
Case report

Olfactory dysfunction in children with Kallmann syndrome: relation of smell tests with brain magnetic resonance imaging

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ABSTRACT

OBJECTIVE: Kallmann syndrome (KS) is a genetic disorder with the distinctive features of hyposmia or anosmia and hypogonadotropic hypogonadism. Though hyposmia/anosmia can be evaluated by both objective and subjective smell tests, there is no study comparing these two methods in KS. The aim of the present case series was to discuss the results of objective and subjective smell tests and compare them to volumetric magnetic resonance imaging (MRI). **METHODS:** A total of six adolescent males (aged between 14-18 years) with KS were examined by objective and subjective olfactometry to test smell function and by specific MRI sequences to measure the olfactory bulbs. **RESULTS:** The objective smell test showed anosmia in all six of the patients. However, the subjective test revealed anosmia in five patients and hyposmia in one patient. Brain MRI showed olfactory bulb aplasia in all six cases. **CONCLUSION:** MRI provides robust evaluation of the olfactory bulb volume. Our data show excellent compatibility between the results obtained via objective olfactometry and those obtained by measuring olfactory bulb volume as determined by MRI and therefore demonstrate that objective olfactometry remains a highly reliable test. Furthermore, although the number of subjects studied was small, these data also suggest that cheaper and more easily available subjective tests could be used in preference to the more expensive as well as labor-intensive and time-consuming objective smell tests. In the event of doubts as to the validity of the subjective tests, the objective olfactometry tests can confirm the diagnosis. The bulb volumetric MRI may be also used in difficult cases.

Key words: Anosmia, Kallmann syndrome, Magnetic resonance imaging, Smell test

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INTRODUCTION

Kallmann syndrome (KS) is a genetic disorder resulting from impaired physiologic migration of the olfactory and GnRH neurons during embryonic life. It is characterized by hypogonadotropic hypogonadism and anosmia/hyposmia.¹ The estimated prevalence of KS is 1/8,000 and it is five times more common in males than in females.² Approximately 60% of cases with KS are sporadic.³ Mutations in the *KAL1* gene are detected in 14% of familial cases and in 11% of sporadic cases.⁴ Apart from *KAL1* (Xp22.3), the genes responsible for the KS phenotype are the *KAL2* [*fibroblast growth factor receptor 1*] (*FGFR1*) gene (10%) and the *KAL4* [*prokinetecin receptor 2*] (*PROKR2*) and *KAL3* [*prokinetecin 2*] (*PROK2*) (9%) genes.⁵ In addition, the *KAL5* [*Chromodomain-helicase-DNA-binding protein 7*] (*CHD7*) gene and *KAL6* [*fibroblast growth factor 8*] (*FGF8*) are also candidate genes for KS.⁶ In a recent study, mutations in the *SEMA3A* gene were also reported to cause KS.⁷

In recent years, olfactometry has been increasingly performed for the detection, diagnosis and monitoring of many medical conditions, such as Parkinson's disease,^{8,9} Alzheimer's disease,^{10,11} multiple sclerosis^{12,13} and Kallmann syndrome.^{14,15} However, the number of olfactory performance-related studies in patients with KS is limited and the results of these studies are controversial.¹⁴⁻¹⁷ The existing studies have generally used subjective smell tests in the diagnosis of KS.^{14,17} Subjective tests are more individual-specific than objective tests and can be affected by many factors such as the sociocultural and socioeconomic levels of patients.^{18,19} In these subjective tests in which the patient's answers are critical, the patient can easily manipulate the test results. By contrast, because they are based on brain waves, objective tests seem to be more specific for the diagnosis of hyposmia/anosmia. For this reason, in our study smell function was analyzed using both subjective (Sniffin' Sticks Test) and objective (olfactometer-EEG) tests.

In 1987, magnetic resonance imaging (MRI) was first used to investigate alterations in structures related to olfactory function.²⁰ Thin-section MR images of the brain can be used to evaluate the olfactory bulbs in suspected KS patients.^{16,21-24} To date, there is no childhood study evaluating the relation of subjective

and objective smell tests with olfactory bulb volumes derived from specific MRI.

The aims of the present study were to measure olfactory bulb volumes of adolescents with KS by using special MRI sequences and to compare the results between objective and subjective tests and olfactory bulb volumes.

PATIENTS AND METHODS

Subjects

In all KS patients, clinical information including age at diagnosis, presenting symptoms, medical history, anthropometric measurements, puberty stage and treatment was obtained retrospectively from the hospital records.

Luteinizing Hormone Releasing Hormone (LHRH) test was performed in all of the patients. Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH) and testosterone levels were measured by the Chemiluminescent Microparticle Immunoassay (CMIA) method (Abbott Architect i2000, USA); in our laboratory, the intra-assay, inter-assay coefficients of variation (CV%) and sensitivity were 4.98%, 4.62%, 0.03 mIU/mL for LH; 4.97%, 5.34%, 0.05 mIU/mL for FSH; 7.12%, 7.63%, 0.07 ng/mL for testosterone, respectively.

