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Olfactory disorders in patients with mild to moderate COVID-19: spontaneous recovery in one-month follow up

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ABSTRACT

Objective: In this study, we aimed to evaluate olfactory disorders (OD) and recovery processes in patients with coronavirus disease 2019 (COVID-19) infection at three time periods within one month from the time of diagnosis.

Methods: A total of 96 patients with COVID-19 participated in the study. Self-reported changes in olfactory functions and their effects on quality of life (QoL) were evaluated using the National Health and Nutrition Examination Survey, the Questionnaire of Olfactory Disorders-Negative Statements (QOD-NS), and Sino-Nasal Outcome Test (SNOT)-22. At the time of diagnosis, the patients were divided into three groups: anosmia, hyposmia, and no OD (control) group. Subsequently, olfactory functions were retested at the time of the first negative polymerase chain reaction (PCR) control test and one month from the time of diagnosis.

Results: During the COVID-19 infection, 68.7% of patients had OD; of these, 37% had anosmia, and 29% had hyposmia. Dysgeusia was found in 44.8% of the patients. OD was the primary symptom in 10.8% of the patients. The QoL scores of those with anosmia and hyposmia were significantly lower than those with no OD in all three surveys (P <.05). The QOD-NS scores of those with OD lasting more than 14 days were significantly lower in all three surveys (P <.05). Of the patients with OD, 4.34% had no spontaneous recovery at the end of the first month.

Conclusion: Recovery of OD is faster in patients with hyposmia than in those with anosmia. Although COVID-19related permanent OD is not commonly observed, treatment of OD that lasts for more than 15 days would be beneficial to avoid permanent sequelae.

Keywords: Coronavirus, COVID-19 pandemic, olfactory disorder, questionnaire of olfactory disorders, smell disorder

Introduction

Coronavirus disease 2019 (COVID-19) is a viral pandemic that emerged in East Asia and spread rapidly to the rest of the world (1). The commonly reported symptoms of COVID-19 are fever, cough, dyspnea, myalgia, arthralgia, headache, diarrhea, rhinorrhea, and sore throat (2, 3) In addition, the infection also causes smell and taste disorders. However, based on previous research, the prevalence of olfactory disorders (OD) appears to be disproportionate across the world. A Chinese study reported the prevalence of OD as 5.1% (4), a European study reported OD prevalence as 70.2% (5), and the American studies reported OD prevalence between 19%–73% (6, 7).

Although anosmia is often linked with many common cold viruses such as influenza and coronavirus, its exact cellular and molecular mechanisms have not yet been clearly established (8-10). Various possible mechanisms have been suggested to explain the pathogenesis of OD in patients with COVID-19. At the beginning of the pandemic, it was thought that OD could be caused by receptor damage of olfactory neurons, neuronal apoptosis, and invasion of the olfactory bulbus (11, 12). In fact, the results of magnetic resonance imaging in anosmic patients affected by COVID-19 supported this hypothesis; changes in the olfactory bulb and neuroinvasive capacity were observed, which coincided with severe acute respiratory syndrome and coronavirus infections (13). Given that anosmia is often detected early in the disease in both mild and asymptomatic patients (14), excessive and systemic inflammatory responses in the brain are unlikely to play a causative role in the development of anosmia. For these reasons, the focus has been shifted to supporting cells and vascular pericytes of the olfactory

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epithelium and bulb as a possible site of viral damage (8). The radiological evidence of olfactory cleft edema in some patients with anosmia supports the latter hypothesis, proving that the supporting cells of the olfactory epithelium have the highest concentration of viral receptors (15).

The association between COVID-19 infection and taste disorder has been poorly investigated. Isolated taste disorders are highly specific to COVID-19 (16). In this regard, the following two mechanisms have been proposed. First, the virus usesangiotensin converting enzyme 2, receptors commonly expressed in taste buds, to infect cells. Coronavirus binds to these receptors, inhibiting the conversion of chemical taste signals into action potential, rendering them ineffective, and consequently inhibiting sensory perception of taste (17). In addition, coronavirus can bind to sialic acid receptors. The reduction of sialic acid in saliva is associated with an increase in the taste threshold (18).

Although most patients report full recovery from OD within a few weeks, some report severe chemosensitive disorders even after 30 days of clinical onset of symptoms (5, 14). Owing to the paucity of prospective studies, the long-term recovery rate of chemosensitive function has not been determined. There is a need for evaluation of the recovery process of OD in patients with COVID-19. In this study, we aimed to investigate the recovery process of OD in patients with mild and moderate COVID-19 and to study the effects on quality of life (QoL) during the time of diagnosis, the time when the symptoms regressed, and at the end of the first month.

