Assessment of olfactory and gustatory functions in COVID-19 patients

Abstract

Background/aim: This study aims to evaluate of olfactory and gustatory functions of COVID-19 patients and possible risk factors for olfactory and gustatory dysfunctions.

Materials and Methods: The cross-sectional study included adult patients who were diagnosed with COVID-19 in XXXX University Hospital between April 2020 and June 2020. Volunteered patients participated to a survey in which olfactory and gustatory functions and various clinical information were questioned. Sinonasal Outcome Test-22 was also administrated to all patients.

Results: A hundred and seventy-one patients participated in this study. Olfactory and gustatory dysfunctions rates were 10.5% (n:18) and 10.5% (n:18) respectively. Patients without any symptom other than smell and taste dysfunctions were clustered as group 1 and patients who are clinically symptomatic were clustered as group 2. Olfactory dysfunction occurred in 8% of Group 1 and 17.4% of group 2 (p=0.072). Gustatory dysfunction rate of smokers was 19.7% and significantly higher than gustatory dysfunction rate of non-smokers (5.5%) (p=0.007). Twenty-seven-point-eight percent of the patients with olfactory dysfunction (n=5) were male and 72.2% (n:13) were female. Gender did not show significant effect on rate of olfactory dysfunction. Twenty-five patients participated in psychophysical olfactory function test. No participant reported olfactory dysfunction at the time of test. 64% of the participants (n:16) were normosmic and 36% of the participants (n:9) were hyposmic according to Sniffin' Stick test.

Conclusion: Olfactory and gustatory dysfunctions are more common in patients who are clinically symptomatic than those diagnosed during filiation. Objective tests may show that

frequency of olfactory dysfunction is greater than frequency of self-reported olfactory dysfunction.

Keywords: COVID-19, anosmia, ageusia, sniffin sticks

1. Introduction

Corona virus disease 2019 (COVID-19) is a pandemic that emerged from East Asia in late 2019 and rapidly spread to the rest of the world and caused by Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) [1]. The disease is held responsible for more than 2 million deaths worldwide and still poses a threat to the public health in most of the countries. The most common manifestations of the disease are fever, coughing, sore throat, and dyspnea [1, 2].

Smell and taste dysfunctions have been frequently reported since the onset of the disease. In one of the very first reports of the neurologic manifestation of the disease, Mao et al. reported anosmia and ageusia in 5.1% and 5.6% of the cases respectively [3]. Although, incidences of taste and smell dysfunctions vary among the reports, Lechien et al. reported that, 85.6% of the patients in Europa have suffered from olfactory dysfunction and 88.8% had gustatory dysfunction [4]. Early reports claimed chemosensory disorders may be the initial signs of the disease, especially in the asymptomatic patients [4-7]. Sudden onset of anosmia and ageusia within 24-48 hours is reported to be highly predictive for the disease and these symptoms often occur within 5 days from the onset of disease [8].

Alternation of chemosensory functions due to a viral infection is not a new phenomenon for otolaryngologists. In adults, 40% of anosmia cases are caused by a viral upper respiratory tract infection [9]. Common pathogens of upper respiratory tract, rhinovirus, parainfluenza, Epstein-Barr virus, and coronavirus are known to cause olfactory and gustatory dysfunctions [10, 11]. On the other hand, olfactory dysfunction pathogenesis in COVID-19 seems to be on a

different aspect since anosmia may occur without rhinorrhea or any other findings related to upper respiratory tract infection [4, 8]. Lechien et al., reported the occurrence of anosmia or hyposmia in the absence of rhinorrhea and nasal congestion in 79.7% of the patients [4]. To explain mechanism of chemosensory disorders in COVID-19 several hypotheses were raised. SARS-Cov-2 binds directly the angiotensin converting enzyme 2 (ACE 2) cell receptors. ACE2 receptors take place frequently on olfactory epithelium and on oral cavity mucosa particularly on the tongue but may also be detected on glial cells and neurons of Central Nervous System (CNS) as well [12-14]**.** Epithelial damage of nasal and oral mucosa may have a role in olfactory and gustatory dysfunctions [15, 16]. SARS-CoV-2 is shown to be neuro-invasive and invasion of the olfactory nerve and trigeminal nerve may cause olfactory and gustatory dysfunctions [17]. Another hypothesis claims, CNS involvement with focal encephalitis in olfactory and gustatory cortex may be cause of olfactory and gustatory dysfunctions. The detection of viral RNA in cerebrospinal fluid of the patients may support this hypothesis [3].

