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Original Article

Spectrum of MRI findings in a cohort of idiopathic hypogonadotropic hypogonadism in a tertiary care hospital in Eastern India

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ABSTRACT

Introduction: Idiopathic Hypogonadotropic Hypogonadism is related to gonadotropin deficiency leading to delayed or absent sexual maturation. In between normosmic idiopathic Hypogonadotropic Hypogonadism and Kallmann syndrome, there are overlapping features, differentiation between the two conditions can be made by MRI findings, which allows precise depiction of the olfactory bulb, tract and olfactory sulcus.

Methods: The study was conducted on 55 cases of Idiopathic Hypogonadotropic Hypogonadism presenting to the Department of Radiology, Nilratan Sircar Medical College & Hospital, Kolkata.

Observations: Out of these 55 cases, 45 (81.8%) were normosmic Idiopathic Hypogonadotropic Hypogonadism and only 10 (18.2%) cases were Kallmann Syndrome. We found that both the conditions show male predominance. Smell abnormalities were present only in Kallmann group.

Results: All patients with normosmic Idiopathic Hypogonadotropic Hypogonadism have normal olfactory bulb or olfactory tract whereas out of 10 Kallmann patients, 5 (50%) patients had hypoplasia of olfactory sulcus & 5 (50%) had complete aplasia of olfactory sulcus.

Conclusions: Hyposmia & anosmia are related to anatomical abnormalities of olfactory bulbs / tracts in 100% patients of Kallmann Syndrome. MRI is the diagnostic tool to demonstrate abnormalities of olfactory system to differentiate Kallmann Syndrome from normosmic Idiopathic Hypogonadotropic Hypogonadism.

Key words: Hypogonadotropic Hypogonadism, Kallmann Syndrome, Anosmia

INTRODUCTION:

Hypogonadotropic Hypogonadism is a clinical syndrome that results from gonadal failure characterized by a defective embryologic development of the Gonadotropinreleasing hormone (GnRH) pulse generator and the hypothalamo-pituitary-gonadal axis [1]. 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 idiopathic hypogonadotropic hypogonadism approximately 1/3 and 2/3 of cases are normosmic and Kallmann syndrome respectively [3].

Normosmic Idiopathic Hypogonadotropic Hypogonadism (nIHH) is a rare human disease that is characterized 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].

Kallmann Syndrome is a form of hereditary disease characterized by hypogonadotropic hypogonadism in association with anosmia or hyposmia both of which occur as a result of impairment of olfactory axon development & failure of GnRH neurons [1]. The classic form of Kallmann syndrome is characterized 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 [4].

The sense of smell is detected by olfactory receptors located within the nasal epithelium. Their axons assemble into olfactory nerves, which penetrate cribriform plate of the ethmoid bone. It enters the cranial cavity & form ovoid shaped olfactory bulb, which continues posteriorly as olfactory tract. It lies within the olfactory sulcus in the inferior surface of the frontal lobe. Finally it relay smell to the primary olfactory cortex, located within the uncus of temporal lobe. During normal embryonic development, the GnRH neurons and olfactory neurons migrate together from the nasal olfactory epithelium to the basal hypothalamus, therefore a defect in this process may cause hypo/anosmic hypogonadism. The inability to perceive olfactory stimuli results from aplasia or hypoplasia of the olfactory bulbs and tracts. To date, hypogonadism associated with an olfactory deficit is defined as Kallmann syndrome and is distinct from normosmic IHH (nIHH), however both diseases share anatomical and genetic etiopathogenesis with common features. [5]

Although there are overlapping features, differentiation between the two conditions can usually be made, based on specific MRI findings and relevant clinical information. Coronal and axial cranial MRI scans of the olfactory bulbs, tracts and sulcus, unilaterally or bilaterally, reflect this defect in about 90% of cases and can point to the diagnosis, especially in affected infants and prepubertal-age children. Suzuki et al was the first to describe the visualization of olfactory bulbs and tracts on MR scans [6]. Olfactory bulbs are optimally visualized in coronal planes as well-defined structures along cribriform plate. Olfactory sulci are seen between Gyrus rectus and medial orbital gyrus. High resolutions coronal fast spin echo T2W and T1W images are the preferred sequences for morphologic evaluation of the olfactory system [7, 8]. Koenigkam-Santos et al. [9] showed that olfactory bulb and sulcus aplasia were the most common findings in Kallmann Syndrome and demonstrated agreement between MRI findings and the smell test, especially the presence of bulb aplasia and anosmia were consistent. So, MRI occupies a place of choice in the hierarchy of tests and useful adjuvant to differentiate Kallmann Syndrome from normosmic idiopathic hypogonadotropic hypogonadism and confirm the diagnosis, obviating the need for the costly & cumbersome genetic assays. [3].

