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ORIGINAL ARTICLE

The relationships between the clinical and polysomnographic findings and the olfactory function in patients with obstructive sleep apnea syndrome

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Abstract
Purpose This study aimed to investigate the relationships between the clinical and polysomnographic findings and the olfactory test results in patients with obstructive sleep apnea syndrome (OSAS).
Methods Four groups were established: non-snoring controls (group 1), non-apneic snorers (group 2), mild–moderate OSAS (group 3), and severe OSAS (group 4). The polysomnographic findings, otorhinolaryngologic findings, Epworth Sleepiness Scale (ESS), and Sniffin' Sticks olfactory test results of the four groups were compared. The relationships between the clinical data and the olfactory parameters were evaluated.
Results Group 4 had the worst odor identification and discrimination scores. Non-apneic snorers also had worse odor parameters compared with the non-snorer controls. A significant negative correlation was found among the ESS, apnea–hypopnea index (AHI), mean arterial oxygen saturation, and odor identification and discrimination. Significant negative correlations were found between the tongue and tongue base sizes and among all olfactory parameters.
Conclusion Our study revealed olfactory dysfunction in patients with OSAS. A strong negative correlation between the olfactory parameters and the severity of sleep apnea was also found. Olfactory tests may be used to predict the presence and severity of OSAS in the future.

Keywords Obstructive sleep apnea syndrome · Olfactory dysfunction · Polysomnography · Sniffin' Sticks

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Introduction

Obstructive sleep apnea syndrome (OSAS) is a disease characterized by recurrent upper airway obstruction episodes during sleep usually accompanied by arterial oxygen desaturation. The gold standard diagnostic tool for OSAS is polysomnography. A 1-h average of respiratory events, such as apnea and hypopnea during sleep, is called the apnea–hypopnea index (AHI). An AHI of more than 5 is considered OSAS. The prevalence of OSAS has been reported to be 24 % in males and 9 % in females. If left untreated, OSAS may lead to serious complications, such as hypertension, arrhythmia, myocardial infarction, and cerebrovascular diseases; memory and learning problems; and many neurocognitive and psychological diseases such as depression [1, 2]. A detailed systemic and otorhinolaryngologic examination and several questionnaires assessing quality of life and sleep are used in the evaluation of patients with OSAS. The Epworth Sleepiness Questionnaire (ESS), which evaluates daytime sleepiness, is currently one of the most frequently used questionnaires for this purpose [3, 4].

The sense of smell is a sensorineural system closely related to people's quality of life as it has an important role in detecting spoiled food, fire, early gas leak hazards, and flavor of food, as well as in relationships among people and between opposite sexes [5]. Sinonasal diseases, head trauma, central nervous system disorders that affect neurocognitive functions such as Alzheimer's and Parkinson's diseases, drugs, and

toxins are the most important causes of the disruption of the function of smell [6, 7]. Recent studies that investigated the olfactory function in patients with OSAS showed a negative correlation between the olfactory function and the severity of OSAS [8–10]. However, the relationships between the olfactory function and the physical examination findings have not been examined in patients with OSAS. Thus, we aimed to investigate the relationships among the polysomnographic findings, physical examination, ESS, and olfactory test results in patients with OSAS.

Methods

Study design

This double-blind, prospective clinical trial was performed at the Departments of Otolaryngology and Chest Disease in Ondokuz Mayıs University Faculty of Medicine, with the permission of the Ondokuz Mayıs University Faculty of Medicine Clinical Trials Ethics Committee (B.30.2.ODM.0.20.08/1083). Informed consent was obtained from all participants before the study began, and all investigations were conducted in accordance with the Declaration of Helsinki on biomedical studies involving human subjects. The study was conducted on 60 volunteers aged 18–65 years old who underwent all-night polysomnography between March 2014 and July 2014. The ESS was completed by each participant. The visual analog scale (VAS), which measures the intensity of snoring and has scores determined by the sleep partner ranging from 0 (no snoring) to 10 (severe snoring), was also used. We created four groups, namely, group 1: non-snorer healthy controls with AHI<5 and snoring VAS=0; group 2: non-apneic snorers with AHI<5 and snoring VAS>7; group 3: mild–moderate OSAS with AHI: 5–30; and group 4: severe OSAS with AHI>30. In addition, the olfactory parameters of the study group were performed by classifying the subjects as obese (BMI≥28 kg/m^2) and non-obese (BMI<28 kg/m^2) [11]. Each group had 15 volunteers, and 60 volunteers were included in the study for 80 % power with 90 % confidence to conduct comparisons in terms of the olfactory test and the otolaryngologic examination findings.

