Original Article

Correlation of Olfactory Phenotype by Indian Smell Identification Test and Quantitative MRI of Olfactory Apparatus in Idiopathic Hypogonadotropic Hypogonadism

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Abstract

Objectives: Idiopathic hypogonadotropic hypogonadism (IHH) can be associated with anosmia/hyposmia. The objective of this study is to evaluate olfaction by Indian smell identification test (INSIT) and measure olfactory bulbs (OBs) and sulci using dedicated magnetic resonance imaging (MRI) in patients with IHH and correlate MRI findings with INSIT. **Methods:** Forty patients with IHH underwent (a) brief smell identification test (INSIT) and (b) MRI of the olfactory apparatus. The size of olfactory sulcus and bulb was quantified and compared with the normative data obtained in 22 controls. The agreement between INSIT and MRI was assessed using Kappa index. **Results:** Of the 40 patients, 8 patients who reported abnormal smell sensation and 12 of the remaining 32 patients who reported normal smell sensation historically had a low score on INSIT. Thus, there were 20 patients with Kallmann syndrome (KS) and the rest 20 were normosmic IHH (nIHH). Of 40 patients with IHH, MRI finding was suggestive of normal ($n = 16$), hypoplastic ($n = 12$), and aplastic ($n = 12$) olfactory apparatus. All 20 patients with KS have olfactory abnormalities ($n = 12$ aplastic, $n = 8$ hypoplastic), and 4 of 20 nIHH have olfactory abnormalities (hypoplastic only) on MRI. There is (a) significant positive correlation ($r = 0.54$, $P = 0.013$) between the OB volume (MRI) and smell test scores and (b) moderate agreement (Kappa index: 0.49) between smell defect (INSIT score ≤ 4) and aplastic olfactory apparatus. **Conclusion:** Self-reporting of smell significantly underestimates olfactory phenotype, and hence we recommend an objective smell test to differentiate KS from nIHH. Olfactory phenotype significantly correlates with MRI quantification of olfactory apparatus in IHH.

Keywords: Hypogonadotropic hypogonadism, Kallmann syndrome, olfactory bulb, smell test

Introduction

Idiopathic hypogonadotropic hypogonadism (IHH) is characterized by a defect in production, secretion, or action of the gonadotropin-releasing hormone (GnRH).[1] IHH results in delayed or absent puberty and infertility. Biochemically, IHH is characterized by isolated hypogonadotropic hypogonadism with otherwise normal anterior pituitary function. IHH is associated with various nonreproductive phenotypes like cleft lip, cleft palate, ear anomalies, hearing impairment, dental agenesis, renal agenesis, bimanual synkinesis, anosmia/hyposmia, or skeletal anomalies. It is difficult to differentiate IHH from other causes of delayed puberty, so IHH is mostly diagnosed late in adolescence or early in adulthood.[2] About half of the patients with IHH have associated anosmia or hyposmia and are termed as "Kallmann syndrome" (KS). KS results from abnormal migration of GnRH neurons from olfactory placode to the medial basal hypothalamus.[3] Abnormal development of olfactory placode leads to improper development of olfactory bulbs (OBs) and olfactory sulci (OSs).[4] Abnormalities of olfactory apparatus are best detected using dedicated sequences and thin cuts on magnetic resonance imaging (MRI). Various morphological abnormalities in KS on imaging are the hypoplastic/aplastic OBs and OSs.[5] Patients with IHH with a normal sense of smell are labeled as normosmic idiopathic hypogonadotropic hypogonadism (nIHH). There is a paucity of literature on

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olfactory evaluation of nIHH and even more so in Indian patients.[6]

Differentiation of nIHH from KS has been done by subjective historical self-reported smell or various tests like sniff bottle test, Sniffin' sticks, or objective scratch and sniff card tests in previous studies.[7,8] Indian smell identification test (INSIT) has been studied in Parkinson's disease (PD) and compared with Sniffin' sticks and proposed a cut-off value of 4 (values ≤4 indicating disease), with a sensitivity of 79.2% and specificity of 78%.[9] INSIT has not been used in IHH till date in any studies so far.

Objectives

The objective of this study is to measure the volume of OBs and dimensions of OSs using dedicated MRI sequences in patients with IHH and correlate MRI findings with a clinical smell test (INSIT).

Methods

Design and setting

We conducted a cross-sectional, case–control study in the Department of Endocrinology, SMS Medical College, Jaipur, a tertiary care superspecialty center in Rajasthan (India).

Study population

The study population included a total of 62 subjects, of which 40 patients with IHH and 22 age- and sex-matched control subjects attending to the endocrinology outpatient department consented for the study.