Even though mechanism of olfactory and gustatory dysfunctions in COVID-19 patients is not fully discovered, these symptoms keep importance for suspecting of disease and early diagnosis. In this study we aim to evaluate olfactory and gustatory dysfunctions of COVID-19 patients with a subjective self-reported questionnaire. We also investigated long-term effects of COVID-19 on olfaction with an objective psychophysical test.

2. Material and Methods

2.1.Study Design

This cross-sectional study was approved by XXXX University Ethical committee of clinical research. The study included adult patients who diagnosed with COVID-19 in xxxx

University Hospital between April 2020 and June 2020. The diagnosis was made with a positive SARS-Cov-2 PCR test. The patients were invited to this study by phone y. All participants provided informed consent. In the survey, each patient was interviewed about basic demographic info, the time of diagnosis, hospitalization time, presence of olfactory and gustatory dysfunctions, onset of these symptoms (days before or days after diagnosis), recovery of olfactory and gustatory dysfunctions, history of any rhinologic surgery. Sinonasal Outcome Test-22 (SNOT-22) was also administrated to all patients. Patients with the history of smell or taste dysfunctions prior to COVID-19 and history of previous rhinologic surgery were excluded from study. Two hundred and ninety-eight patients had been diagnosed with COVID-19 between April 2020 and June 2020. Ninety-six patients refused to participate in the study. Five patients with olfactory dysfunction prior to COVID-19 and 26 patients with a history of rhinologic surgery were excluded from the study. A hundred and seventy-one patients met the inclusion criteria.

Information on disease severity and treatment modality was obtained from Patients' files. Patients were divided into groups according to disease severity. Patients without any symptom other than smell and taste dysfunction were clustered as group 1 and patients who are clinically symptomatic were clustered as group 2. Group 2 was further divided in two groups as the patients with pneumonia were clustered as group 2b and the others were clustered as group 2a.

2.2.Psychophysical Olfactory Evaluation

Patients whose recovery of the disease was shown with two consecutive negative SARS-CoV2 tests were invited to the clinic for objective assessment of olfaction with Sniffin' stick test battery (Sniffin' Sticks, Burghart GmbH, Wedel, Germany). Twenty-five patients volunteered to participate. The test performed within 45 days and at least 30 days after the

diagnosis of COVID-19. No participant had a history of head trauma or another episode of upper respiratory tract infection after the diagnosis of COVID-19. The tests were performed as previously described by Rumeau et al. [18]. All the tests were performed in a well ventilated, odor-free room. The investigator who performed the test implemented Personal Protective Equipment during the procedure. An interval of at least 8 hours took place between tests to prevent spread of the disease. Threshold (T), Discrimination (D), Identification (I), and global scores (TDI) were recorded for each patient. Patients with a TDI score lower than 15 is considered as anosmic, patients with a score between 15 and 30 is considered as hyposmic and, patients with a score equal to or higher than 30 is considered as normosmic.

2.3.Statistical Analysis

Statistical analysis was performed with IBM SPSS v 22.0 (IBM Corp, Armonk, New York). The Shapiro Wilk test was used for assessing normality. To display demographic information, mean ± Standard Deviation (SD) was used for normally distributed variables and median (min-max) for non-normally distributed variables. Chi-Square was used for categorical data. The Student-t test and Mann-Whitney U test was used to compare the normal and non-normally distributed data between two groups, respectively. Spearman's rank correlation coefficient was used for correlation of non-normally distributed data. The level of statistical significance was set at $p \leq 0.05$ with a 95% confidence interval.

3. Results

3.1.Demographic Findings and The Survey

A hundred and seventy-one patients participated in this study. 58.5% (n:100) of the participants were female and 41.5% (n:71) were male. The median age of the participants was 36 (min-max 18-71). 35.7% of the patients (n:61) were smokers and 12.9% of the patients

(n:22) were previously diagnosed with allergic rhinitis. Participants' demographic and clinic information is summarized on **Table 1**.

