig-1].

Diagnosis	Number (%)	Male, n (%)	Female, n (%)
nIHH	45 (81.8%)	39 (86.7%)	6 (13.3%)
Kallmann	10 (18.2%)	10 (100%)	0 (0%)
Total	55 (100%)	49 (89.10%)	6 (10.9%)

[Table/Fig-1]: Sex distribution of nIHH and Kallmann Syndrome.

[Table/Fig-2] shows no statistically significant difference of serum FSH and LH levels between nIHH and Kallmann group. But nIHH subjects had significantly higher serum testosterone level than patients with Kallmann syndrome. The mean serum testosterone level in nIHH patients was 35.59 ng/dL whereas that of Kallmann syndrome patients was 14.90 ng/dL, though both were below normal level. Other hormonal parameters was within normal limits.

Variables	Hypogonadism type	N	Mean	Std. Deviation	Median (IQR)	p-value
Serum FSH (mIU/mL)	nIHH	45	2.58	1.22	2.60 (1.56-3.28)	0.493 (NS)
	Kallmann	10	2.30	0.70	2.40 (1.59-2.66)	
Serum LH (mIU/mL)	nIHH	45	1.52	0.84	1.40 (1.03-2.07)	0.432 (NS)
	Kallmann	10	1.31	0.40	1.09 (1.03-1.69)	
Serum Testosterone (ng/dL)	nIHH	45	35.59	23.139	31 (20-56)	<0.001
	Kallmann	10	14.90	5.152	15.5 (13.75-17.75)	

[Table/Fig-2]: Serum FSH, LH, Testosterone levels in IHH.
NS: Not Significant; Chi-square test applied

[Table/Fig-3] shows that significantly higher number of subjects of nIHH (68.9%) had stage II grade axillary hair development as compared to only 20% in Kallmann syndrome (p=0.004).

Variables		Axillary hair		Total	p-value
		Stage I	Stage II		
nIHH	Count, n (%)	14 (31.1%)	31 (68.9%)	45 (100%)	0.004
Kallmann	Count, n (%)	8 (80%)	2 (20%)	10 (100%)	
Total	Count, n (%)	22 (40%)	33 (60%)	55 (100%)	

[Table/Fig-3]: Axillary hair development in IHH.
Chi-square test applied

Significant difference in the pubic hair development was noted between nIHH and Kallmann Syndrome (p=0.024) as shown in [Table/Fig-4]. Patients with Kallmann syndrome showed reduced pubic hair development. Most of them (90%) fell into stage II category of pubic hair development according to the Tanner-Stage score system [14]. But patients with nIHH mostly fell into Stage III category of pubic hair development.

Variables		Pubic hair			Total	p-value
		Stage I	Stage II	Stage III		
nIHH	Count, n (%)	1 (2.2%)	19 (42.2%)	25 (55.6%)	45 (100%)	0.024
Kallmann	Count, n (%)	0 (0%)	9 (90%)	1 (10%)	10 (100%)	
Total	Count, n (%)	1 (1.8%)	28 (50.9%)	26 (47.3%)	55 (100%)	

[Table/Fig-4]: Pubic hair development in IHH.
Chi-square test applied

There was also significant difference in the smell abnormalities between the two groups (p<0.001). Smell abnormalities were present only in Kallmann group and none of the nIHH patients were found to have olfactory abnormalities. Among the ten patients with Kallmann syndrome, five (50%) patients had partial and five (50%) patients had complete loss of smell sensation.

Gonadal development in male patients was more severely affected in Kallmann than in nIHH. Most of the patients (55.6%) with nIHH fell into stage II category whereas all the patients (100%) with Kallmann syndrome fell in stage I category only.

Breast development was suboptimal in all six females with nIHH of stage I or prepubertal of tanner staging. Since no female patient affected by Kallmann syndrome could be found, this is rather an evaluation of nIHH female patients.

DISCUSSION

In present study, nIHH is the most common form of IHH. Out of total 55 cases, 45 (81.8%) were nIHH and only 18.2% were Kallmann Syndrome. This finding is contradictory to the findings of Kallmann FJ et al., who found that Kallmann Syndrome is the most common form of IHH [9]. In another study conducted by Versiani BR et al., 22 out of 26 patients with IHH (85%) were found to be Kallmann Syndrome [15]. However, the study was done in American population, whereas present study was done on Indian population.