Study procedure

Forty patients with IHH underwent (a) an objective olfaction test by INSIT and (b) MRI of the olfactory apparatus. The size of OS and OB was quantified and compared with the normative data obtained in 22 controls. Ethical clearance from the Institutional Review Board and written consent from each subject were taken.

Olfaction

Olfactory dysfunction was estimated with a detailed history and with a qualitative olfaction test using INSIT. The essence of 10 commonly used items were used as odorants. The essence of cardamom, kewra, khus, lemon, mango, orange, pineapple, rose, thinner, and vanilla in 20-mL airtight bottles commercially available were used. Cotton buds dipped in the essence were used as test material, which was placed 1 cm in front of the one nostril with the other nostril closed and repeated in the other side. The subjects were asked to sniff and identify the smell from the answer card containing four choices for each odorant. The first response was taken and scored 1 for correct response and 0 for wrong response. A cut-off value of 4 was used, that is, values ≤4 indicating disease (hyposmia/anosmia) while >4 indicating normosmia.[9]

MRI technique

All 40 subjects and 22 controls underwent MRI of olfactory apparatus on a 3 Tesla MR system (Sonata Vision; Siemens, Germany) using the CP-head coil. All the MRIs were reported by a single, experienced radiologist blindfolded for clinical findings. Volumes of the right and left OBs were determined using MRI scans of the olfactory apparatus and a standardized protocol for OB analysis. The protocol included 2-mm T2-weighted constructive interface at steady state (CISS) in the coronal plane covering the anterior and middle segments of the base of the skull. The bulb area was measured in consecutive slices and added, and then multiplied with the slice thickness to obtain its volume. If no bulb was identified on MRI, it was termed as aplasia and the volume was considered as zero. The maximum olfactory sulcus depth (OSd) was measured using the coronal images, while the olfactory sulcus length (OSl) was measured on axial images [Figure 1a and b]. An immeasurable or absent sulcus was considered aplastic. The OB of the patient was considered hypoplastic if its volume was less than mean minus two standard deviations of the control subjects. OS was considered hypoplastic if either OSl or OSd or both were lower than mean minus two standard deviations of the control subjects.[4,10]

Inclusion criteria

The diagnosis of IHH was based on the following criteria: (1) age at diagnosis more than 18 years; (2) clinical signs or symptoms of hypogonadism; (3) low or normal gonadotropins along with (a) in men, serum testosterone levels below 100 ng/dL, (b) in women, primary amenorrhea, and estradiol levels below 20 pg/mL; (4) otherwise normal biochemical tests of anterior pituitary function; and (5) normal imaging (MRI) of the hypothalamic and pituitary area (to rule out panhypopituitarism).[11]

Statistical analysis

The data were analyzed using SPSS version 16.0. Data were presented as mean and standard deviation. Pearson's correlation coefficient was used to measure the strength of association between INSIT score and OB volume. To evaluate the agreement between the INSIT and MRI findings to diagnose

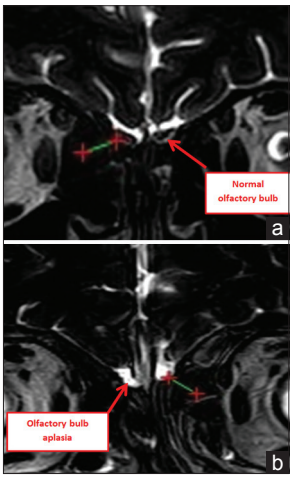

Figure 1: (a) Coronal T2 CISS MR images showing normal olfactory bulbs in a control. (b) Coronal T2 CISS MR images showing aplastic olfactory bulbs in Kallmann syndrome

KS, we used Cohen's Kappa interrater reliability index. Although Kappa index is used to test reliability between two observers, we used it to test reliability between INSIT and MRI olfactory apparatus to diagnose KS, which was used in previous studies also and it has limitations.[4,10] Analysis of variance test was used to compare OB volume and OSl, OSd, and INSIT score between control, nIHH, and KS patients. A *P* value of less than 0.05 is considered as statistically significant.

Results

Baseline parameters, including anthropometry, hormonal profile, reproductive, and nonreproductive phenotypes of the study subjects, are shown in Table 1.

Olfaction by history and smell test

Of the total 40 subjects with IHH, on initial detailed history taking, 8 reported abnormal smell sensation and 32 reported normal smell sensation. All 8 patients who reported an abnormal sense of smell had a low score on INSIT, while 12 of the 32 who reported normal smell sensation historically also had a low score on INSIT. Hence, of the total 40 patients with IHH, there were 20 subjects with KS and 20 with nIHH.

