


Evaluation of Olfactory Function With Objective Tests in COVID-19-Positive Patients: A Cross-Sectional Study

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Abstract

Objective: Olfactory dysfunction is relatively high in coronavirus disease 2019 (COVID-19) patients. The aim of this study is to investigate the incidence of olfactory disorder objectively in patients with laboratory-confirmed COVID-19 infection. **Material and Method:** The study included 31 healthy controls and 59 COVID-19 patients who were diagnosed and treated in the COVID departments in a tertiary hospital. The patients with corona virus infection were screened by a questionnaire and were classified into 2 groups as either group 2 (patients without self-reported smell loss) or group 3 (patients with self-reported smell loss). Age and gender matched healthy controls who do not have chronic nasal condition or nasal surgery history comprised the control group (group 1). All of the patients and subjects in the control group were tested by the Sniffin' Sticks test. All of the answers and scores were recorded, and the comparisons were made. **Results:** The rate of self-reported smell and taste loss in all COVID-19 patients in this study was 52.5% and 42%, respectively. There was a significant difference in threshold, discrimination, identification, and Threshold, Discrimination, Identification (TDI) scores between groups 1 and 2. When the comparisons between group 1 and 3 were made, again threshold, discrimination, identification, and TDI scores were significantly different. The comparison between groups 2 and 3 demonstrated a significant difference in discrimination, identification, and TDI scores, but threshold score was not different statistically. With questionnaire, the rate of olfactory dysfunction in COVID-19 patients was 52.5%, but with objective test, the rate was calculated as 83%. **Conclusion:** Olfactory and gustatory dysfunctions are common in COVID-19 patients. According to findings with the objective test method in this study, smell disorder in COVID-19 patients was much higher than those detected by questionnaires.

Keywords

COVID-19, olfactory dysfunction, Sniff Stick test, objective olfactory evaluation

Introduction

After severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus, another highly pathogenic coronavirus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) appeared in December 2019 in China and rapidly spread around the world. The World Health Organization (WHO) recently named this disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19).¹ Although more common symptoms are fever, dry cough, shortness of breath, and myalgia; upper respiratory tract symptoms such as nasal congestion, rhinorrhea, sore throat, and hyposmia/anosmia can also be seen in patients with COVID-19.² It was also reported that COVID-19 could manifest as an isolated sudden hyposmia/anosmia.³

Many viruses may lead to olfactory dysfunction (OD) through an inflammatory reaction of the nasal mucosa and the

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development of rhinorrhea or nasal congestion; the most familiar agents being rhinovirus, parainfluenza Epstein–Barr virus, and some coronaviruses.⁴ However, OD linked to COVID-19 infection seems particular as it is not associated with rhinorrhea or marked nasal congestion. In light of the current findings, testing the olfaction of subjects who may be at risk or have subtle COVID-19 signs, such as low-grade fever, may aid in identifying COVID-19 patients who are in need of early treatment or quarantine. In addition, the proportion of COVID-19 patients with true odor impairment is still unknown.⁵ Most of the studies published on this subject until now are observational. The rate of smell loss in some series of COVID-19 patients were found as 53% up to 73% with questionnaires^{6,7} and was seen in 73.6% of the patients with objective testing.⁸ Due to disparities of the real olfactory loss incidence in COVID-19 and lack of objective tests to identify the rate of OD, we conducted this study to evaluate smell loss in COVID-19 patients objectively. We investigated the incidence of olfactory disorder by *The Sniffin' Sticks test* in patients with laboratory-confirmed COVID-19 infection.

Materials and Methods

This cross-sectional study included 31 healthy controls and 59 COVID-19 patients who were diagnosed and treated in the COVID departments of Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Istanbul, between April 10 and May 10, 2020. The patients and the healthy controls were recruited in predetermined 1-month period. The patients with confirmed diagnosis of COVID-19 by either nasopharyngeal swabs or by chest CT who were under 60 years of age without other comorbidities or using chronic medication for other disorders were included in the study. Since it is not possible to perform a smell test to patients having severe or critical disease according to WHO's classification of COVID-19 severity, our subjects were patients having mild or moderate disease. Patients with previous nasal surgery history, allergic rhinitis, or chronic rhinosinusitis were excluded. The healthy subjects were age-matched volunteers who were the health care providers, employees of our hospital, who had no previous nasal complaint, nasal surgery, or acute or chronic nasal disorder.

