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Loss of smell but not taste in adult women with Turner's syndrome and other congenital hypogonadisms

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ABSTRACT

Objectives: To assess the impact of Turner's syndrome (TS) and other congenital hypogonadisms (OCH) on the sense of smell and taste.
Design: An analytical study of three independent cohorts was designed: patients affected by TS, OCH, and a control group of healthy women taking contraception.
Setting: Gynaecological Endocrinology Unit and Smell Clinic in Rhinology Unit of Hospital Clinic of Barcelona.
Participants: Thirty TS patients between 20 and 50 years of age receiving hormone replacement treatment (HT) were included as the exposed cohort; fourteen age-matched women with OCH taking HT were recruited; forty-three age-matched healthy controls receiving hormone contraception treatment were selected as the control group. This group was matched with an historical cohort of forty healthy women without contraception, used to validate BAST-24 in Hospital Clinic of Barcelona.
Interventions: Clinical history, presence of nasal symptoms, general physical examination, nasal endoscopy, and Barcelona Smell Test-24 (BAST-24) and gustometry were carried out on all patients.
Main measures: TS physical dysmorphology features, intensity of nasal symptoms and signs of nasal obstruction were collected. BAST-24 test included 24 odours to assess both sensory (detection, memory and forced choice) and sensitivity (intensity, irritability, freshness and pleasantness) odour characteristics, as well as 4 tastes to evaluate taste domains (detection and forced choice).
Results: Healthy women taking hormone contraception felt odours with more intensity ($p = 0.002$) and less irritability ($p < 0.001$) than the historical cohort. TS patients showed a significant impairment in smell memory ($p < 0.005$) and forced-choice ($p < 0.001$) compared with controls taking contraception, whereas no differences were found in odour sensitivity. Detection of taste was successful in 100% of patients. When considering only individual tastes, none of them showed statistically significant differences between groups.
Conclusion: Patients with TS show the impairment of smell but not of taste, compared to OCH and healthy controls taking contraception. Smell sensitivity was not affected.

1. Introduction

Disorders in olfactory function are common in the general population, frequently associated with chronic sinusitis and nasal polyposis, traumatic brain injury, upper respiratory tract infection or allergic rhinitis [1,2]. However, more than 200 conditions have been related with changes in olfaction, such as neurodegenerative disorders, chemical toxic agents or congenital diseases. As Kallmann syndrome, Turner's syndrome (TS) has been associated in medical literature with disordered olfactory and taste function [3]. Unfortunately, this association is based on anecdotal observations, and the mechanisms responsible for the loss of smell are poorly understood.

TS is a human genetic disorder affecting females, characterized by the absence of all or part of one X chromosome. It is the most common chromosomal disorder among women, with a prevalence of up to 1/2500 in living females [4,5]. The most important features of TS are short height and gonadal dysgenesis. In most cases, this condition leads to oestrogen insufficiency, with delayed puberty and primary amenorrhoea. Heart and kidney congenital malformations are associated, as well as several physical dysmorphology

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[6,7]. Increased morbidity with a number of medical conditions, such as osteoporosis, hypothyroidism, diabetes, dyslipemia, hearing loss or non congenital cardiac or neprho-urological changes, has been documented. Therefore, follow-up in specific gynaecological and endocrinological units is recommended with co-ordination between different specialities [7–10].

Considering smell and taste dysfunctions, only two studies have been published on TS patients. Nine TS women were found to have elevated detection and recognition thresholds to three odourants assessed, as well as sour and bitter thresholds using a taste test [11]. Valkov published similar findings in 20 patients with TS eight years later [12]. Some authors have reported that olfactory detection is higher in females than in males [13,14], although the explanation for these gender differences is not yet clear. The nature of odour identification, closely related to cultural items, usually limits the use of olfactory tests to the country or region where they have been developed and validated. Therefore, different odour-identification tests for clinical use have been developed in different countries [16,15–18]. Cardesín et al. [19] validated the Barcelona Smell Test 24 (BAST-24) as a reliable method to assess olfactory function in clinical practice for the Spanish and Mediterranean population.

The aim of this project was to analyse the type and prevalence of smell and taste abnormalities in adult patients with TS. Symptoms, physical and nasal examination, and olfactometry–gustometry by the BAST-24 were used for this purpose. Remarkably, to the best of our knowledge, no previous studies where TS women were compared with patients with other congenital hypogonadisms (OCH) in terms of smell and taste do exist. On the above evidence, the current investigation was undertaken to deal with this subject using TS patients, but also three appropriate comparator groups: OCH, a reference control group taking exogenous hormones, and an historical cohort of age-matched women not receiving hormones [19].