Patients were clustered in three groups according to disease severity, 73.1% of the patients (n:125) were in Group 1 (asymptomatic other than smell or taste dysfunction), 20.5% (n:35) were in group 2a (symptomatic disease without pneumonia) and 6.4% (n:11) were in group 2b (with pneumonia). In total, 26.9% of the patients (n:46) were clinically symptomatic (group 2).

Patients who suffered olfactory dysfunction and gustatory dysfunction comprised 10.5% (n:18) and 10.5 (n:18) of all patients, respectively. Olfactory and gustatory dysfunctions were together in 6.4% of the patients (n:11). Clinical information of patients with and without olfactory dysfunction was summarized on **table 2** and clinical information of patients with and without gustatory dysfunction was summarized on **table 3.** Olfactory dysfunction occurred before diagnosis in 8 patients. The median time between onset of olfactory dysfunction and diagnosis was 2.5 days (min-max:1-5). In 10 of the patients, olfactory dysfunction occurred after diagnosis with a median interval of 1 day (min-max:1-7). All but one patient recovered from olfactory dysfunction in in a median time of 7 days (min-max:0-30). One patient was still suffering olfactory dysfunction 45 days after diagnosis. Gustatory dysfunction was occurred before diagnosis in 8 participants within a median time of 2 days (min max:1-5) and after diagnosis in 10 participants within a median time of 1 day (min-max:1-3). Gustatory dysfunction resolved in 16 of the patients within a median time of 8.5 days (min-max 1-30).

Olfactory dysfunction occurred in 8% of Group 1 and 17.4% of group 2**.** Olfactory dysfunction rate in group 1 was lower than group 2 but that was not statistically significant (p=0.072). Olfactory dysfunction rates in group 2a and 2b were 17.1% and 18.2% respectively. Gustatory dysfunction occurred in 8% of Group 1 and in 17.4% of group 2 and that was not

144 statistically significant (p=0.072). Gustatory dysfunction rates in group 2a and 2b were 17.1%
145 and 18.2% respectively.

146 The median ages of the patients who suffered olfactory dysfunction and who did not were
147 39.5 years (min-max:18-55) and 36 years (min-max:19-71) respectively (p>0,005).

148 Patients with a previous diagnosis of allergic rhinitis had a higher olfactory dysfunction
149 rate compared to the other patients (22.7% and 8.7% respectively) but that was not statistically
150 significant (p>0.05). Gustatory dysfunction rates were also higher in the patients with allergic
151 rhinitis (22.7% vs 8.7%) (p>0.05).

152 Olfactory dysfunction rates in smokers and non-smokers were 13.1% and 9.1%
153 respectively. Gustatory dysfunction rate of smokers was 19.7% and significantly higher than
154 gustatory dysfunction rate of non-smokers (5.5%) **(p=0.007).**

155 Olfactory dysfunction occurred in 7.0% of the male patients and 13.0% of the female
156 patients but that difference was not significant (p=0.16).

157 Mean recovery time of olfactory dysfunction was 17.3±12.3 days in Group 2 and 9.2±8.2
158 days in group 1. The difference was insignificant. (p>0.05) The mean recovery time of olfactory
159 dysfunction of smokers was 12.6±11.5 days and was similar with the mean recovery time of
160 non-smokers (12.4±10.3 days).

161 **3.2.SNOT-22 questionnaire**

162 The mean SNOT-22 score of all patients was 11.6±13.2 (min-max 0-59). In group 1, 2a
163 and 2b mean scores were 10.3±11.7, 17.9±17.2, 6.73±9.9 respectively. There was not
164 statistically significant difference between SNOT-22 scores of group 1 and group 2 (p=0.19).

165 The mean SNOT-22 score of patients who suffered olfactory dysfunction was 20±13.4
166 and the mean score of patients who did not, was 10.6±12.9. The difference was statistically

significant. (p=0.001) **(Table 4)**. The mean SNOT 22 scores of patients who had gustatory dysfunction and who did not were 27.2±14.9 and 9.8±11.8 respectively. The difference was also statistically significant p<0.001). Analysis of the correlation between SNOT-22 scores and recovery times (days) of olfactory and gustatory dysfunctions did not show significance (p>0.05 R:0.315).