The exclusion criteria included patients with obstructive nasal pathology that causes conductive type olfactory dysfunction (nasal septum deviation, turbinate hypertrophy, nasal polyps, allergic rhinitis, etc.), metabolic and endocrine disorders (morbid obesity (BMI of ≥35 kg/m^2), diabetes mellitus, hypertension, malignancy, etc.), active upper respiratory infections within 2 weeks, previous nasal surgery, history of head trauma, antithyroid, antihistamine, antidepressant, or steroid medication history within the last 1 month, and current history of smoking.

Sleep study

Standard overnight polysomnography was performed in all subjects using the Embla® 54500 (UK). Polysomnography included eight electroencephalogram channels, an electrocardiogram, electrooculogram, surface electromyograms of the submentalis and bilateral anterior tibialis muscles, and position sensors to record body position and movements. Respiratory monitoring consisted of pulse oximetry, oral and nasal airflow measures, and thoracic and abdominal respiratory efforts. Apnea was defined as the complete cessation of airflow for at least 10 s, and hypopnea was defined as the period of reduction of at least 30 % oronasal airflow for a minimum of 10 s. The AHI was defined as the number of apneas and hypopneas per hour [10]. Sleep staging was conducted according to the standard criteria set by the American Academy of Sleep Medicine (Mild OSAS: AHI 5 and <15, moderate OSAS: AHI 15 and <30, and severe OSAS: AHI 30) [12].

Physical examination

The volunteers who underwent polysomnography and fulfilled the ESS were evaluated with a detailed otorhinolaryngologic examination, including the Muller maneuver with flexible nasopharyngoscopy (MMFN). The age, gender, height, weight, and body mass index of the patients were recorded. The otorhinolaryngologic examination findings, including nasal septum deviation, turbinate hypertrophy, status of the nasal mucosa and nasal cavities, uvula, soft and hard palates, palatine tonsils, and tonsillar pillars, oropharynx, maxillofacial anomalies, and laryngeal examination, were recorded by two examiners who were blind to the patients' polysomnography and olfactory findings. Each examiner has scored the findings independent from the other, and the final score was the average of two scores for all examinations. While in neutral position, tongue size was classified into grades 1 to 4 (1: soft palate and palatine tonsils visible; 2: soft palate visible but tonsils not visible; 3: hard palate visible but soft palate not visible; and 4: only hard palate visible), and palatine tonsils were classified into grades 0 to 3 (0: tonsils, pillars, and soft palate are clearly visible; 1: uvula, pillars, and upper pole are visible; 2: only part of the soft palate is visible but the tonsils, pillars, and base of the uvula are not visible; and 3: only the hard palate is visible) using the Friedman classification [13]. The nasal endoscopic examination was conducted with 0° rigid endoscope, and septal deviation was classified into grades 0 to 3 according to the Dreher classification (0: no deviation; 1: slight deviation; 2: moderate deviation; and 3: severe deviation). The hypertrophy of the inferior turbinates was classified into grades 0 to 2 (0: no hypertrophy; 1: slight hypertrophy; and 2: severe hypertrophy [14]. Pathologies of the middle turbinate, nasopharynx, and adenoid hypertrophies were noted, if any. Subsequently, each patient

underwent a flexible nasopharyngoscopy. The size of the tongue base was graded from 0 to 3 (0: vallecula completely visible; 1: vallecula partly visible; 2: tongue base touching the epiglottis; and 3: tongue base pushing the epiglottis), followed by the Muller maneuver to estimate the degree of obstruction in the oropharynx, the base of the tongue, and the velum. The degree of obstruction was graded from 1 to 4 (1, 0–25 %; 2, 25–50 %; 3, 50–75 %; and 4, 75 %<) for the two directions as lateral or anteroposterior at the retropalatal, oropharyngeal, and retrolingual levels.