Following ethical committee approval of the study protocol, patients with corona virus infection and healthy subjects were screened by a questionnaire which included age, gender, previous history, presence/absence of self-reported smell, and taste dysfunction. A careful physical examination was performed to all patients and healthy subjects with PPE in a well-aerated examining room to rule out nasal disorders that could impair olfaction. The physical examination of the patients and control subjects revealed no nasal pathology that could impair olfaction.

According to results of questionnaire patients were classified into 2 groups as either group 2 (patients without self-reported smell loss) or group 3 (patients with self-reported smell loss). Age- and gender-matched healthy controls who do not have

chronic nasal condition or nasal surgery history comprised the control group (group 1).

Group 1 was composed of 31 healthy subjects (19 females and 12 males) with ages ranging between 22 and 58 years with a mean of 36.97 ± 9.3 years. In group 2, there were 28 COVID-19-positive patients (12 females, 16 males, ages ranging between 20 and 58 years with a mean of 39.25 ± 12.48 years) who did not notice OD during the clinical course of the disease. Group 3 was composed of COVID-19-positive patients (14 females, 17 males; ages ranging between 20 and 57 years with a mean of 36.19 ± 9.8 years) who experienced OD during the disease course. All of the patients and subjects in the control group were tested by the Sniffin' Sticks test (Burghardt). *The Sniffin' Sticks test* was done in 3 steps, and results were presented as 4 scores as defined by Hummel et al⁹: threshold score, discrimination score, identification score, and Threshold, Discrimination, Identification (TDI) global olfactory score. The results for each score were interpreted according to normal values. Odorants were presented in commercially available pens. The pens were presented to subjects for 3 seconds, 2 cm away from the nostrils. *Thresholds* were assessed using n-butanol as the odorant and increasing concentration method was used. (16 triplets of pens; 1 containing a certain concentration of the odorant, other 2 without any odorant). Sixteen triplets were presented to the subject, starting from the lowest concentration (concentration gradually increases from triplet number 16 to 1). First triplet that the subject gets the smell was determined as the threshold. *Discrimination* was performed by means of triplets of odorants (16 pairs of odorants, 1 different odorant for each triplet, triple forced choice). The subject was presented with 3 odorants and the task was to identify the sample that had a different smell. The discrimination score corresponds to the number of correct responses out of 16. *Identification* consisted of 16 pens. Each pen was presented to the subjects and they were asked to choose an answer from the list (16 common odorants, multiple forced choice from 4 verbal items per test odorant). As the 4th score, *TDI* was calculated which was the sum of previous test scores. All of the answers and scores were recorded, and the comparisons were made. Patients with TDI score >30 was considered normosmia, TDI score 16 to 30 was considered hyposmia, and TDI score <16 was considered anosmia.⁹ Statistical analysis was made by SPSS 21 program. For the comparison of the numeric variables (age, threshold score, discrimination score, identification score, and TDI score), Mann-Whitney *U* (for the comparison of 2 groups) and Kruskal–Wallis (for the comparison of three groups) tests were applied. For the analysis of ordinal and nominal parameters, χ^2 was used. Correlation analysis were made by Spearman analysis. $P \leq .05$ was considered significant.