Methods

Study design and patient characteristics

This study was conducted in a tertiary hospital between March and September 2020. The diagnosis of COVID-19 was confirmed by positive polymerase chain reaction (PCR) result of the combined rhino-pharyngeal swab. Consecutive adult patients (18 years and above) who were diagnosed with mild to moderate COVID-19 and who did not require intensive care were included in the study. Patients with a history of olfactory and taste disorders, allergic rhinitis, head trauma, nasal or paranasal sinus surgery, or neurological or psychiatric disorders were excluded from the study. Patient demographics (age, sex) and characteristics (symptoms, smoking history, and systemic diseases) were recorded. Written informed consent was obtained from all the patients included in this study. This study was approved by Başkent University institutional review board and ethics committee (Project no: KA 20/184, Approval Date: 21 March 2020). No funding has been received for the study.

Main Points:

- During coronavirus disease 2019 (COVID-19), 68.7% of the patients had OD, independent of other symptoms.
- Of the included patients, 81.5% agreed that the OD they experienced was associated with COVID-19.
- Within a month from the time of initial diagnosis, spontaneous improvement was seen in OD, but did not reach the no OD level.
- Recovery of OD was faster in patients with hyposmia than those with anosmia.
- No spontaneous recovery was found in 4.34% of patients with OD at the end of one month.

Patient-reported outcome measures

During this study, three telephone surveys were conducted with all the participants. The first survey was conducted at the time of diagnosis, the second survey when the participants' PCR test result was negative (control PCR test was performed after complete recovery of symptoms and repeated every day until the PCR test became negative), and the third survey a month after the first diagnosis.

The scope of the survey questions is described below:

The first section of the survey included 11 questions structured to understand the characteristics of OD.

1) The Sino-Nasal Outcome Test -22 (SNOT-22) questionnaire related to smell and taste disorder, which has been tested for validity in Turkish population, was used (19). The answer was scored on a scale of 0–5, where 0 referred to no problem and 5 referred to problem as bad as it can be. This question was a part of the first survey.

2) To classify the change in the sense of smell, the patients were asked to select one of the following options: anosmia- complete loss of the sense of smell, hyposmia- decreased sense of smell, phantosmia- to be able to smell even though there is no odorous stimulus, parosmia- misperception of the existing odor, and cacosmia- perceiving odors in the form of bad odor (20). This question was a part of the first survey.

3) The patients were asked about the onset of the smell disorder and whether it was the primary symptom. This question was a part of the first survey.

4) The patients were asked about the duration of OD, which was classified into four categories (1–4, 5–8, 8–14, > 14 days) (21). This question was a part of the third survey.

5) The patients were asked about the change in OD over time. This question was a part of the second survey.

6-10) The patients were asked questions related to the taste disorder (sweet, salty, bitter, sour taste sensation, and dysgeusia) (22). These questions were part of the first survey.

11) In this question, the patient's olfactory functions related to COVID-19 were assessed. This question was a part of the first survey.

The second section of the survey included nine items related to the effects of OD on QoL. The Questionnaire of Olfactory Disorders - Negative Statements (QOD-NS), a valuable measurement method for evaluating olfactory-specific QoL with proven validity and reliability (23), were used in this study. QOD-NS is a patient-reported outcome questionnaire that includes social, eating, annoyance, and anxiety questions. Each of the nine items were rated on a scale of 0–3, with higher scores reflecting better olfactory-specific QoL. The total score ranged from 0 (severe impact on QoL) to 27 (no impact on QoL). QOD-NS has been shown to be compatible with objec-

tive olfactory loss (24). QOD-NS has been previously used in the Turkish population (25).

Statistical analysis

The Statistical Package for Social Sciences version 23.0 software (IBM Corp.; Armonk, NY, USA)was used for statistical analysis of the data. Categorical measurements were presented as number and percentage, whereas continuous measurements were expressed as mean and standard deviation (median and minimum-maximum, where necessary). The chi-squared and Fischer's precision tests were used to compare categorical variables. The Shapiro-Wilk test was used to determine whether the parameters in the study showed normal distribution. In comparing the continuous measurements between the groups, the distributions were checked, and independent student t-test was used for the parameters with normal distribution, the Mann-Whitney U test was used for the parameters not showing normal distribution, and the Kruskall-Wallis test was used for more than two variables. The relationship between quantitative variables was examined with the Pearson and Spearman correlation analyses. The level of statistical significance was accepted as 0.05 in all tests.