Olfactory testing

After the otolaryngologic examination, all volunteers underwent a validated Sniffin' Sticks (Burghart GmbH, Wedel, Germany) smell test. The test was performed by a different physician who was blind to the patients' clinical status and study group. Odorants were presented using commercially available felt-tip pens. During odor presentation, the pen's cap was removed by the experimenter for 3–4 s, and the tip of the pen was placed 15 to 25 mm in front of the participant's nostrils. Odor identification and discrimination were assessed using 12 common odors. Using a multiple forced-choice paradigm, the subjects identified individual odors from a list of four verbal descriptors each, with an interval of at least 30 s, to prevent olfactory desensitization [15]. The subjects were free to sample the odors as often as necessary to make a decision. The test result was the sum score of the correctly identified odors. The maximum score for each subtest is 12, resulting in a maximum composite score of 24 (discrimination and identification score).

Statistical analyses

Data analysis was performed using SPSS 21.0 (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL, USA). The distribution of the variables was first evaluated using the Kolmogorov–Smirnov test. The number of cases was used for categorical variables and mean±standard deviation for continuous variables. Using the general linear model, ANOVA was used for intergroup comparisons. Correlational analyses were conducted according to Pearson's correlation. A p value of 0.05 was considered statistically significant.

Results

The 60 volunteers who participated in the study had a mean age of 51±13.6 and were composed of 44 males (73 %) and 16 females (27 %). No significant difference was found among the four groups in terms of age and gender distribution ($p>0.05$). Group 1 had the best and group 4 had the worst odor identification, discrimination, and total odor scores. The descriptive statistical data and results of the olfactory test of the four groups are presented in Table 1.

When the relationship between the olfactory parameters and the polysomnographic data was examined, significant negative correlations were found among all the olfactory parameters and the mean arterial oxygen saturation, lowest oxygen saturation, AHI, and AHI-REM. The AHI and total odor scores of all the participants are presented in Fig. 1. No significant correlation was found between the AHI in the non-REM sleep stage and the olfactory parameters. A significant negative correlation was detected between the AHI-supine

Table 1 Descriptive statistics of results from polysomnography, olfactory testing, and Epworth Sleepiness Scale (ESS) results

	Group 1 (controls, n=15)	Group 2 (non-apneic snorers, n=15)	Group 3 (mild–moderate OSAS, n=15)	Group 4 (Severe OSAS, n=15)	p value
Age	50.2±13.5	51.7±12.6	52.1±9.8	51.5±10.6	0.551
Gender (Female/male)	4/11	5/10	3/12	4/11	0.926
BMI (kg/m^2)	27.2	27.8	29.4	32.6	0.024[a]
AHI	2.6	3.9	18.7	49.5	<0.001[a]
AHI-REM	3.2	4.6	25.6	58.4	<0.001[a]
AHI-non-REM	2.3	2.8	13.1	44.5	<0.001[a]
AHI-supine	4.6	5.8	28.0	62.3	<0.001[a]
AHI-non-supine	0.8	1.7	11.7	38.7	<0.001[a]
Ort. SaO_2 %	95.8	96.5	92.3	90.6	<0.001[a]
Min. SaO_2 %	91.6	91.4	85.8	82.2	<0.001[a]
ESS	7.1	8.2	9.8	11.2	<0.001[a]
Odor identification score	9.1	8.5	7.2	6.1	<0.001[a]
Odor discrimination score	10.8	10.4	9.4	8.1	<0.001[a]
Total odor score	19.9	18.9	16.6	14.2	<0.001[a]