AIMS & OBJECTIVE:

The objective of this study was to differentiate the features of Kallmann syndrome and normosmic idiopathic hypogonadotropic hypogonadism by the assessment of olfactory bulb, tract and sulcus by MRI study. The specific objective was to evaluate the role of MRI in confirming the diagnosis of patients with Kallmann syndrome.

MATERIALS AND METHODS:

The study was undertaken on 55 patients who were presented with idiopathic hypogonadotropic hypogonadism to the department of Radiology during January 2018 to June 2019 in Nil Ratan Sircar medical College & Hospital, Kolkata. Patients with constitutional delay of growth and puberty, with combined pituitary hormone

deficiency and patients with contraindications for doing MRI were excluded from study. With the help of department of Endocrinology, patients of IHH were identified. Study tools used to do this study were-

- Serum cortisol (Basal) level , serum prolactin level
- Serum Testosterone , Serum LH & FSH level
- Thyroid function test, Fasting and postprandial blood glucose test
- MRI machine: 1.5 Tesla MRI machine (GE Healthcare) was used.

Coronal T1 (TR/TE 600/15) & T2 (TR/TE 4500/90) weighted images from the anterior margin of the Frontal sinus to the Hypothalamus was acquired for the morphological evaluation of the olfactory system. Images were obtained at 3mm slice thickness with 0.3mm inter-slice gap. Axial T1 & Sagittal T2 sections were also taken. Axial MR images allow the visualization of the olfactory sulcus of the frontal lobe. Sagittal sections at the base of frontal lobe were also taken.

- A proforma was designed for recording the details of the patient including history, biochemical reports, and MRI findings. Consent forms were also signed by patient. The statistical software SPSS 21.0 was used for the analysis of the data. The p value of 0.05 was accepted as indicating statistical significance.

RESULTS:

The study included 55 patients who presented with idiopathic hypogonadotropic hypogonadism referred from the department of Endocrinology to the Department of Radiology, Nil Ratan Sircar Medical College and Hospital.

Table 1: Distribution of Cases

	Number	**Percentage**
nIHH	45	81.80
Kallmann	10	18.2
Total	55	100

Out of these 55 cases, 45 (81.8%) were nIHH and only 10 (18.2%) cases were Kallmann Syndrome. So, we can see that most of the cases were nIHH & not Kallmann Syndrome.

Table 2: Sex Distribution

	Male	**Percentage**	**Female**	**Percentage**	**Total**
nIHH	39	86.7%	6	13..3%	45
Kallmann	10	100%	0	0%	10
Total	49	89.10%	6	10.9%	55

Both the conditions show male (89.10%) predominance. In our study no female patient was affected by Kallmann syndrome. However, we found only 6 (13.3%) female patients among the 45 cases of nIHH.

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Table 3: Olfactory Bulbs & Tracts , Olfactory sulci development in IHH

		Olfactory Bulbs & Tracts , Olfactory sulci				p
		Aplasia	Hypoplasia	Normal	Total	
nIHH	Count	0	0	0	45	<0.001
	%	0%	0%	0%	100%	
Kallmann	Count	5	5	0	10	
	%	50%	50%	0%	100%	
Total	Count	5	5	45	55	
	%	9.10%	9.10%	81.80%	100%	

From the above table we can see that there is significant difference in the olfactory bulb or olfactory tract development between nIHH & Kallmann groups ($p<0.001$) as computed by chi-square test. All patients with nIHH have normal olfactory bulb or olfactory tract whereas out of 10 Kallmann patients, 5 (50%) had completely absent and 5 (50%) had hypoplasia. No single patient with Kallmann syndrome had a morphologically normal olfactory bulb, tract & sulcus. This is a significant finding & this finding can be a useful tool to differentiate between these two groups of entities presenting with Hypogonadotropic Hypogonadism.