Results

Patient characteristics and symptoms

A total of 96 patients (64 women, 32 men) were included in the study. The mean age was 41.4 (range, 20-73) years. Although 28.1% of the patients had comorbidities, 71.9% did not. The most common comorbidities were hypertension (9.4%), diabetes mellitus (7.3%), and asthma (7.3%). Of the total number of patients, 17.7% were smokers. The most common symptoms recorded were cough (78.1%), sore throat (42.7%), fever (37.5%), dyspnea (21.9%), and nasal congestion (16.7%) (Table 1).

At the time of the COVID-19 diagnosis (first survey), 68.7% of patients had OD; of these, 37% had anosmia, and 29% had hyposmia. During follow-up of the hyposmia group, one patient had cacosmia, and one had parosmia. There were 52 (54.1%) patients who experienced loss of taste. Of these, 52.1% reported a loss in savory taste, 51% in sweet taste, 38.5% in bitter taste, and 39.2% in sour taste. Dysgeusia was found in 44.8% of the patients.

There was no difference in age and sex distribution between the groups of patients with OD and without (p=0.702 for age, p=0.217 for sex). In addition, both the groups (with and without OD) did not significantly differ in terms of symptoms such as fever, cough, nasal congestion, runny nose, and dyspnea (p>0.05).

With regards to the onset of OD, 50% of the patients stated that the symptom appeared suddenly, 36.4% stated that it developed over time, and 13.5% did not notice the onset of OD. OD was the primary symptom in 10.8% of the patients. Of these, 81.5% believed that the OD they experienced was associated with COVID-19, whereas 18.5% partially agreed.

Recovery process of olfactory disorders in patients with COVID-19

The scale-based SNOT-22 questionnaire, which was related to smell and taste disorder, showed that 31.3% of patients had no problem (scale 0), 18.8% had very mild problem (scale 1), 3.1% had mild problem (scale 2), 16.7% had moderate problem (scale 3), 14.6% had severe problem (scale 4), and 15.6% had very severe problem (scale 5).

The mean time for the PCR test to be negative was 13.03±5.85 days. At the time of second survey, the mean time for the PCR test to be negative was 13.78±5.14 days in the anosmia group, 14.71±7.15 days in the hyposmia group, and 10.53±4.54 days in the control group. The identification time of control PCR as negative was longer in patients with OD (p=0.028).

Table 1. Characteristics of COVID-19 patients according to their olfactory status

	Anosmia	Hyposmia	No OD	Total	p
Sex (n [%])					
Male	16 (43.2)	9 (31)	7 (23.3)	32 (33.3)	
Female	21 (56.8)	20 (69)	23 (76.7)	64 (66.7)	0.217
Age (± SD)	41.1 (15)	37.6 (11.8)	42.9 (15.2)	41.4 (14.2)	0.702
Co-morbidities (n [%])					0.448
Yes	11(29.7)	10 (34.5)	6 (20)	27 (28.1)	
No	26 (70.3)	19 (65.5)	24 (80)	69 (71.9)	
Smoking (n [%])	5 (13.5)	5 (17.2)	7 (23.3)	17 (17.7)	0.576
Symptoms (n [%])					
Cough	27 (73)	24 (82.8)	24 (80)	75 (78.1)	0.606
Sore throat	14 (37.8)	13 (44.8)	14 (46.7)	41 (42.7)	0.739
Fever	13 (35.1)	13 (44.8)	10 (33.3)	36 (37.5)	0.614
Dyspnea	7 (18.9)	5 (17.2)	9 (30)	21 (21.9)	.425
Nasal congestion	8 (21.6)	5 (17.2)	3 (10)	16 (16.7)	.445

OD: Olfactory disorder, SD: Standard deviation

The duration of OD recovery was 1–4 days in 14.3%, 5-8 days in 19%, 9-14 days in 11.1%, and more than 14 days in 44.4% of patients with COVID-19. Furthermore, the recovery time of OD was significantly longer in the anosmia group than in the hyposmia group (p=0.001) (Figure 1).

