Original Article

# Clinical and Biochemical Characteristics of Male Idiopathic Hypogonadotropic Hypogonadism Patients: A Retrospective Cross Sectional Study

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## Abstract

**Background:** Idiopathic hypogonadotropic hypogonadism (IHH) is a medical condition where there is a deficiency or insensitivity of gonadotropin-releasing hormone (GnRH) without a known cause. Not only are the sexual characteristics of a person affected by this condition but also are the psychological and physical development, thus necessitating its early recognition and treatment. This research was carried out to identify the laboratory parameters and to present symptoms of the patients with complaints of IHH.

**Materials and Methods:** This retrospective, center, single-center, cross-sectional study was carried out in Aga Khan University from December 2000 until December 2020 on the patients that presented to the clinic with IHH. The patients included in the study were those that presented with hypogonadism, a low concentration of sex steroid hormone, and an abnormal gonadotropin level without any expansive pituitary or hypothalamic lesion.

**Results:** Seventy nine patients presenting with IHH were included with their mean age of 24.2 ± 7.5 years. Of these, 64 (81.0%) had genital atrophy, 50 (63.6%) showed an absence of secondary sexual characteristics, 53 (67.1%) complained of infertility, 44 (55.7%) had not shown signs of puberty, 52 (65.8%) had erectile dysfunction, 46 (58.2%) had a decrease in libido, 11(13.9%) had a previous familial history, 24 (30.3%) had gynecomastia, 9 (11.4%) had non-descended testes, and 6 (7.6%) had anosmia. These patients had serum testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels of 26.3 ± 60, 1.3 ± 2.4, and 2.7 ± 5.0 (IU/L), respectively.

**Conclusion:** Thus, it can be stated that small genitalia is the most common complaint among patients with IHH, followed by infertility and lack of secondary sexual characteristics. The testosterone level in serum is also found to be low among these patients.

***Keywords:*** Hypogonadism, Infertility, Male, Pakistan

**Citation:** Saleem M, Khan SA, Khan MMM, Suchal ZA, Ram N. Clinical and biochemical characteristics of male idiopathic hypogonadotropic hypogonadism patients: a retrospective cross sectional study. Int J Fertil Steril. 2023; 17(1): 57-60. doi: 10.22074/IJFS.2022.540499.1201.


## Introduction

Idiopathic hypogonadotropic hypogonadism (IHH) is a lack of sexual development associated with low levels of sex steroid hormones and gonadotrophs without any structural or functional abnormality in the gonadal axis (1). An integrated hypothalom-pitutiary-gonadal axis is needed for proper testicular function i.e. spermatogenesis and andrgorenic hormone synthesis (2). Gonadotropin-releasing hormone (GnRH) is necessary to be secreted from the hypothalamus to allow the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These hormones then have a downstream effect on Sertoli and Leydig cells in the testis for appropriate male characteristics and sperm production (3).

Hypogonadism is a clinical condition that results in hormone deficiency. It can either be primary hypogonadism from a primary defect or secondary to a hypothalamic/pituitary defect (4).

In adult men, the most common reason for hypogonadism is hypogonadotropic hypogonadism or primary hypogonadism. In American men the aged 40 to 69 years, the incidence rate of 12.3 cases per 1000 led to the prevalence of 481000 cases of late onset hypogonadism , according to the Male Aging Study of Massachusetts (MMAS) (5).

Hypogonadotropic hypogonadism or secondary hypogonadism, in contrast, can be either acquired or congenital. The congenital causes are then further divided into congenital normosmic isolated (IHH) causes or anosmic causes (Kallmann syndrome) (6). The congenital causes have approximately an incidence of 1-10:100000 live births, and 2/3 and 1/3 of cases are caused by Kallmann syndrome (KS) and IHH, respectively (7).

**Received: 18/October/2021, Revised: 13/March/2022, Accepted: 31/May/2022**
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**Royan Institute**
**International Journal of Fertility and Sterility**
**Vol 17, No 1, January-March 2023, Pages: 57-60**

For diagnosing male hypogonadism, a comprehensive history, detailed clinical examination, and hormonal evaluation are needed. In some cases, more testing is indicated to conclude etiology and the degree of hypothalamus-pituitary axial defect. These tests can be radiological imaging, genetic testing, DEXA scans, testicular ultrasounds and biopsy, serum hormone testing, and semen analysis in patients who desire fertility.