Results

The demographic data, self-reported olfactory and taste dysfunction rates, threshold, discrimination and identification, and TDI scores among the groups were presented in Table 1. In

Table 1. The Demographic Data, Self-reported Olfactory and Taste Dysfunction Rates, Threshold, Discrimination and Identification and TDI Scores Among the Groups Were Presented.^a

| | Group 1 | Group 2 | Group 3 | All patients |
|--------------------------------------|------------------------------|------------------------------|------------------------------|---|
| n | 31 (34.4%) | 28 (31.1%) | 31 (34.4%) | 59 |
| Gender (f/m) | 19 F, 12 M | 12 F, 16 M | 14 F, 17 M | 26 F, 33 M |
| Taste (yes/no) | No: 31 (100%) | No: 28 (100%) | No: 6 Yes: 25 | No: 34 (58%) Yes: 25 (42%) |
| Smell (yes/no) | No: 31 (100%) | No: 28 (100%) | Yes: 31 | No: 28 (47.5%) Yes: 31 (52.5%) |
| Age, range; mean \pm SD | 22-58; 36.97 \pm 9.3 | 20-58; 39.25 \pm 12.48 | 20-57; 36.19 \pm 9.8 | 20-58; 37.41 \pm 10.5 |
| Threshold, range; mean \pm SD | 6.25-8.25; 7.3 \pm 0.56 | 4.75-7.25; 6.12 \pm 0.64 | 5-7.5; 6.22 \pm 0.64 | 4.75-7.5; 6.5 \pm 0.83 |
| Discrimination, range; mean \pm SD | 11-16; 13.42 \pm 1.4 | 7-13; 10.89 \pm 1.2 | 5-13; 9.4 \pm 1.73 | 5-13; 11.28 \pm 2.21 |
| Identification, range; mean \pm SD | 11-15; 13.39 \pm 1.2 | 7-14; 11.5 \pm 1.5 | 8-13; 10.32 \pm 1.3 | 7-14; 11.74 \pm 1.88 |
| TDI, range; mean \pm SD | 29.75-39.25; 34.12 \pm 2.4 | 23.75-33.25; 28.5 \pm 2.3 | 18-31.25; 26 \pm 2.9 | 18-33.25; 29.59 \pm 4.3 |
| Interpretation | Normosmic: 30 Hyposmic: 1 | Normosmic: 8 Hyposmic: 20 | Normosmic: 2 Hyposmic: 29 | Normosmic: 10 (17%) Hyposmic: 49 (83%) |

Abbreviation: TDI, Threshold, Discrimination, Identification.

^aBold values are showing the rates of taste and smell loss among the patients.

group 2, 12 patients were classified as having moderate disease and hospitalized (42%), while in group 3, 15 patients were classified as moderate and treated in hospital (48%). Sixteen patients were having mild disease in each group (58% in group 2, 52% in group 3). The comparison of ages and genders among the groups yielded no significant difference (Table 2).

In groups 1 and 2, none of the patients had self-reported taste loss (Table 1). However, in group 3, 25 of the patients had taste loss (80%). For all COVID-19-positive patients, the rate of taste loss was 42% (Table 1). Taste loss was significantly different between controls and group 3 patients and between patients in groups 2 and 3 (Table 2).

In group 1, none of the patients had smell loss. In group 2, again none of the patients had smell dysfunction. In group 3, all of the patients had OD (Table 1). The rate of self-reported OD in COVID-19 patients was 52.5%.

The range and mean values of threshold, discrimination, identification, and TDI scores of the subjects were presented in Table 1. In group 1, mean threshold was 7.3 \pm 0.56, mean discrimination value was 13.42 \pm 1.4, mean identification value was 13.39 \pm 1.2, and mean TDI score was 34.12 \pm 2.4 (Table 1). In group 2, mean values of threshold, discrimination, identification, and TDI score were 6.12 \pm 0.64, 10.89 \pm 1.2, 11.5 \pm 1.5, and 28.5 \pm 2.3, respectively (Table 1). In group 3, mean threshold, discrimination, identification, and TDI score values were 6.22 \pm 0.64, 9.4 \pm 1.73, 10.32 \pm 1.3, and 26 \pm 2.9, respectively.

In the intergroup comparisons, there was a significant difference in threshold, discrimination, identification, and TDI scores between groups 1 and 2 ($P = .000$; Table 2). When the comparisons between groups 1 and 3 were made, again threshold, discrimination, identification, and TDI scores were significantly different ($P = .000$; Table 2). The comparison between groups 2 and 3 demonstrated a significant difference in discrimination, identification, and TDI scores ($P = .001$, .002,

.001, respectively), but threshold score was not different statistically ($P = .57$; Table 2).