Table 4: Anosmia / Hyposmia in Idiopathic Hypogonadotropic Hypogonadism

		Smell				p
		Anosmia	Hyposmia	Normal	Total	
nIHH	Count	0	0	0	45	<0.001
	%	0%	0%	0%	100%	
Kallmann	Count	5	5	0	10	
	%	50%	50%	0%	100%	
Total	Count	5	5	45	55	
	%	9.10%	9.10%	81.80%	100%	

The above table shows significant difference in the smell abnormalities between the two groups ($p<0.001$) as computed by chi-square test. Smell abnormalities are present only in Kallmann group and none of the nIHH patients are found to have olfactory abnormalities. Among the 10 patients with Kallmann syndrome, 5 (50%) patients had partial & 5 (50%) patients had complete loss of smell sensation.

DISCUSSION:

In our 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 et al. [10] who found that Kallmann Syndrome is the most common form of IHH. In another study conducted by Beatriz R. Versiani et al.[11], 22 out of 26 patients with IHH (85%) were found to be Kallmann Syndrome. However, the first study was done in USA, the second one done in Brazilian subcontinent; ours was done in Indian subcontinent.

In our study, both Kallmann syndrome & nIHH show male preponderance. All the Kallmann Syndrome affected people in our study are male. No female patient affected by Kallmann was found. This finding is consistent with the studies conducted by N, Kagami M et al. [12], Grumbach [13], Vogl TJ[14], who also found male preponderance in Kallmann Syndrome.

In our study, we found significant difference in the smell abnormalities between the two groups Kallmann syndrome & nIHH, ($p<0.001$) as computed by chi-square test. Ahmet Anik et al.[15] also studied 6 patients of Kallmann Syndrome & found anosmia in all 6 patients. M.Koenigkam-Santos et al.[16] evaluated 21 patients of Kallmann syndrome & all patients showed altered findings on smell tests, mostly presenting with anosmia.

In our study, we found significant difference ($p<0.001$) in the olfactory bulb, olfactory tract & olfactory sulcus development between the two groups Kallmann syndrome & nIHH. All patients with nIHH had normal olfactory bulb, olfactory tract & olfactory sulcus whereas out of 10 Kallmann patients, 5 (50%) had completely absent and 5 (50%) had hypoplasia of olfactory bulb, olfactory tract & olfactory sulcus. Beatriz R. Versiani et al.[17] also found out abnormalities of olfactory bulbs/sulci in 79% of Kallmann syndrome patients. Houneida Zaghouani et al.[18] studied 5 patients of Kallmann Syndrome who also found that all patients had absent olfactory bulbs. However, olfactory sulci were absent in 3 patients and hypoplastic in 2 patients.

Vogl et al.[14] also documented the ability of MR imaging to demonstrate abnormalities of the olfactory pathway in patients with congenital anosmia. In their study 18 patients diagnosed with Kallmann syndrome and 10 patients diagnosed with IHH were included in that study. In 17 of the 18 patients with Kallmann syndrome, the olfactory bulbs and tracts were absent; 8 of these 18 individuals had normal olfactory sulci. However, olfactory bulbs and tracts were present in the 10 patients with IHH.

R. Madan et al.[19] also conducted a study trying to find out MRI findings in patients of Kallmann Syndrome. Abnormalities of olfactory sulci and bulbs were noted in all 5 patients. All patients had absent olfactory bulbs. Olfactory sulci were absent in 3 patients and hypoplastic in 2 patients. Ahmet Anik et al.[20] also studied 6 patients of Kallmann Syndrome & found Olfactory bulb aplasia in all 6 patients.

Conclusion:

Idiopathic hypogonadotropic hypogonadism showed male predominance with normosmic IHH being the most common type in our study in Eastern Indian population. Among idiopathic hypogonadotropic hypogonadism, hyposmia or anosmia are only related to anatomical abnormalities of olfactory bulbs, tracts and sulcus in all patients of Kallmann Syndrome. MRI occupies a place of choice in the hierarchy of tests to demonstrate abnormalities of olfactory system to differentiate Kallmann Syndrome from normosmic Idiopathic Hypogonadotropic Hypogonadism. MRI is the easiest diagnostic tool for Kallmann Syndrome which is as reliable as genetic study but relatively easy, safe, cheap, less time consuming and widely available procedure.