Clinical presentations included tiny genitalia, absence of secondary sexual features, unreached puberty, infertility, erectile dysfunction, and libido loss (8). Along with low testosterone levels in the blood, a decreased pituitary hormone level is required to confirm the diagnosis of hypogonadotropic hypogonadism (9). Patient clinical assessment and diagnosis are complex, particularly before puberty. Basal determinations of the luteinizing hormone gonadotropins, follicle-stimulating hormone, testosterone and estrogen gonadal sex steroids and gonadal function markers like inhibin B and anti-müllerian hormone are helpful, but only at particular ages, thus requiring meticulous physical evaluation of combined hormonal tests (10).

IHH adversely affects the sexual, bone, and metabolic health of male patients and their psychological development. Accurate early detection and prompt care are therefore necessary. Previous studies have mainly concentrated on the molecular and genetic basis of IHH, but only about 30 percent of IHH cases are considered to have a genetic basis (11).

Most of the previous studies have been conducted to determine the characteristics of hypogonadotropic hypogonadism as a whole. Very few studies have directly addressed the idiopathic variant in males, which may lead to a more robust response in terms of care and fertility if diagnosed earlier (12). We performed this research so that this unique disease entity in our population can be properly studied.

This research was conducted to see the laboratory parameters and physical signs and symptoms of the patients with complaints of IHH in a tertiary hospital.

## Materials and Methods

This retrospective, center, single-center, cross-sectional research was conducted at Aga Khan University Hospital, Karachi. Data on the male patients with IHH who visited the Endocrine clinics from December 2000 to December 2020 was reviewed. Approval for carrying out this study was taken from the Ethical Review Committee of the Hospital (2021-5855-17038).

The patients were included in the study if they showed characteristics of hypogonadism, a low level of serum sex steroid hormone and an uncharacteristically low serum level of gonadotropins. This study included patients in whom lesions in the hypothalamus or pituitary region were absent, nor did they have pituitary hormone defects. Patients with a body mass index of fewer than 18.5 kg/m$^2$, those who exercised five hours or more in a week, or those with prolonged medical illnesses were excluded from our study. Patients diagnosed with IHH in adolescence were re-evaluated between the ages of 17-20 after cessation of treatment and those who had a constitutional delay of puberty were excluded for this study.

The Statistical package for social science SPSS (Release 21.0, Version 25.0, IBM, USA, copyright © SPSS; 1989-02) was used for the analyses, with a descriptive analysis. Features were presented as mean ± standard deviation for quantitative variables like age, and percentages were estimated for qualitative variables like symptoms at onset.

## Results

During our study, 79 patients who met our criteria came to the endocrinology clinic with a mean age of 24.2 ± 7.5 years. Their clinical presentation has been summarized in Table 1, showing that out of these 79 patients, 64 (81.0%) had small genitalia; 50 (63.6%) had absent secondary sexual characteristics; 53 (67.1%) had infertility at presentation; 44 (55.7%) had not attained puberty; 52 (65.8%) had a complaint of erectile dysfunction, 46 (58.2%) experienced the loss of libido; Gynecomastia was found in 24 (30.3%); undescended testis was present in 9 (11.4%) patients; 6 (7.6%) experienced anosmia/hyposmia and 11 (13.9%) had a positive family history of IHH.

**Table 1:** Clinical presentation of 79 idiopathic hypogonadotropic hypogonadism patients

| Symptoms and history | Frequency | Percentage |
|---|---|---|
| Small genitalia | 64 | 81.0 |
| Absent secondary sexual characteristics | 50 | 63.6 |
| Infertility | 53 | 67.1 |
| Not attained puberty | 44 | 55.7 |
| Erectile dysfunction | 52 | 65.8 |
| Loss of libido | 46 | 58.2 |
| Family history | 11 | 13.9 |
| Gynecomastia | 24 | 30.3 |
| Undescended testis | 9 | 11.4 |
| Anosmia/hyposmia | 6 | 7.6 |

The mean level of testosterone in the serum of these patients was found to be 26.3 ± 50 (ηg/dL), while mean serum FSH levels were 2.7 ± 5.0 (IU/L), and mean serum LH levels were 1.3 ± 2.4 (IU/L) .