3.3.Psychophysical Olfactory Evaluation

Objective olfactory evaluation with Sniffin' sticks test battery was performed to 25 volunteered patients. 52% of them (n:13) were female and 48% (n:12) were male. The median age of the patients was 38 years (min-max 23-52). Twenty-two patients were in group 1 and three patients were in group 2a. 24% of the patients had a previous diagnosis of allergic rhinitis and 48% of the patients were smokers. None of the participant had self-reported olfactory dysfunction at the time of Sniffin' sticks test. Only 2 patients reported olfactory dysfunction due to COVID-19 and both claimed to be totally recovered.

The median SNOT-22 score of these 25 patients was 9 (min-max 0-59). The median T, D, I and, TDI scores were 10,33 (min-max:1-16), 10 (min-max:6-16), 11 (min-max 8-15) and, 32 (min-max: 19,33-43) respectively. 64% of the patients (n:16) were normosmic and 36% of the patients (n:9) were hyposmic. Eleven-point-one percent (n:1) of the hyposmic patients had self-reported olfactory dysfunction due to COVID-19. Eighty-one-point-three percent of normosmic patients were in grup 1. All the hyposmic patients were in group 1. Sixty-three-point-six percent of the hyposmic patients and 42.1% of tne normosmic patients were smokers. Twenty-five percent of normosmic patients and 22.2% of normosmic patients were diagnosed with allergic rhinitis. Smoking habit and previous diagnosis of allergic rhinitis did not differ significantly between hyposmic and normosmic patients. Demographic and clinical information of the patients participated in Sniffin' Stick Test was summarized on **table 5**.

4. Discussion

Anosmia is a well-known symptom of viral upper respiratory tract infections. A viral infection is the reason of anosmia in 40% of the cases in adult patients [9]. Many viruses such as Rhinovirus, Epstein-Barr virus and Parainfluenza may cause mechanical obstruction with mucosal inflammation and rhinorrhea, resulting in olfactory dysfunction [10, 11]. However, the smell disorder associated with COVID-19 has a different pathogenesis that can occur without rhinorrhea and nasal obstruction [4, 8] Lechien et al. claimed that 79.7% of COVID-19 patients with anosmia or hyposmia did not complain of rhinorrhea and nasal obstruction [4]. On the other hand, in our study mean score of "nasal obstruction" (question-2 of SNOT-22) of the patients with self-reported olfactory dysfunction was significantly higher than the patients without.

In the literature, rates of olfactory dysfunction vary among studies between 3.2% and 98.3% [19, 20] , gustatory dysfunction varies between 5.6% and 88% [3, 4]. In a meta-analysis reported by Agyeman et al. olfactory dysfunction and gustatory dysfunction rates were found to be 41.0% (95% CI, 28.5% to 53.9%) and 38.2% (95% CI, 24.0% to 53.6%) respectively [21]. In our study we found that, rates of olfactory and gustatory dysfunctions were both 10.5%. We attribute our low rates of olfactory and gustatory dysfunctions to the fact that most of the participants in the study were asymptomatic patients diagnosed during filiation.

COVID-19 may present in a wide clinical spectrum, from asymptomatic cases to severe illness, with or without pneumonia [22]. In our study, patients were clustered in three groups according to disease severity, 73.1% of the patients were in Group 1 (asymptomatic other than smell or taste dysfunction), 20.5% were in group 2a (symptomatic disease without pneumonia) and 6.4% were in group 2b (presented with pneumonia). The patients in group 1 had a lower rate of olfactory dysfunction compared to group 2 but that was not statistically significant. Several authors reported lower olfactory disorder rates in severe COVID-19 [23-26] But in the

studies that used psychophysical olfactory tests showed no relationship between disease severity and olfactory dysfunction [8, 20, 26, 27].