Smell function was analyzed using both subjective (Sniffin' Sticks Test) and objective (EEG olfactometry) tests.

To assess the subjective smell function of patients, the Sniffin' Sticks Test was performed, this being a clinically widely-used olfactory test consisting of three subtests: a phenyl ethanol (rose odor) threshold test, a discrimination test and an identification task. In these tests the pens, which are 14 cm long with a 1.3 cm diameter, have a tampon which is filled with 4 ml liquid odorants dissolved in propylene glycol. For odor presentation, the cap was removed by the experimenters for approximately 3 seconds and the pen's tip was placed at an approximate distance of 2 cm from both nostrils. Applications were carried out in properly ventilated rooms with the use of odorless gloves and an eye mask. Application of the whole test took about 30-35 minutes. Previously published and recently updated norm values are available. Each

subtest has a maximum score of 16 points resulting in a maximum composite score of 48 points. The score is expressed as TDI (threshold, discrimination, identification) value, where values below 16 points denote functional anosmia and values above 30 points represent normosmia. The scores in between are considered to reflect hyposmia.^{25,26}

An olfactometer (Om2b, Burghart, Germany) was used for the assessment of objective olfactory function of the patients and to validate the results of the subjective tests. The main purpose of the use of the olfactometer is to produce isolated chemosensory stimulation without creating a temperature and pressure gradient between the odorant and air, thereby preventing stimulation of thermo- and mechanoreceptors located in the nose. Two different odors were used in the olfactometry procedure: carbon dioxide (CO₂) as a trigeminal stimulant and 2-phenyl-ethyl-alcohol (PEA) as a pure olfactory stimulant. Volumetric concentration values of both stimulants were 60%.^{27,28} An electroencephalography (EEG) recording was also performed by a 64-channel Synamps (Neuroscan, USA) system synchronously with the olfactometer and the recordings were analyzed by Scan 4.5 software programs.

MRI Technique

All patients were examined by means of a 1.5 Tesla MR unit equipped with a standard head coil. Turbo spin echo dual-echo T2 weighted axial (TR/TE/slice thickness: 2200/100-15/2mm) and fluid-attenuated inversion-recovery (FLAIR) axial (TR/TE/slice thickness: 1100/15/2mm), T2 weighted (TR/TE/slice thickness: 2200/100/2mm) and T1 weighted (TR/TE/slice thickness: 600/15/2mm) coronal sequences were performed.

In all patients both smell tests and MRI were performed at diagnosis before testosterone replacement was initiated.

RESULTS

Clinical and Laboratory Findings

All patients presented with short penile length and/or delayed sexual development between the ages of 14 and 18. Medical history revealed cryptorchid-

ism (n=3, cases 2, 5 and 6) and poor sense of smell (n=3, cases 1, 2 and 6) in three subjects. Physical examination revealed testicular volumes ranging between 0.5 and 5 mL. Out of six patients only one (case 5) had a family member (his two year-old male sibling) with cryptorchidism and micropenis. Basal and stimulated gonadotropin levels were consistent with hypogonadotropic hypogonadism (Table 1).

Smell Tests

The Sniffin' Sticks Test revealed anosmia in five patients and hyposmia in one patient (Table 2). In addition, EEG-olfactometry analysis showed normal brain responses to trigeminal stimuli and no response to pure olfactory stimuli, indicating anosmia in all of the patients. Individual EEG signals are depicted in Figure 1 for five subjects (the olfactometry record of one case could not be obtained).

Imaging

Brain MRI showed an aplasia of the olfactory bulb in all of the patients (Figure 2).

DISCUSSION

The present study demonstrated olfactory bulb agenesis in cranial MRI and anosmia in objective olfactometry in six adolescents. On the other hand, the subjective smell test showed anosmia in five and hyposmia in one adolescent with KS. Our cases presented with delayed puberty, consistent with the literature knowledge.¹ In one of our cases (case 1), short stature was the only presenting complaint. However, since short stature is an unusual finding in KS and the patient's target height was also short (data not given), his short stature was considered to be familial rather than being related to KS.