## Discussion

We have described a group of 79 males who presented to the clinics with various complaints due to deficiency of gonadotrophs and were diagnosed with IHH. Our mean age of presentation was 24.2 years, of which 52.4 percent had a pubertal delay. Similarly, in a study conducted in 2002 on IHH, the mean age of presentation for IHH was 27, 71 percent had not attained puberty, and 21 percent had partially attained puberty (13).

In a normal male without any abnormality, testosterone and its derivative androgenic hormones are responsible for the increase in penile length, testicular size, sperm production, and the development of secondary sexual characteristics (13). In our study group, the primary complaints were small genitals, infertility, underdeveloped secondary sexual characteristics, and erectile dysfunction, thus indicating a lower than required concentration of testosterone. The mean concentration of testosterone in our patients was 26.3 ηg/dL. Our conclusion is further corroborated by previous studies, which have shown that those with a testosterone concentration lower than 300 ηg/dL are likely to show characteristics of classic hypogonadism (14).

IHH, as seen in our patients and corroborated with previous studies, is a delay in puberty at the age of 18 or more with a lower than average testosterone level and a low or normal level of LH and FSH in the absence of any lesion in pituitary region or hypothalamus. It is likely due to a defect in GnRH secretion or in the GnRH receptor in the anterior pituitary, where it exerts its action (15-17). Deficiency of GnRH is known as congenital hypogonadotropic hypogonadism (CHH) and it can present with a number of congenital abnormalities. When CHH is associated with anosmia or hyposmia it is known as Kallman Syndrome (18). Kallman Syndrome is in 2/3 of the patients with IHH, with its occurrence being five times more common in men (19). In our study, 6 patients reported anosmia/hyposmia. Moreover, 13.9% percent of patients in our study had a family history of hypogonadism. It has been observed in previous studies that IHH is a multifactorial disease influenced by multiple hormonal, environmental and genetic factors (20). Several genetic mutations such as GPR54, DAX-1, FGR-1, KAL-1, and Prop1 have been identified as causing hypogonadotropic hypogonadism (21).

IHH is known to be a disease with complex genetics and interaction with environmental factors, which make it be variably expressed in different individuals (22, 23). The mainstay treatment for patients with IHH is testosterone replacement therapy, sometimes in conjugation with other therapy like spermatogenesis-inducing therapy (12). Although the studies on the outcome of IHH treatment are still scarce, the effects are reversible after testosterone therapy, with approximately 10-20% of patients showing complete recovery (18).

This study provides valuable data to describe features of IHH in the local population and would be helpful for future research projects. The lower number of patients and absence of any control group are the significant limitations of this study. Thus, future multi-centric studies with a larger sample size and a control group are advised.

## Conclusion

The majority of the patient with IHH present with complaints of small genitalia followed by infertility and no secondary characteristics of puberty and have a lower level of testosterone in serum which can be useful information in reaching an accurate diagnosis once known causes of hypogonadotropic hypogonadism are ruled out.

## Acknowledgments

There is no financial support and conflicts of interest in this study.

## Authors' Contributions

M.S.; Supervision, study design, and manuscript writing. S.A.Kh.; Supervision and study design. M.M.M.Kh.; Manuscript writing and data collection. Z.A.S.; Manuscript writing, data collection, and analysis. N.R.; Supervision, study design, and finalization of draft. All authors read and approved the final manuscript.