2. Materials and methods

2.1. Study design and population

An analytical study of three independent cohorts was designed. One cohort corresponds to TS patients recruited at the Gynaecological Endocrinology Unit of the Hospital Clinic of Barcelona. The diagnosis of TS was confirmed by blood karyotype showing total or partial absence of X chromosome, or other X abnormalities, in at least, more than 10% of read cells. Inclusion criteria were TS subjects between 20 and 50 years of age receiving hormone replacement treatment.

A second cohort was composed by women with OCH and wild-type karyotype. From this group, Kallman's syndrome patients were excluded due to the well-known absence of the smell sense. All of them were also receiving hormone replacement treatment due to their congenital hypoestrogenism.

The third cohort included non-exposed age-matched cases, as the study's control group, who were all treated with oestrogen and progestagens with the aim of contraception. They were recruited by the gynaecological department, none of them taking any other drug that may alter the study results.

Additionally, the sense of smell of the third cohort was compared with an historical cohort from 120 healthy volunteers without subjective olfactory disturbances, used for the validation of BAST-24 test in Hospital Clinic of Barcelona [19]. Only females between 20 and 50 years of age were selected from the 120 volunteers to match characteristics of the study's group, in order to avoid possible bias.

Exclusion criteria for the exposed and healthy cohort were the presence of acute or chronic pathologies non-related with the syndrome being studied which could interfere with the analysis, such as head injury, nasal polyps, exposure to toxics or severe asthma. The study was approved by the Ethics Committee of the Hospital Clinic of Barcelona and all patients were informed about the study and the interventions that would be performed. Signed informed consent was obtained from all patients at the time of inclusion.

2.2. Interventions

Clinical history and physical examination: Ages at diagnosis of hypogonadism, spontaneous menarche or primary amenorrhoea, diagnosis of cardiac or renal malformations were collected. Height, weight, description of phenotypic dysmorphology described in TS patients (epicanthus, ocular ptosis, strabismus, deformity in the pinna, micrognathia, cleft palate, short neck, pterygium colli, limbs lymphedema, cubitus valgus, genu valgum, low-set ears or low hair implantation, syndromic facies) were examined.

Nasal symptoms: The intensity of nasal obstruction, rhinorrhoea, nasal itching, sneezing, loss of smell, and facial pain were scored on a visual analogical scale (VAS). Score was performed on a 10 cm line where patients had to cross with a short perpendicular line from 0 (no symptom) to 10 (the most severe symptom).

Nasal endoscopy: A rigid endoscope (2.8 mm diameter and 30° angle) was used to examine the nasal cavities to evaluate nasal mucosa, septum deviation, turbinate and adenoid hypertrophy, and chronic rhinosinusitis with or without nasal polyps.

2.2.1. BAST-24 test – olfactometry

As previously described [19], 24 odours were used in the BAST-24: (a) 20 odours to assess the 1st cranial nerve (olfactory): banana, gasoline, lemon, rose, onion, smoked, anis, coconut, vanilla, melon, mandarin, bitter almond, pineapple, cheese, strawberry, mushroom, eucalyptol, clove, turpentine, and peach; and (b) 4 odours to asses the 5th cranial nerve (trigeminal): formaldehyde, vinegar, ammonia, and mustard. After being exposed for 5 s to an odourant, patients were asked to answer three questions for smell sensory domains: (1) to test smell detection: "Did you smell any odour?"; (2) to test smell recognition/memory: "Did you recognize this odour?"; and (3) to test smell forced-choice: "Which of these four odours did you smell?".

For smell sensitivity domains, four more questions were asked: (1) to test smell intensity: "Was the odour intense?"; (2) to test smell irritability: "Did you find the odour irritable, causing nasal itching or tearing?"; (3) to test smell freshness: "Did you find the same odour refreshing?"; and (4) to test smell pleasure: "Did you like this odour?". Answers to these questions were "yes/no".

2.2.2. Gustometry

Four powdered tastes were used for the gustometry test: sweet, salty, sour and bitter. After leaving with a hyssop a small quantity of each powder on the tongue, patients spread the powder all over the mouth for 5 s to detect the taste. Patients were asked two questions by the researcher: (1) to test taste detection: "Did you taste any substance?"; and (2) to test taste forced-choice: "How did the powder taste: sweet, salty, sour or bitter?"

2.2.3. Statistical analysis

Qualitative variables were described using frequency tables, whereas quantitative variables were described by their average and standard deviation. An unpaired Student's *t*-test was performed to compare quantitative variables, whereas a binomial test was undertaken to compare qualitative variables. To analyse the possible differences in BAST-24 and gustometry outcomes, a Kruskall–Wallis test was performed. In those cases showing significant difference, a *U*–Mann–Whitney test was carried out to know between which groups these differences existed. All statistical hypotheses to be tested were carried out considering an alpha