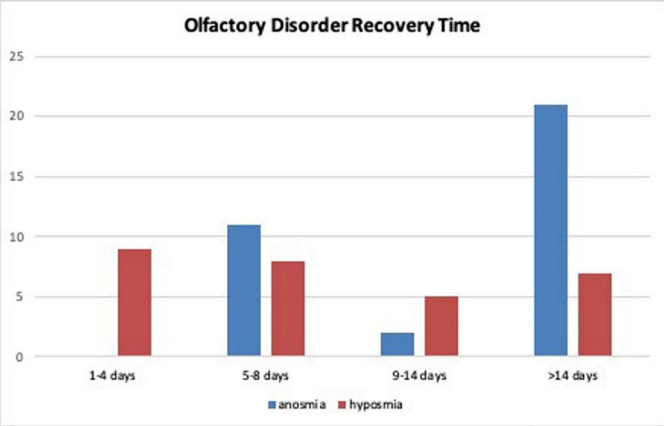

Figure 1. Duration of recovery from olfactory disorder in the anosmia and hyposmia groups (vertical axis shows the number of patients)

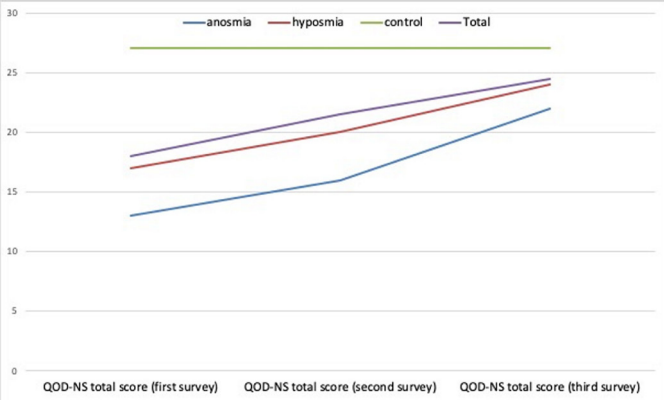

Figure 2. Curve of QNS-NS total scores between anosmia, hyposmia, and control (no olfactory disorder) groups at the time of diagnosis (first survey), when control polymerase chain reaction is negative (second survey), and at the end of the first month (third survey)
QNS-NS: Questionnaire of Olfactory Disorders- Negative Statements; vertical axis shows QNS-NS scores

Effect of olfactory disorders on quality of life

At the time of the first survey (positive PCR test result), the QOD-NS total score was 11.73±4.83 in the anosmia group, 16.76 ± 6.15 in the hyposmia group, and 27±0 in the control group. At the time of the second survey (negative PCR test result), the QOD-NS total score was 14.49±5.51 in the anosmia group, 18.83±6.81 in the hyposmia group, and 27±0 in the control group. At the time of third survey (one month from the time of diagnosis), the QOD-NS total score was 19.7±5.39 in the anosmia group, 24.38±2.45 in the hyposmia group, and 27 ± 0 in the no OD group. In all the three surveys, the total scores of QOD-NS significantly increased from the anosmia group to the control group (p<0.001 for all the surveys) (Figure 2). Furthermore, at the time of the first survey, QOD-NS scores for seven items were significantly different between the anosmia, hyposmia, and the control groups (Table 2). At the end of one month, three patients (4.34%) still did not show any improvement in QOD-NS scores. All the non-recovery patients were in the anosmia group.

Discussion

The presence of a wide range of COVID-19 symptoms with varying degrees of severity, or even asymptomatic cases, made containment of the virus spread difficult. Following the rapid spread of the infection in Europe, publications on OD development reported that OD was an early symptom of COVID-19. As a result, presence of OD was considered important in identifying COVID-19 positive cases. However, the recovery process of OD in patients with COVID-19 has been poorly investigated. In this study, patients with and without OD were evaluated during three periods: at the time of diagnosis, the time when symptoms regressed, and one month after the initial diagnosis. There was no difference between age and sex distribution between those with and without OD. In this study, the patients did not receive any treatment for olfactory and taste disorders.