The interpretation of the TDI scores yielded that 30 subjects were normosmic and 1 subject was hyposmic in group 1, 8 patients were normosmic and 20 patients were hyposmic in group 2, and 2 patients were normosmic and 29 patients were hyposmic in group 3 (Table 1). The rate of OD in COVID-19 patients with *The Sniffin' Sticks test* was 83% (Table 1).

Discussion

In January 2020, SARS-CoV-2 was identified as the cause of a severe pneumonia epidemic, known as a complication of coronavirus disease.⁹ Even without other symptoms and signs, odor loss alone in COVID-19 may represent the only manifestation of the disease.¹⁰

Post viral olfactory disorders are usually seen after a cold or an upper respiratory tract infection associated with influenza. The cause of 11% to 40% of olfactory disorders is considered viral infections. The exact location of the damage after upper respiratory tract infection is not yet known. However, central mechanisms cannot be completely ignored.⁹ The basis for loss of smell due to SARS-CoV-2 is not entirely clear, but it is well known that viruses can damage the olfactory neuroepithelium. Acute upper respiratory viral infections that damage epithelium are the main cause of chronic OD.¹¹ The receptors for SARS-CoV-2 to enter the cells are angiotensin-converting enzyme 2 and transmembrane protease serine 2, and these receptors are found in olfactory support cells but not on the neurons.¹² The proposed mechanism for OD in COVID-19 was stated as the inflammation of the olfactory epithelia that may result in conductive olfactory loss.¹³

Decreased smell function is a major marker for SARS-CoV-2 infection and suggests the possibility that smell testing may help, in some cases, to identify COVID-19 patients

Table 2. The Intergroup Comparisons of the Groups.^{a,b}

| All patients and subjects | | | | |
|---------------------------|--|----------------|------|--|
| χ^2 | | Kruskal-Wallis | P | |
| Gender | $P = .29; r = 0.13$ | Age | .63 | |
| | | Threshold | 0 | |
| Smell (yes/no) | $P = .000, r = 0.87$ | Discrimination | 0 | |
| | | Identification | 0 | |
| Taste (yes/no) | $P = .000, r = .73$ | TDI | 0 | |
| Groups 1 and 2 | | | | |
| χ^2 | | MWU | P | |
| Gender | $P = .12, r = 0.18$ | Age | .61 | |
| | | Threshold | 0 | |
| Smell (yes/no) | | Discrimination | 0 | |
| | | Identification | 0 | |
| Taste (yes/no) | $P = .22, r = 0.19$ | TDI | 0 | |
| Groups 1 and 3 | | | | |
| χ^2 | | MWU | P | |
| Gender | $P = .15, r =$ | Age | .68 | |
| | | Threshold | 0 | |
| Smell (yes/no) | $P = .000, r = 1$ | Discrimination | 0 | |
| | | Identification | 0 | |
| Taste (yes/no) | $P = .000, r = 0.82$ | TDI | 0 | |
| Groups 2 and 3 | | | | |
| χ^2 | | MWU | P | |
| Gender | $P = .53, r =$ | Age | .32 | |
| | | Threshold | .57 | |
| Smell (yes/no) | $P = .000, r = 1$ | Discrimination | .001 | |
| | | Identification | .002 | |
| Taste (yes/no) | $P = .000, r = 0.73$ | TDI | .001 | |

Abbreviations: MWU, Mann Whitney U test; TDI, Threshold, Discrimination, Identification.

^aP is the significance value, r is the Spearman correlation value.

^bBold values are the results that are statistically significant.

early.⁵ Giacomelli et al detected taste or olfactory disorders in up to 53% of the cases.⁶ Yan and colleagues reported that 68% of COVID-19-positive patients described odor impairment and 71% had taste impairment and stated that sudden loss of smell and taste were markers of COVID-19.¹⁴ In 237 patient reports published, anosmia was found in 73% of the patients before the diagnosis of COVID-19 and anosmia was the first symptom in 27% of them.⁷ Most of the studies published on this subject until now are anamnestic–observational. One of the first studies that used objective smell test was performed by Moein et al. They used the University of Pennsylvania Smell Identification Test Quantitative smell testing and reported that 59 (98%) of the 60 patients exhibited some smell dysfunction.⁵ In this study, we objectively evaluated the olfactory function in COVID-19 patients treated in our institution with the “Sniffin” Sticks’ test.