[a] Statistically significant

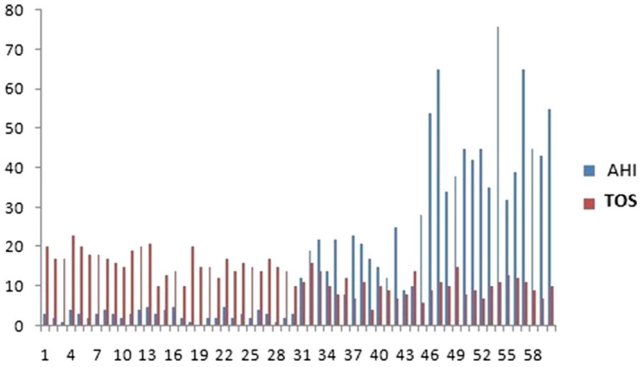

Fig. 1 The AHI and total odor scores of the participants

and the olfactory parameters when the positional AHI and olfactory test results were compared. However, no significant relationship was found between the AHI in the lateral and prone positions and the olfactory test parameters. A significant negative correlation was found between ESS and the olfactory parameters (Table 2).

Significant negative correlations were found between tongue and tongue base size and among all the olfactory parameters. No significant relationship was found between tonsil grade and the olfactory parameters. When the relationships between the grade, level, and side of narrowing during the MMFN and the results of olfactory test were evaluated, significant negative correlations were found between the odor identification scores and the severity of the anteroposterior narrowing at the tongue base at the retropalatal level and that of the lateromedial narrowing at the oropharyngeal level. Moreover, a significant negative correlation was found between the anteroposterior narrowing at the tongue base level and the odor discrimination scores (Table 3). The comparisons revealed no significant differences in terms of odor parameters, when the subjects were evaluated as obese (BMI≥28 kg/m^2) and non-obese (BMI<28 kg/m^2) in the total group (Table 4).

Discussion

Healthy sleep is crucial to the memory function of many tissues and organs and also to synaptic homeostasis. The complicated processes observed during sleep result in the resetting of synaptic circuits and thereby facilitate the storage of previous and new data. In the slow-wave phase of sleep, the piriform cortex is desensitized against olfactory stimuli, while the connections between the piriform cortex and other cortical and limbic regions are more active during sleep when compared to the waking period. Olfactory experiences gained during awakeness are stored through this mechanism [16, 17]. Our study demonstrated that odor identification and discrimination are reduced in patients with OSAS compared to in healthy adults and that there is a strong negative correlation between the severity of sleep apnea and the olfactory parameters. The interruption of sleep, insomnia, intermittent night hypoxia, deterioration of REM and non-REM sleep quality, and daytime sleepiness observed in patients with OSAS result in the reduction of activity in the thalamus and the prefrontal and posterior parietal cortexes, cellular loss in the hippocampus and the prefrontal cortex, cognitive failure, and loss of attention [8, 16, 17]. We believe that these changes and their clinical outcomes are the major causes of the reduction in the odor identification and discrimination abilities in patients with OSAS. Studies have demonstrated that the basic olfactory perception was not sufficient for normal olfactory function and that memory, olfactory memory, and synaptic plasticity were needed as well. It has been known that in OSAS characterized by apnea and hypopnea attacks and frequently accompanied by arterial oxygen desaturation during the night, very frequent interruption of sleep, shortening of the REM period, and excessive sleepiness during daytime, the memory and cognitive functions are negatively affected [16–20]. It has been known for a long time that many disorders impairing

Table 2 Pearson correlation coefficient between the olfaction parameters, polysomnographic parameters and Epworth Sleepiness Scale (ESS)