Imaging

The control subjects had normal and symmetric OB volumes, OSl, and OSd. [Figure 1a, Figure 2a and b]. The mean OB volumes, OSl, and OSd of patients with KS with nIHH and control are as shown in Table 2. There was a statistically significant difference of OB volume between control, nIHH, and KS, but the significant difference of OSl/OSd was seen only between KS and nIHH [Table 2]. Of the 40 patients with IHH, MRI finding was suggestive of normal (n = 16), hypoplastic (n = 12), and aplastic (n = 12) olfactory apparatus. Of the 20 patients with KS, 12 and 8 had aplastic and hypoplastic OB findings, respectively, on MRI [Figure 1b]. All patients with aplastic KS (n = 12) were affected bilaterally. Of the 20 patients with nIHH, 16 had normal OB and 4 had hypoplastic OB. Aplastic OS was seen in 4 patients with KS (2

Table 1: Baseline parameters of study subjects and controls

Parameter	nIHH (n=20, M:F=18:2)	KS (n=20, M:F=16:4)	Control (n=22, M:F=19:3)
Age (years, mean±SD)	20.6±2.48	22.4±5.04	21.4±3.9
Height (cm, mean±SD)	167.4±13.8	176.7±11.2	165.4±5.78
AS (cm, mean±SD)	176.9±15.68	187±13.46	166.6±5.1
US: LS (mean±SD)	0.805±0.073	0.798±0.056	0.88±0.027
BMI (kg/m^2, mean±SD)	22.9±5.7	21.7±5.7	23.69±2.015
Average testicular volume in male (mL, mean±SD)	2.4±1.38	2.12±1.31	16.95±2.75
Tanner breast staging in female (mean±SD)	1.5±0.71	1.25±0.5	4.67±0.58
LH (IU/L, mean±SD)	0.27±0.279	0.257±0.457	4.16±1.64
FSH (IU/L, mean±SD)	1.077±1.05	0.574±0.64	5.62±1.59
Testosterone in male (ng/mL, mean±SD)	28.86±9.68	22.8±16.1828	547.9±155.7
Estradiol in female (pg/mL)	<20	<20	63.67±13.05
Synkinesis (no. of patients)	0	3	0
Hearing defect (no. of patients)	0	3	0
Unilateral renal agenesis (no. of patients)	0	2	0
Unilateral undescended testis (no. of patients)	1	3	0
Clinodactyly (no. of patients)	2	2	0
Short 4th/5th metacarpals (no. of patients)	1	1	0

nIHH=Normosmic idiopathic hypogonadotropic hypogonadism; KS=Kallmann syndrome; SD=Standard deviation; US=Upper segment; LS=Lower segment; BMI=Body mass index; M=Male; F=Female

Table 2: MRI measurements# of olfactory apparatus and INSIT score*

	Olfactory bulb volume (mm^3)		Olfactory sulcus				INSIT score
			Depth (mm)		Length (mm)		
	Right	Left	Right	Left	Right	Left	
Control (n=22)	57.1±14.11	53.2±10.42	0.98±0.11	0.91±0.08	3.2±0.31	3.4±0.34	7.6±0.73
nIHH (n=20)	35.67±15.74	38.17±17.85	0.86±0.13	0.87±0.14	3.55±0.46	3.45±0.55	6.2±1.13
KS (n=20)	4.35±8.3	4.3±7.7	0.42±0.27	0.38±0.28	1.44±0.95	1.08±0.89	2.3±1.45
P^a (95% CI)	**<0.05** (11.42-31.44)	**0.001** (5.36-24.65)	0.08 (−0.1-0.26)	1.0 (−0.1-0.18)	0.19 (−0.84-0.12)	1.0 (−0.54-0.41)	0.001 (0.53-2.25)
P^b (95% CI)	**<0.05** (42.74-62.76)	**<0.05** (39.23-58.52)	**<0.05** (0.42-0.69)	**<0.05** (0.39-0.67)	**<0.05** (1.28-2.24)	**<0.05** (1.82-2.78)	**<0.05** (4.43-6.15)
P^c (95% CI)	**<0.05** (21.07-41.57)	**<0.05** (24-43.74)	**<0.05** (0.29-0.57)	**<0.05** (0.35-0.64)	**<0.05** (1.63-2.61)	**0.05** (1.88-2.86)	**<0.05** (3.02-4.78)

#Values are in mean±SD. *Analysis of variance was used to study the difference between KS, nIHH, and control. Bold values are significant. CI=Confidence interval. P^a statistical significance of differences between nIHH and control, P^b statistical significance of differences between KS and control, P^c statistical significance of differences between KS and nIHH

left sided and 2 bilateral) and none of the patients with nIHH. Hypoplastic OS was seen in 14 KS and 4 nIHH (2 left sides and 2 bilateral) patients, respectively. Normal OS was seen in 2 patients with KS.