Coronavirus disease 2019 patients in this series were classified according to a questionnaire (yes or no) to screen whether they had taste and smell dysfunction. In the patients of group 3 (COVID+ and olfactory loss in questionnaire), the rate of self-reported smell loss was 100% and taste loss was 80% (Table 1). Also the rate of self-reported smell and taste loss in all COVID-19 patients in this study was 52.5% and 42%, respectively, which are higher than some observational studies.^{10,6} On the contrary, some studies reported higher rates. In the multicenter European study by Lechien et al, 85.6% and 88.0% of patients reported olfactory and gustatory dysfunctions, respectively.¹⁵ The other study with objective testing, the chemosensory loss was seen in 73.6% of the patients.⁸ Yet in another study that evaluated self-reported loss of smell and objective olfactory testing, the authors reported that only 62% of COVID-19 patients with subjective OD had anosmia or hyposmia on objective olfactory evaluation.¹⁶ Another study in which olfactory and gustatory functions were evaluated by self-administered olfactory and gustatory psychophysical test, the rate of OD was only 67%.¹⁷ Hintschich et al also reported that the subjective loss of smell was confirmed with objective testing in 72% of the patients, while that was not the case with taste loss.¹⁸ In our study, the rate of OD detected by objective measures was even higher than previous studies (83%).

One important finding of our study was that we were able to detect hyposmia in patients without smell complaint (group 2). Significant odor loss was observed in patients who did not describe odor loss compared to the control group (Table 2). Similar but contrary finding was reported in the study of Lechien et al where they found that 38% of patients with subjective OD was normosmic in objective testing.¹⁶ This disparity may be explained by lack of validated surveys in our study; smell complaint might be underestimated by the patients. When Groups 2 and 3 were compared that the thresholds of the patients were not different, but other parameters were significantly different in patients with self-reported smell loss as expected (Table 2). Also, complete loss of smell and taste was not detected in any of the patients. According to the objective findings, change in thresholds in our cases was related to decreased discrimination and identification, but in group 2, the discrimination and identification scores were better than group 3 (Table 2). Also, in COVID-19 patients, we detected 83% of hyposmia which was far higher than the self-reported OD (52%). Le Bon et al¹⁹ also used Sniffin’ Sticks test to evaluate smell loss in COVID-19 patients and reported that using screening tests relying upon smell identification may cause misdiagnosis; so compound tests assessing threshold, discrimination, and identification scores were to be more accurate.

There were several weaknesses of our study. We were not able to evaluate the patients having severe or critical disease because performing the test was not possible due to their state of respiratory distress. So the correlation between OD and disease severity still remains to be enlightened. Lechien et al¹⁶ evaluated loss of taste with National Health and Nutrition Examination Survey; but in our study, we could not use a validated questionnaire not to elongate the duration of contact

with the patient furthermore; instead, we inquired the patients for the presence or absence of taste loss. Also subjective evaluation of smell loss was not performed by validated questionnaires, but only screened by absence or presence of dysfunction. This might underestimate the self-reported smell loss.

As a result, in our study, it was observed that smell disorder in COVID-19 patients was much higher than those detected by questionnaires and use of objective methods were to be needed to discriminate these patients.

Conclusion

Olfactory and gustatory dysfunctions are common in COVID-19 patients. In the differential diagnosis of OD, COVID-19 should also be considered especially in the patients without nasal complaints.

Authors' Note

The data of the study can be shared on demand. All participants were informed and informed consents were retrieved. All the patients and all the authors consented the publication of the data. Informed consent was obtained from all of the patients. Study design has been submitted for approval of ethics committee. There is no disclosure of personal information and images of patients in this paper.


Declaration of Conflicting Interests

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