While hypogonadism is a constant clinical finding in patients with KS, the severity of anosmia may differ.²⁹ Since anosmia cannot usually be recognized by the affected individual, olfactory screening tests are recommended in the event of a clinical suspicion of KS, even when the patient reports a normal sense of smell.³⁰ Despite the absence of self-reported olfaction problems in cases 3, 4 and 5, detection of anosmia in olfactory testing supports the absolute requirement for testing the sense of smell in these patients. The

Table 1. Clinical and Laboratory Characteristics of the Patients with Kallmann syndrome

Finding	Patients					
	1	2	3	4	5	6
Age (years)	16	14	14.5	18	14	17
Major complaint	short stature and delayed sexual maturation	short penile length	short penile length	delayed sexual maturation	short penile length	delayed sexual maturation
Medical history						
Sense of smell	Poor	Poor	Normal	Normal	Normal	Poor
Undescended testes	No	Yes	No	No	Yes	Yes
Consanguinity	No	First degree	No	First degree	Second degree	No
Physical signs						
Testicular volumes (mL)	3	2	0.5	5	1	2
Pubic hair (Tanner stage)	IV	III	I	V	I	I
Basal						
LH	<0.1	<0.1	<0.1	0.5	<0.1	<0.1
FSH	0.4	0.4	0.4	0.8	0.2	0.5
Testosterone (ng/dL)	<20	<20	38	<20	<20	<20
LHRH test						
Peak LH	3.5	2.2	1.2	8	3.6	1.25
Peak FSH	3.6	4.3	3.0	3.0	2.8	3.05

LH: Luteinizing Hormone (mIU/mL); FSH: Follicle Stimulating Hormone (mIU/mL); LHRH: Luteinizing Hormone Releasing Hormone.

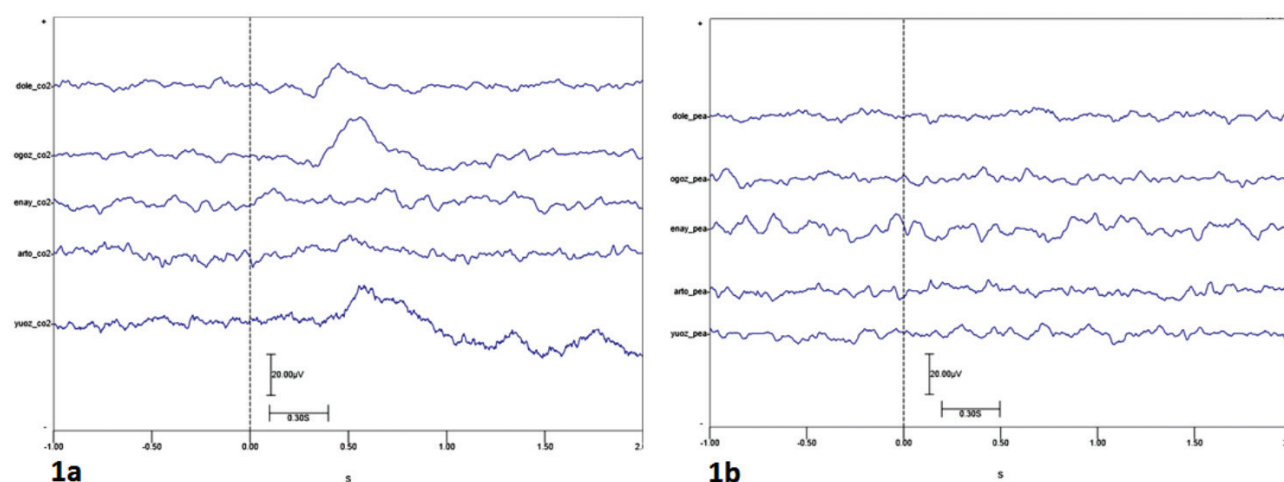


Figure 1. EEG signals of the five KS patients having undergone EEG olfactometry recording. **1a.** The brain responsiveness to the CO₂ (carbon dioxide) stimulant; **1b.** Brain responsiveness to the PEA (2 phenyl ethyl alcohol) stimulant. While the responsiveness to CO₂ stimulant is observed, no response is observed to the PEA stimulant.

number of subjective or objective odor measurement studies in KS patients is limited and their results do not show consistency with each other.^{14,16,17} Currently, widely-used subjective tests are Sniffin' Sticks, UPSIT (the University of Pennsylvania Smell Inventory Test),

CC-SIT (Cross Cultural Smell Identification Test), CCCRC (the Connecticut Chemosensory Clinical Research Center Test), ETOC (the European Test of Olfactory Capabilities) and SOIT (Scandinavian Odor Identification Test).^{17,25,26,31-33} Due to the involve-

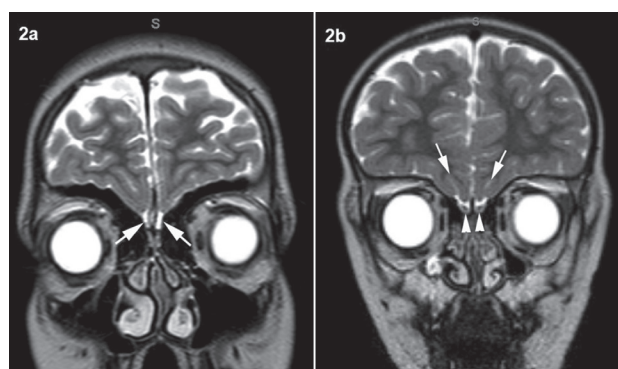


Figure 2. MR images of a case with Kallmann syndrome and a normal individual. **2a.** Coronal T2-weighted MR image: bilateral agenesis of the olfactory bulbs (arrows); **2b.** Coronal T2-weighted MR image shows normal olfactory tract (arrows) and olfactory bulbs (arrowheads).