We assessed responses of patients with COVID-19 to questions from the National Health and Nutrition Examination Survey, SNOT 22, and QNS; the prevalence of OD in our study population was 68.7%. This finding is in accordance with the findings of other European studies. A study conducted in Italy investigated odor thresholds in patients with COVID-19

Table 2. Examples of QNS-NS items and scores (first survey)

QNS-NS items and scores (first survey)	Anosmia Mean±SD	Hyposmia Mean±SD	No OD Mean±SD	p
Q1. I am always aware of the changes in my sense of smell.*	0.43±0.72	1.45±0.93	3±0	0.026
Q3. Because of the changes in my sense of smell, I don't enjoy drinks or food as much as I used to.*	0.50±0.89	1.18±0.87	3±0	0.041
Q4. Because of the changes in my sense of smell, I try harder to relax.	2.18±0.91	2.63±0.50	3±0	0.635
Q5. Because of the difficulties with smelling, I am scared of getting exposed to certain dangers (for e.g., gas, rotten food). *	0.56±0.89	1.54±1.03	3±0	0.019
Q7. Because of the changes in my sense of smell I eat less than I used to or more than I used to. *	0.56±0.72	1.45±0.82	3±0	0.015
QOD-NS total score*	11.73±4.83	16.76±6.15	27±0	0.000

QOD-NS: Questionnaire of Olfactory Disorders-Negative Statements, First survey: at the time of diagnosis
*p<0.05

and found a 73.6% reduction in odor thresholds (26). Another multi-center study in Europe evaluating patient-reported OD found OD prevalence of 85.6%, and anosmia was observed in 79.7% of the patients (5). In Spain, Beltrán-Corbellini et al. (27) have found OD in 31.9% of patients with COVID-19, which was significantly higher than OD reported in patients with influenza. Similar OD prevalence rates were also reported in the United States (28, 29). Interestingly, none of the aforementioned studies reported nasal congestion or runny nose in patients with COVID-19. Similarly, in this study, there was no relationship between OD and other symptoms, such as nasal congestion, runny nose, fever, and cough. Therefore, some researchers have emphasized that OD may be a more effective marker than fever in early recognition of COVID-19 (30).

In this study, patients who were previously diagnosed with allergic rhinitis were excluded. However, we asked the patients whether the OD they experienced was associated with COVID-19 or with seasonal allergies; the time of pandemic coincided with the time of seasonal allergies in our region. Of the total number of patients, 81.5% agreed that OD was associated with COVID-19, whereas 18.5% partially agreed. Further, we asked the patients regarding the development of OD; 50% stated that OD developed suddenly, whereas 13.5% stated that it appeared over time. OD was the primary symptom in 10.8% patients. These rates suggest that changes in the sense of smell emerged prior to development of other COVID-19 symptoms.

The QOD-NS olfactory-specific questionnaire is a valuable measurement tool for QoL evaluation. In patients with OD, QOD-NS scores in the hyposmia group were significantly higher in all the three surveys than in the anosmia group. There was no negative effect on QoL in any of the three time periods in the control group. This finding is in agreement with another study (5) that found a significant difference in all statements of the questionnaire between the anosmia, hyposmia, and the control groups.

The important finding of our study is that COVID-19 infection-related OD spontaneously improved within a month from the initial diagnosis. When general symptoms improved, swab controls were performed, and the mean time for negative detection was 13 days. A previous study monitoring OD in patients with COVID-19 for 60 days reported that 5.8% of patients had moderate to severe OD (31). In this study, a month from the initial diagnosis and without any treatment for OD, three patients (4.34%) still had no improvement in QNS-NS scores. All the patients who did not recoverwere in the anosmia group. Patients who had no OD at the time of diagnosis developed OD at follow-up. At the end of the first month, the patients were asked about the duration of OD. OD lasted for more than 14 days in 44% of the patients. The QOD-NS scores of those with OD lasting for more than 14 days were significantly lower in all three surveys. Consistently, the improvement of the OD in the anosmia group took longer compared with that of the hyposmia group. Vaira et al. (31) have reported that 84.8% of patients with COVID-19 had gradual improvement in chemosensitive dysfunction within the first four days. They also stated that the most significant improvement occurred between 10 and 20 days. Similarly, in our study, improvement in OD was seen after 14 days in most patients. Another study reported that there was a significant improvement in COVID-19associated OD in the first few weeks and that it plateaued after three weeks (28). Amer et al. (32) have reported that patients with hyposmia recovered more rapidly than those with anosmia, whereas the middle-aged group carried the best prognosis in OD recovery.

In conclusion, OD is a frequent symptom in patients with COVID-19, independent of other symptoms, such as nasal congestion, runny nose, fever, and cough. There was a spontaneous improvement in OD in the first month after diagnosis. The improvement in the QoL scores of patients with a more severe OD occurs towards the end of the first month. Although COVID-19related permanent OD is not commonly observed, treatment of OD that lasts for more than 15 days would be beneficial to avoid permanent sequelae.

Ethics Committee Approval: This study was approved by Ethics committee of Başkent University, (Approval No: KA 20/184).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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