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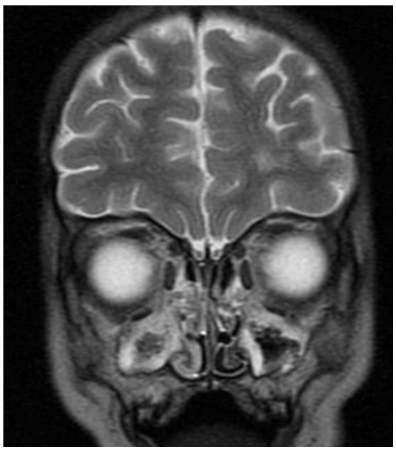
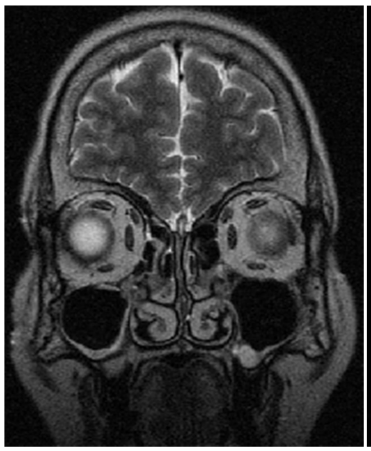
Case 1:



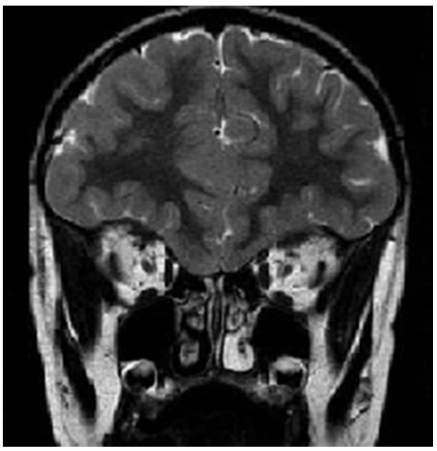
Coronal T2WI through the anterior cranial fossa shows bilateral normal olfactory bulbs, tract and sulcus in a patient of nIHH.

Case 2:



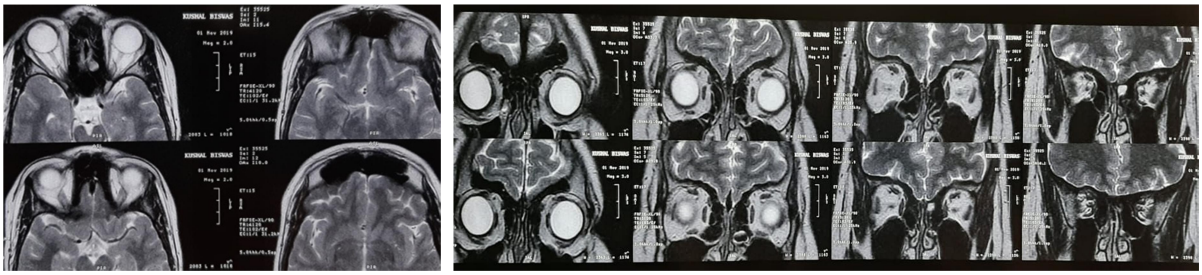
Coronal T2WI through the anterior cranial fossa shows bilateral hypoplastic olfactory bulb, tract and sulcus in a patient of Kallmann Syndrome

Case 3:



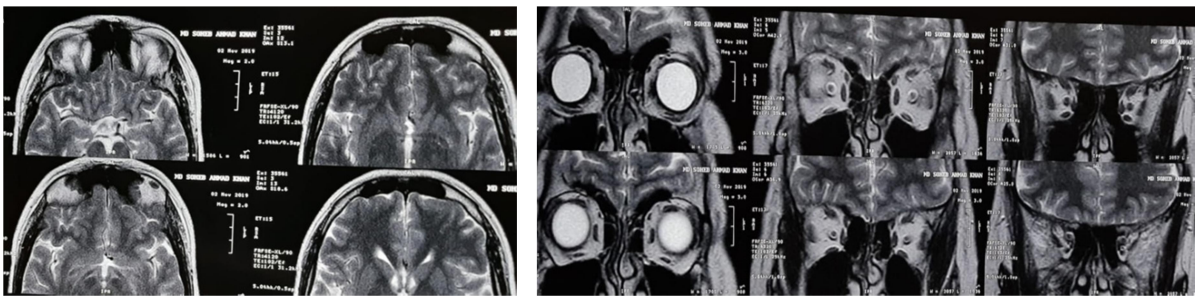
Coronal T2WI through the anterior cranial fossa shows bilaterally absent olfactory bulbs, tract and sulcus in a patient of Kallmann

Case 4:



Axial & coronal T2WI through the anterior cranial fossa shows absent olfactory bulb, tract and sulcus bilaterally in a patient of Kallmann Syndrome.

Case 5:



Axial & coronal T2WI through the anterior cranial fossa shows absent olfactory bulb, tract and sulcus bilaterally in a patient of Kallmann Syndrome.

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