	Odor identification score		Odor discrimination score		Total odor score	
	Pearson correlation coefficient	*p*	Pearson correlation coefficient	*p*	Pearson correlation coefficient	*p*
AHI	−0.82	<0.001	−0.87	<0.001	−0.85	<0.001
AHI-REM	−0.86	<0.001	−0.89	<0.001	−0.87	<0.001
AHI-non-REM	−0.19	0.053	−0.24	0.032	−0.23	0.045
AHI-supine	−0.64	<0.001	−0.61	<0.001	−0.62	<0.001
AHI-right lateral	−0.16	0.061	−0.21	0.105	−0.18	0.047
AHI-left lateral	−0.13	0.070	−0.19	0.085	−0.17	0.076
AHI-prone	−0.20	0.056	−0.27	0.051	−0.23	0.054
Mean SaO_2 %	−0.44	<0.001	−0.40	<0.001	−0.42	<0.001
Minimum SaO_2 %	−0.53	<0.001	−0.58	<0.001	−0.55	<0.001
ESS	−0.75	<0.001	−0.85	<0.001	−0.81	<0.001

Table 3 Pearson correlation coefficient between the olfaction parameters and the grade of tongue, tonsil, and tongue base sizes and the severity of anteroposterior (AP) and lateromedial (L) narrowing at the retropalatal, oropharyngeal, and tongue base levels

	Odor identification score		Odor discrimination score		Total odor score	
	Pearson correlation coefficient	*p*	Pearson correlation coefficient	*p*	Pearson correlation coefficient	*p*
Tongue size	−0.78	0.001	−0.83	<0.001	−0.81	<0.001
Tonsil size	−0.16	0.070	−0.19	0.083	−0.17	0.075
Tongue base size	−0.19	<0.001	−0.24	0.032	−0.23	0.005
Retropalatal AP	−0.60	<0.001	−0.11	0.063	−0.42	<0.001
Retropalatal L	−0.16	0.061	−0.21	0.105	−0.18	0.072
Oropharyngeal AP	−0.16	0.072	−0.19	0.085	−0.17	0.079
Oropharyngeal L	−0.60	0.002	−0.27	0.051	−0.43	0.034
Tongue base AP	−0.34	<. 001	−0.70	<0.001	−0.57	<0.001
Tongue base L	−0.21	0.084	−0.58	0.075	−0.45	0.079

the cognitive functions, especially Alzheimer's and Parkinson's diseases, schizophrenia, and depression, also negatively affect the olfactory sense, which has been shown by a number of studies [19–21]. However, no sufficient study exists on the relationship of OSAS and olfactory disorders, which seems to possibly cause olfactory impairment due to the two impairments in the cognitive functions, memory and reduced attention, and to the abnormalities and obstructions within the upper respiratory tract anatomy. In one of the several studies conducted on the subject, Fu et al. [9] reported that the olfactory test parameters were negatively affected by the structure of the nose and the section of the nasal area in patients with OSAS. It is obvious that obstructive nasal pathologies, particularly nasal septum deviations, would cause some type of olfactory loss. In our study, we excluded patients with obstructive nasal pathologies that may cause conductive type olfactory disorders and aimed to investigate the effects of OSAS primarily through memory and cognitive functions. In a recent study by Salihoğlu et al. [8], a strong negative correlation was detected between AHI and mean oxygen saturation during the night and olfactory parameters in patients with OSAS. In the same study, a negative correlation was detected between AHI and bilateral olfactory bulbus volume as well, but no effect of OSAS was reported on the retronasal olfactory scores. Accordingly, the exclusion of patients with obstructive nasal septum deviation in the study [8] resulted in the influence of conductive type olfactory loss on the olfactory scores as well, and the inability to exhibit the absolute cognitive effects of OSAS on the olfactory sense. Similar to the findings of Salihoğlu et al. [8], a strong negative correlation was detected between AHI and mean arterial oxygen saturations and ESS and olfactory parameters in our study. However, no significant difference was detected between the olfactory parameters in REM and non-REM periods in their study, whereas we detected a significant correlation between AHI-REM and olfactory parameters. On the other hand, no significant correlation was observed between AHI-non-REM and olfactory parameters. This difference may be due to the possibility of using minimal oxygen saturation in the REM period instead of in the AHI-REM period in the study conducted by Salihoğlu et al. [8] during the investigation of REM-olfactory relationship. Our results demonstrate that the impairments related to the REM period in which partial muscle paralysis is observed and which have important effects on memory functions may be accompanied by olfactory disorders. Miyomoto et al. [10] reported that an olfactory recognition test could be an indicator of REM-related sleep behavior disorders.