Correlation between smell test and MRI

There was a good linear correlation between OB volume and the smell test score among all IHH subjects (r = 0.54, P = 0.013). Kappa index of 0.49 [95% confidence interval (CI): 0.10–0.88] indicated a moderate agreement between MRI olfactory apparatus and INSIT. All the patients with KS with aplastic olfactory apparatus had anosmia/hyposmia on the smell test.

Discussion

Few studies have used quantitative olfactory function testing and/or detailed radiological evaluation of the olfactory apparatus to assess the olfactory phenotypic spectrum in subjects with IHH.[10-12] The primary objective of our study was to measure the volume of OBs and dimensions of OSs using dedicated MRI sequences and objective smell testing with a clinical INSIT in patients with nIHH. The INSIT has already been used in Indian study to identify olfactory dysfunction in PD and compared with Sniffin' sticks test. In this study using a cut-off value of 4 (values ≤4 indicating disease), INSIT showed a sensitivity of 79.2% and specificity of 78%. INSIT is cheap, convenient, and more acceptable in the Indian population.[9] Some studies have used the history of decreased smell as a measure of olfaction.[13] This can underestimate the true prevalence of KS as exemplified in our study. Self-reporting of anosmia correlates well with the smell test, but self-reporting of normal smell is not reliable in all patients. The quantification of olfaction can be done using University of Pennsylvania smell identification test (UPSIT) which is well-validated, easy to use, and a reproducible test that correlates with odor detection thresholds, but is very expensive.[10] In our study, 12 of 32 patients reporting a normal sense of smell were actually found to have hyposmia/anosmia on formal smell testing by INSIT. This is similar to a observation made by Lewkowitz-Shpuntoff *et al.*[11] This would imply that the self-reporting of normosmia is an inaccurate measure of olfactory function; hence, there is a need to administer a quantitative olfaction test. However, those reporting anosmia need not undergo this test.

In our study, measurements were done using T2-weighted CISS images. Three-dimensional CISS is a refocused steady-state gradient echo MRI sequence that is flow compensated. CISS sequence plays an important role in evaluating structures surrounded by cerebrospinal fluid with high contrast and spatial resolution.[14] The advantages of CISS are high signal-to-noise ratio, high contrast-to-noise ratio, and intrinsic insensitivity to flow and motion.[15] The limitation includes long image acquisition times. We carried out MRI using this sequence in age- and sex-matched eugonadal controls also. Olfactory finding of control (mean OB volume, OSl, and OSd) is comparable to Koenigkam-Santos *et al.*[10] There was a statistically significant difference of OB volume between KS, nIHH, and control, and of OSl/OSd between KS and nIHH, but no statistically significant difference of OSl/OSd between control and KS/nIHH; similar findings were reported by Ottaviano *et al.*[16] We found that all the patients with KS have olfactory abnormalities on MRI. Four of 20 patients with nIHH have olfactory abnormalities. Previous studies have reported that 60%–90% of KS have olfactory abnormalities.[4,12,17,18] But a majority of these studies have defined KS on the basis of history only and did not use objective methods for olfaction testing. Comparison of previous similar study from India and developed countries with our study is shown in Table 3. The presence of bulb aplasia is a specific feature of KS and was not seen in any patient with nIHH; as against this OB/OS, hypoplasia is not specific to KS and is also seen in nIHH, and a similar finding was reported by Lewkowitz-Shpuntoff *et al.*[11] Vogt *et al.* also documented olfactory hypoplasia in 3 of 10 patients with nIHH.[6]

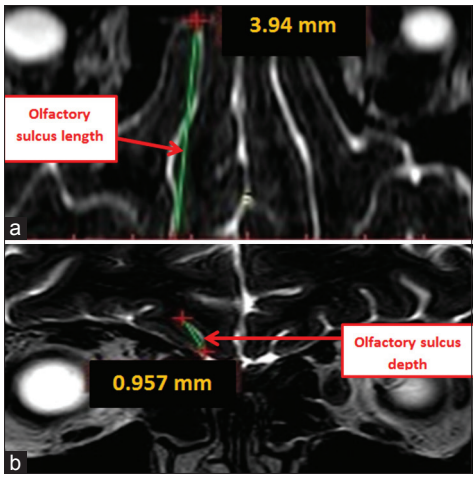

Figure 2: Measurements as shown in the images of a normal control: (a) Olfactory sulcus length (axial T2). (b) Olfactory sulcus depth (coronal T2)