In current study, both Kallmann syndrome and nIHH showed male preponderance. This finding is consistent with the studies conducted by Grumbach MM, Sato N et al., and Vogl TJ et al., who also found preponderance in Kallmann Syndrome respectively.

In contrary to the study of Anik A, who documented all six patients of Kallmann Syndrome had anosmia, present study showed half of patients presented with anosmia and rest half with hyposmia [18]. Koenigkam-Santos M et al., evaluated 21 patients of Kallmann syndrome and all patients showed altered findings on smell tests, mostly presenting with anosmia [19].

Based on the Tanner Staging, in present study 68.9% patients of nIHH had Stage II grade of axillary hair development whereas 80% patient of Kallmann syndrome showed Stage I or prepubertal growth. In development of pubic hair, 55.6% patients of nIHH had Stage III grade whereas 90% patient of Kallmann syndrome were on Stage II. According to the study of Chinese largest IHH network social group, there were 62.2% patients at stage I of pubic hair development and 37.8% patients at stage II, and nobody was at stage III, IV, or V [20]. Based on gonadal development, 55.6% patients of nIHH were on Stage II, rest on stage I. But 100% patient of Kallmann syndrome were on Stage I which means the testis, scrotal sac and penis had a size and proportion like early childhood. Zhao W et al., found in their study that there were 51.35% patients at genital development stage I and 48.65% patients at stage II, and nobody was at stage III, IV, or V, which was almost similar to present findings [20].

There was significant higher serum testosterone level in nIHH patients-35.59 (range 20-56) ng/dL than Kallmann syndrome patients-14.90 (range 13.75-17.75) ng/dL. Though both the values were extremely low than normal values. Serum FSH varies from (1.56-3.28) mIU/mL and serum LH varies from (1.03-2.07) mIU/mL. Which were also toward lower level. Zhao W et al., revealed in their study that the serum testosterone levels at disease onset were decreased in all of the 74 patients. Serum FSH levels were decreased in 71 (95.9%) patients, and serum LH levels were decreased in 69 (93.2%) patients [20].

The main biochemical parameters of Kallmann syndrome in men are extremely low serum testosterone and low levels of the gonadotropins LH and FSH. The development of gonads, pubic and axillary hair is almost infantile in nature in Kallmann syndrome. So, the presence of anosmia/hyposmia and history of delayed or absent puberty or infertility, with markedly low serum testosterone with low serum FSH and LH are helpful in establishing the diagnosis of Kallmann syndrome in absence of genetic study which is confirmatory but very expensive and not readily available everywhere.

The first goal to achieve in therapy for hypogonadotropic hypogonadism is induction of puberty and virilisation in males. Testosterone replacement therapy can be performed by intramuscular injections of testosterone esters or using transdermal testosterone patches [21]. This treatment successfully substitutes for the lack of normal Leydig cell function but will not induce spermatogenesis. Gonadotropin (hMG, hCG) and pulsatile GnRH therapy are used to induce fertility [22]. The condition of IHH patients can be improved or reversed after hormone replacement therapy. Prolonged sex hormone deficiency may otherwise produce adverse effects on the development, metabolism, and psychology. Choice of therapy depends on the age of diagnosis, psychosocial factors and pubertal changes can be achieved by administration of exogenous sex steroids, appropriateto the gender of the patient. If fertility is desired, pulsed gonadotropin-releasing hormone can be administered with variable success [23].

Limitation(s)

Magnetic Resonance Imaging (MRI) findings of hypoplasia or absent olfactory bulb, tract, sulcus are corroborative with the findings of hyposmia or anosmia of Kallmann syndrome. In present study relatively subjective method of smell testing was used instead of 'Brief smell identification test' (microencapsulated odour scratch and sniff test with 12 items) which would have been a better choice for smell testing. Larger study population with MRI study and genetic study would have given better results.

CONCLUSION(S)

IHH showed male predominance and normosmic IHH is more common than Kallmann Syndrome in Eastern Indian population in comparison to Western countries. In the study, Kallmann group showed significantly reduced or absent pubertal changes and significantly decreased sex steroids than normosmic IHH. Moreover, all cases of Kallmann Syndrome presented with history of hyposmia/anosmia. So in absence of imaging and genetic study, differentiation of these two groups via careful physical and hormonal studies, is very helpful for early diagnosis and management of these patients.

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