Table 2. The results of the subjective olfactometry, objective olfactometry and brain MRI in Kallmann syndrome

Age (year)	MRI	TDI (subjective)	Sniffin' Sticks test (subjective)	Olfactometry (objective)
16	Aplasia	10	Anosmia	Anosmia
14	Aplasia	11	Anosmia	Anosmia
14.5	Aplasia	0	Anosmia	Anosmia
18	Aplasia	28	Hyposmia	Anosmia
14	Aplasia	14.5	Anosmia	Anosmia
17	Aplasia	0	Anosmia	Anosmia

Age in years; MRI: magnetic resonance imaging; TDI-Score: threshold-discrimination-identification.

ment of the factors related to the sociocultural and socioeconomic properties, subjective tests are more individual-specific than objective tests. Furthermore, in the case of a translation from the original test language to another language, the effectiveness may not be preserved in most of the aforementioned tests.^{18,19} Electroolfactography or EEG-olfactometry combination are the objective smell tests in which potential changes in the olfactory epithelium or brain responsiveness to olfactory stimuli are assessed regardless of the declaration of the individual. Consequently, objective tests are not affected by the individual.^{34,35} Simmen et al³⁶ emphasize that the objective measurement of the sense is the only way to assess olfaction in non-compliant patients or malingerers. On the other hand, Hummel et al³⁷ stated that if there is a brain

response to an olfactory stimulant, one can assume that there is an ability to smell and these signals have importance for medico-legal questions. Wortsman et al¹⁷ showed that pure odor discrimination was defective in KS and a trigeminal discriminatory ability was maintained in a decreasing pattern. The results of the objective smell tests in our study also supported the theory of decrement in brain responsiveness to trigeminal stimuli. In addition, Qu et al¹⁴ also did not find any brain responsiveness in 12 patients with KS, which is also demonstrated in this study (Figure 1).

The reported sensitivity of brain MRI in diagnosis of KS is high, ranging between 76% and 100%.^{16,21,22,38} Koenigkam-Santos et al¹⁶ compared the scores of quantitative MRI assessments and UPSIT tests in a group consisting of 21 patients with KS and 16 healthy controls and demonstrated agreement between MRI findings and a clinical smell test, especially in the presence of olfactory bulb aplasia and anosmia. They demonstrated rhinencephalon alterations in 18 of the 21 KS patients, with olfactory bulb and sulcus aplasia being the most common finding. They also emphasize MRI accuracy in the diagnosis of KS, especially when it is necessary to differentiate KS and idiopathic hypogonadotropic hypogonadism patients who may present an apparent normal sense of smell or olfactory function that is difficult or impossible to evaluate.¹⁶ It should also be noted that normal olfactory bulbs and sulci in MRI does not exclude the diagnosis of KS and normal anatomy of the olfactory structures can be found in patients with confirmed olfactory dysfunction.³⁹ In our study, bilateral agenesis of the olfactory bulbs in the brain MRI and anosmia in the objective smell test were detected in all of the patients. In addition, according to the results of the Sniffin' Sticks test, five patients were found to be anosmic, while one of them was hyposmic. Although hyposmia was detected in a patient in the subjective smell test, in this study the results of subjective and objective smell tests appear to be similar. However, there is at present no study comparing the sensitivities of these tests in the literature. This situation led us consider that subjective tests can be manipulated by the patients and that, as a result, objective olfactometry yielded a more reliable diagnosis of olfactory dysfunction. Nevertheless, larger studies are needed to confirm this hypothesis.

Limitations of the present study are the small number of study participants and the lack of a control group, which did not allow us to compare our data with those of healthy adolescents.

In conclusion, the present study is the first to demonstrate the compatibility between the results of MRI-derived olfactory bulb volumes and objective smell tests, suggesting that on suspicion of childhood olfaction disorder, the objective smell test is the most reliable diagnostic tool. However, although the number of cases is limited, these case reports indicate that the sensitivity of the subjective smell test is similar to that of the objective test. Our recommendation is that the subjective test should be employed primarily in KS cases because it is easier, cheaper and more readily available, while the objective test and/or cranial MRI investigations should be performed in cases yielding suspicious or unreliable results.

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