Some studies reported significantly higher olfactory dysfunction rates in females than in males [4, 28, 29]. In our study rate of self-reported olfactory dysfunction was higher in females (13% vs. 7%) but that was not statistically significant. The relation between smoking and self-reported olfactory dysfunction varies among studies [24, 30]. In our study rate of olfactory dysfunction of smokers were similar with non-smokers. The mean ages of the patients with and without self-reported olfactory dysfunction were 39.5 (min-max:18-55) and 36 (min-max:19-71) respectively. Vaira et al. evaluated a large group of patients with psychophysical olfactory tests and did not find a relationship between age, gender, smoking and olfactory dysfunction [31].

In our study, gustatory dysfunction rate of smokers was significantly higher than non-smokers. No information was found in the literature on how smoking affects the susceptibility to gustatory dysfunction in COVID-19 patients. On the other hand, smoking is known to cause alternations of gustatory function [32].

All but one patient recovered from olfactory dysfunction in median time of 7 days (min-max:0-30). One patient was still suffering olfactory dysfunction 45 days after diagnosis. Gustatory dysfunction resolved in 16 of the patients within a median time of 8.5 days (min-max 1-30). These findings were in line with literature. In the study of Lechien et al. 96.7% of the patients recovered in two weeks [4]. Klepfenstein et al. pointed out that the average duration of anosmia was 8.9 days and ≥14 days for 20% of individuals [33]. Lee et al. reported that patients with olfactory or gustatory dysfunctions recovered within 3 weeks; with the average recovery time of 7 days [29].

SNOT-22 score of Group 2a was higher than the others. Lechien et al. also reported higher SNOT-22 scores in the patients with moderate disease than patients with mild or severe disease [34]. Since first 12 questions of SNOT-22 mostly cover the symptoms of upper respiratory tract infection, it was not surprising to have higher SNOT-22 scores in patients with moderate symptoms without pulmonary disease. Samaranayake et al. pointed out that “nasal blockage” (question 2) and “runny nose” (question 4) were more prevalent in patients with mild or moderate disease than patients with severe disease [35].

In the second step of our study, we aimed to evaluate olfactory function of recovered patients with sniffin’ sticks test battery. All the tests were performed at least 30 days after the diagnosis. No participant reported olfactory dysfunction at the time of test. According to TDI scores, 64% of the patients were normosmic and 36% were hyposmic. Moein et al reported nearly 65% of the patients were unaware of their olfactory dysfunction [20]. Vaira et al. reported that 14.5% of patients without self-reported olfactory dysfunction were actually hyposmic [31]. On the other hand being unaware of olfactory dysfunction is not rare with a prevalence of %22 in normal population [36]. According to this information, it may be wrong to say that hyposmia in our patients is caused by COVID-19, but it could be speculated that olfactory dysfunction is more common in COVID patients than patients self-report.

There was not any significant difference of age, gender, severity of disease, and diagnosis of allergic rhinitis between normosmic and hyposmic patients. The median SNOT-22 score was higher in hyposmic patients.

This study has several limitations. First, both the survey and psychophysical olfactory tests were performed after patients' recovery. The survey was based on patients’ self-reported data. That posed a risk for recall bias. Second, almost all the patients participated in psychophysical olfactory tests were those who did not reported olfactory dysfunction during COVID-19. Therefore, no comment could be made on the permanence of the olfactory

dysfunction caused by COVID-19. A third limitation was that the olfactory function of the patients who underwent psychophysical olfactory tests were not objectively known prior to disease. Therefore, it could not be clarified whether the hyposmia in our patients was due to COVID or not.

5. Conclusion

Olfactory and gustatory dysfunctions have been a remarkable issue for physicians since the beginning of the COVID 19 outbreak. These symptoms occur in early period of the disease. Olfactory and gustatory dysfunctions are more common in patients who are clinically symptomatic than those diagnosed during filiation. Olfactory dysfunction is not related to the severity of the disease. Objective tests may show that frequency of olfactory dysfunction is greater than frequency of self-reported olfactory dysfunction.