## References

1. Salonia A, Rastrelli G, Hackett G, Seminara SB, Huhtaniemi IT, Rey RA, et al. Paediatric and adult-onset male hypogonadism. Nat Rev Dis Primers. 2019; 5(1): 38.
2. Topaloğlu AK. Update on the genetics of idiopathic hypogonadotropic hypogonadism. J Clin Res Pediatr Endocrinol. 2017; 9 Suppl 2: 113-122.
3. Pivonello R, Menafra D, Riccio E, Garifalos F, Mazzella M, de Angelis C, et al. Metabolic disorders and male hypogonadotropic hypogonadism. Front Endocrinol (Lausanne). 2019; 10: 345.
4. Richard-Eaglin A. Male and female hypogonadism. Nurs Clin North Am. 2018; 53(3): 395-405.
5. Raivio T, Miettinen PJ. Constitutional delay of puberty versus congenital hypogonadotropic hypogonadism: Genetics, management and updates. Best Pract Res Clin Endocrinol Metab. 2019; 33(3): 101316.
6. Young J, Xu C, Papadakis GE, Acierno JS, Maione L, Hietamäki J, et al. Clinical management of congenital hypogonadotropic hypogonadism. Endocr Rev. 2019; 40(2): 669-710.
7. Dhindsa S, Ghanim H, Batra M, Dandona P. Hypogonadotropic hypogonadism in men with diabesity. Diabetes Care. 2018; 41(7): 1516-1525.
8. Ram N, Asghar A, Hashmi F, Islam N. Male hypogonadism at a tertiary care hospital in Karachi, Pakistan. J Ayub Med Coll Abbottabad. 2012; 24(2): 65-67.
9. Ross A, Bhasin S. Hypogonadism: its prevalence and diagnosis. Urol Clin North Am. 2016; 43(2): 163-176.
10. Dwyer AA, Smith N, Quinton R. Psychological aspects of congenital hypogonadotropic hypogonadism. Front Endocrinol (Lausanne). 2019; 10: 353.
11. Tang Ry, Chen R, Ma M, Lin Sq, Zhang Yw, Wang Yp. Clinical characteristics of 138 Chinese female patients with idiopathic hypogonadotropic hypogonadism. Endocr Connect. 2017; 6(8): 800-810.
12. Yang L, Chen HS, Qu R, Zhang SX. Diagnosis and treatment of idiopathic hypogonadotropic hypogonadism in males. Zhonghua Nan Ke Xue. 2018; 24(8): 744-747.
13. Bettocchi C, Rinaldi M, Sebastiani F. GnRH in the treatment of hypogonadotropic hypogonadism. Curr Pharm Des. 2021; 27(24): 2754-2756.
14. Wheeler KM, Sharma D, Kavoussi PK, Smith RP, Costabile R. Clomiphene citrate for the treatment of hypogonadism. Sex Med Rev. 2019; 7(2): 272-276.
15. Travison TG, Vesper HW, Orwoll E, Wu F, Kaufman JM, Wang Y, et al. Harmonized reference ranges for circulating testosterone levels in men of four cohort studies in the United States and Europe. J Clin Endocrinol Metab. 2017; 102(4): 1161-1173.
16. Grinspon RP, Bergadá I, Rey RA. Male hypogonadism and disorders of sex development. Front Endocrinol (Lausanne). 2020; 11: 211.
17. Topaloglu AK, Kotan LD. Genetics of hypogonadotropic

hypogonadism. Endocr Dev. 2016; 29: 36-49.
18. Boehm U, Bouloux P-M, Dattani MT, De Roux N, Dodé C, Dunkel L, et al. European consensus statement on congenital hypogonadotropic hypogonadism—pathogenesis, diagnosis and treatment. Nat Rev Endocrinol. 2015; 11(9): 547-564.
19. Stamou MI, Georgopoulos NA. Kallmann syndrome: phenotype and genotype of hypogonadotropic hypogonadism. Metabolism. 2018; 86: 124-134.
20. Sonne J, Lopez-Ojeda W. Kallmann Syndrome. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538210/ (19 Jun 2022).
21. Peña VN, Kohn TP, Herati AS. Genetic mutations contributing to non-obstructive azoospermia. Best Pract Res Clin Endocrinol Metab. 2020; 34(6): 101479.
22. Khera M, Broderick GA, Carson CC 3rd, Dobs AS, Faraday MM, Goldstein I, et al. Adult-onset hypogonadism. Mayo Clin Proc. 2016; 91(7): 908-926.
23. Khan SA, Nooralam S, Khan MM. Characteristics of male idiopathic hypogonadotropic hypogonadism (IHH) patients; an experience from a developing country. Endocr Pract. 2021; 27(6): S116.