We found a 50% prevalence of KS among patients with IHH. Previous studies reported 60%–65% prevalence of KS among IHH.[4,9] In our study, the male-to-female ratio was 6:1, which was higher than that seen in previous studies, which can be explained by less health-seeking behavior of females in India.[4,16]

We found a good linear correlation between OB volume and the smell test score among all subjects with IHH (r = 0.54, P = 0.013), similar to Jagtap *et al.* (r = 0.61, P < 0.01) and Ottaviano *et al.* (r = 0.64; P < 0.001).[4,19] We also noted that there is a moderate agreement between MRI findings and INSIT scores, especially between bulb aplasia and anosmia with a Kappa index of 0.49 (95% CI: 0.10–0.88). Koenigkam-Santos *et al.* reported a Kappa index of 0.87 (P = 0.001) between bulb aplasia and anosmia.[10] Jagtap*et al.* also reported Kappa index of 0.49 indicating moderate agreement between MRI olfactory apparatus and UPSIT.[4]

Table 3: Comparison of previous similar studies with our study

Reference	Patient characteristics	Smell test	MRI of olfactory apparatus	Correlation between OB volume and smell test score	Agreement between olfactory finding and smell test
Koenigkam-Santos *et al*. 2011[10]	21 KS, 16 control	UPSIT (14 anosmia, 6 hyposmia), 1 patient could not perform due to cognitive dysfunction	16 of 21 had OB aplasia, 2 of 21 OB hypoplasia	-	Kappa index 0.55; $P<0.001$ (moderate agreement)
Lewkowitz-Shpuntoff *et al*. 2012[11]	39 patients with nIHH	UPSIT (of 39 patients, 14 anosmic, 11 hyposmic, and 14 normosmic)	All anosmic, 7 of 11 hyposmic subjects and 1 of 14 normosmic subject showed olfactory abnormalities		
Jagtap *et al*. 2013[4]	41 patients with IHH (25 KS, 16 nIHH)	UPSIT (all 13 patients who reported anosmia and 12 of 28 patients who stated normosmia had low score on UPSIT)	Of the 41 patients, MRI showed normal (n=17), hypoplastic (n=14), and aplastic (n=10) olfactory apparatus, of 25 KS aplasia (56%) and hypoplasia (44%), all 6 patients with nIHH with abnormal MRI had hypoplasia	r=0.61; $P<0.01$	Kappa index: 0.72 (good agreement)
Anik *et al*. 2015[19]	6 KS	Sniffin' sticks test: of 6, 5 had anosmia and 1 had hypoplasia	Olfactory bulb aplasia in all 6	-	-
Ottaviano *et al*. 2015[16]	38 KS patients and 17 controls	Sniffin' sticks test (36 subjects were anosmic and 2 were hyposmic)	Anosmic patients had bilaterally significantly smaller OBs compared with hyposmic patients, whereas hyposmic patients did not differ significantly from controls	r=0.64; $P<0.001$	-
Our study	40 IHH (20 KS, 20 nIHH) and 22 control	INSIT (all 8 patients who reported anosmia and 12 of 32 patients who reported normosmia historically had a low score on INSIT, n=20 suggestive of KS)	Of the 20 patients with KS, 12 and 8 had aplastic and hypoplastic OB findings, respectively; of the 20 patients with nIHH, 16 had normal OB and 4 had hypoplastic OB	r=0.54, P=0.013	Kappa index: 0.49 (moderate agreement)

IHH=Idiopathic hypogonadotropic hypogonadism; KS=Kallmann syndrome; INSIT=Indian smell identification test; UPSIT=University of Pennsylvania smell identification test; OB=Olfactory bulb, r=Correlation coefficient

To the best of our knowledge, this is the first detailed study correlating objective smell test by INSIT with structural abnormalities in the olfactory apparatus on dedicated MRI from India in a sizable number of patients. The limitation of our study is that INSIT is not validated with UPSIT in patients with IHH. Although further studies are required to support these findings and clinical utility of INSIT in Indian patients.

Conclusion

Self-reported normal sense of smell grossly underestimates olfactory dysfunction in IHH. We suggest an objective smell test to distinguish KS from nIHH. Olfactory phenotype with quantitative smell test correlates well with MRI quantification of olfactory apparatus in IHH. INSIT, being cheap, convenient, and more acceptable in the Indian population, can be considered as a better alternative in the evaluation of olfaction in Indian subjects.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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