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Table 1: Demographic and Clinical Information of Patient Participated in Survey

	n	%
Gender		
Male	71	41.5
Female	100	58.5
Disease Grups		
Group 1	125	73.1
Group 2a	35	20.5
Group 2b	11	6.4
Allergic Rhinitis	22	12.9
Smoking	61	35.7
Olfactory Dysfunction	18	10.5
Gustatory Dysfunction	18	10.5

Table 2: Comparison of patients with and without olfactory dysfunction

	With Olfactory Dysfunction (18)	Without Olfactory Dysfunction (153)	p
Age median (min-max)	39.5 (18-55)	36 (19-71)	0.772
Gender			
Male	27.8% (5)	43.1% (66)	0.159
Female	72.2% (13)	56.9% (87)	
Allergic Rhinitis	27.8% (5)	11.1% (17)	0.061
Smoking Habit	44.4% (8)	34.6% (53)	0.411

401 **Table 3: Comparison of patients with and without gustatory dysfunction**

	With Gustatory Dysfunction (18)	Without Gustatory Dysfunction (153)	p
Age median (min-max)	41 (18-59)	35 (19-71)	0.199
Gender			
Male	27.8% (5)	43.1% (66)	0.159
Female	72.2% (13)	56.9% (87)	
Allergic Rhinitis	27.8% (5)	11.1% (17)	0.061
Smoking Habit	66.7% (12)	32.0% (49)	**0.007**

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404 **Table 4: SNOT-22 questionnaire and mean scores for each question**

Question	All	With Olfactory Dysfunction	Without Olfactory Dysfunction	p
1. Need to blow nose	0.36±0.9	0.83±1.2	0.31±0.8	**0.02***
2. Nasal Obstruction	0.56±1	1.39±1.3	0.46±0.9	**0.001***
3. Sneezing	0.63±1	1.28±1.4	0.55±1	**0.007***
4. Runny nose	0.46±0.9	0.61±1.2	0.44±0.9	>0.05
5. Cough	0.61±1	0.61±1	0.61±1	>0.05
6. Post-nasal discharge	0.50±1	0.83±1.3	0.46±0.9	>0.05
7. Thick nasal discharge	0.15±0.5	0.50±0.9	0.10±0.4	**0.005***
8. Ear fullness	0.19±0.6	0.44±0.9	0.16±0.5	>0.05
9. Dizziness	0.31±0.7	0.28±0.8	0.31±0.7	>0.05
10. Ear pain	0.08±0.3	0.00±0	0.08±0.4	>0.05
11. Facial pain/pressure	0.40±1	0.28±1	0.42±1	>0.05
12. Loss of smell or taste	0.42±1.1	2.78±0.9	0.14±0.7	**0.000***
13. Difficulty falling asleep	0.55±1.1	0.94±1.3	0.50±1.1	>0.05
14. Waking up at night	0.63±1.2	1.06±1.3	0.58±1.2	**0.029***
15. Lack of a good night's sleep	0.74±1.3	1.17±1.5	0.68±1.3	>0.05
16. Waking up tired	0.88±1.4	1.22±1.4	0.84±1.3	>0.05
17. Fatigue	0.91±1.4	1.39±1.5	0.85±1.3	>0.05
18. Reduced productivity	0.49±1	0.61±1	0.47±1	>0.05
19. Reduced concentration	0.48±1	0.78±1.3	0.44±1	>0.05
20. Frustrated/restless/irritable	0.47±1	0.78±1.3	0.44±0.9	>0.05
21. Sad	0.87±1.3	1.11±1.4	0.84±1.3	>0.05
22. Embarrassed	0.95±1.3	1.11±1.4	0.93±1.3	>0.05
TOTAL	11.61±13.2	20.0±13.4	10.62±13	**0.001***

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406 **Table 5: Demographic and clinical information of the patients participated in Sniffin'**
407 **Stick Test**

	Normosmic (n:16)	Hyposmic (n:9)
Age median (min-max)	38 (25-52)	40 (23-50)
Gender		
Male	43.8%	55.6%
Female	56.3%	44.4%
Smoking	42.1%	63.6%
Allergic rhinitis	25%	22.2%
Disease group		
Group 1	81.3%	100%
Group 2	18.8%	-
Self-Reported Olfactory Dysfunction	6.3%	11.1%
SNOT-22-median (min-max)	8.5 (0-59)	13 (0-22)

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