Table 4 The comparisons in terms of odor parameters, when the subjects were classified as obese (BMI≥28 kg/m^2) and non-obese (BMI<28 kg/m^2) in the total group

	Obese	Non-obese	*p*
N	23	37	
BMI (kg/m^2)	31.23	23.54	<0.001
Odor identification	7.46	7.57	0.665
Odor discrimination	8.89	8.94	0.421
Total odor score	15.62	15.37	0.480

Our study was the first to investigate the correlation between the examination findings and the olfactory parameters in patients with OSAS. Furthermore, the correlation between the positional distribution of respiratory disorders during sleep and olfactory parameters has not been studied previously. In our study, a strong negative correlation was detected between the tongue and tongue base hypertrophy and the severity of the anteroposterior narrowing at the tongue base level during Muller maneuver and odor identification and discrimination. Furthermore, a significant negative correlation was detected between the severity of the obstruction at the lateral diameter of the oropharynx level and the anteroposterior diameter of the palatal level and the odor identification scores. Another important outcome of the study was the comparison of the olfactory functions of healthy controls and simple snoring patients,

which had not been studied before. The odor identification and discrimination scores of the snoring patients were found to be significantly reduced compared to those of the healthy controls. This demonstrates that it is not only the oxygen desaturation and apnea–hypopnea, but also the snoring which causes a frequent entry in the REM sleep phase and disrupts the distribution of the sleep cycles affected the olfactory function, when compared to the non-snoring patients. The effect however was not as severe as it is in patients with OSAS.

The duration of the OSAS is just as important as the severity of the disease measured by AHI. It was a limitation of our study that disease duration was not a parameter. The majority of patients who underwent polysomnography and were diagnosed with OSAS have been treated with positive airway pressure or surgical treatment. We did not use disease duration as a parameter because we came to the conclusion that it can be problematic to include in the study the PAP non-compliant patients who had been diagnosed a long time ago, or to classify patients by querying only the duration of symptoms without a previous polysomnography. On the other hand, in our study, the pathologies which have been proven to affect the olfactory function independently from OSAS were excluded. In this context, we excluded subjects with endocrine and metabolic disorders. It was shown that many neurocognitive and mood factors are very similar in obese patients with and without OSAS [22]. Although morbid obesity was an exclusion criterion, patients who were overweight or severely obese were not excluded from the study. We believed their exclusion might adversely affect the reliability of our results in evaluating OSAS independently from its major etiologic factor. In addition, the lack of objective clinical evidence showing the negative impact of obesity on olfactory functions independent from OSAS has also affected our exclusion criteria. Regardless, our findings did not show a significant effect of obesity on olfactory parameters, which may be due to the non-normal distribution of the number of patients within the groups or the exclusion of morbidly obese patients.

Conclusion

Our study demonstrated that odor identification and discrimination are reduced in obstructive sleep apnea syndrome compared to healthy adults and that a strong negative correlation is present between the severity of the sleep apnea, daytime sleepiness, and olfactory parameters. Two clinical results can be concluded from the findings of this study. First, patients with OSAS should be carefully evaluated for olfactory dysfunction. Second, the strong correlation between the severity of sleep apnea and olfactory parameters showed that olfactory tests may be used as a parameter to predict the presence and severity of OSAS in the future. We believe that our study should be followed by further studies conducted with larger sample sizes and the investigation of the effects of treatment on olfactory function.

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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