



Quantitative evaluation and progress of olfactory dysfunction in COVID-19

Burak Numan Ugurlu¹ · Ozlem Akdogan² · Yasemin Ari Yilmaz³ · Derya Yapar² · Gulay Aktar Ugurlu¹ · Huseyin Serdar Yerlikaya¹ · Sevim Aslan Felek¹

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Abstract

Purpose Since many different rates have been reported in the literature and the studies conducted are mostly based on the patient anamnesis, it was aimed to analyze the olfactory dysfunction in Coronavirus Disease 2019 (COVID-19) quantitatively and to reveal its progress by time.

Methods Patients who described new-onset olfactory dysfunction, who were treated in the COVID-19 departments of our hospital and whose PCR tests demonstrated SARS-CoV-2 presence were included in the study and they were investigated prospectively. Clinical information of all the patients was taken and the levels of olfactory function were detected using the Brief Smell Identification Test (BSIT). Scores equal to or below 8 are considered as olfactory dysfunction. Patients who were followed up for 3 months were reevaluated with the BSIT test at the end of the third month and the progression of the symptom was investigated.

Results The mean BSIT test score of the 42 patients (23 female patients, 19 male patients, mean age: 41.2 ± 14.6) was 5.2 ± 2.2 . There was severe olfactory dysfunction in 16.7% of the patients (0–2 points), moderate olfactory dysfunction in 31% (3–5 points), and mild olfactory dysfunction in 52.4% (6–8 points). After a follow-up for 3 months, full recovery was observed in 36 patients (85.7%) and the mean test score rose to 9.9 ± 1.8 . Although olfactory dysfunction persisted in 6 patients, an elevation in test scores was noted. Olfactory dysfunction was the first symptom in 17 patients (40%) and the other symptoms occurred after 2 days (1–6) on average.

Conclusion We investigated olfactory dysfunction caused by COVID-19 using BSIT, and found a high rate of moderate-mild level symptoms with a high level of recovery in the 3-month follow-up. The finding revealing that olfactory dysfunction was the first symptom in 40% of the patients suggests the importance of inquiry on olfactory functions for the early diagnosis of the disease.

Keywords COVID-19 · Anosmia · Hyposmia · Olfactory dysfunction

Introduction

The most frequent reason for olfactory dysfunction in adults is post-viral anosmia with rates reaching 40% [1]. It has been demonstrated that viruses that affect the upper respiratory tract have an impact on the olfactory function by olfactory cell damage. Coronaviruses are responsible for 10–15% of these upper respiratory tract infections [2]. Symptoms of olfactory dysfunctions have also been reported with strong evidence in COVID-19, which is caused by a new type of coronavirus.

In the first study on olfactory functions in COVID-19 patients in Wuhan by Mao et al., 214 patients were investigated, and accompanying neurological diseases were

✉ Burak Numan Ugurlu
bnumanugurlu@gmail.com

¹ Department of Otolaryngology, Hitit University Erol Olçok Training and Research Hospital, Çorum, Turkey

² Department of Infectious Diseases and Clinical Microbiology, Hitit University Erol Olçok Training and Research Hospital, Çorum, Turkey

³ Department of Pulmonary Medicine, Hitit University Erol Olçok Training and Research Hospital, Çorum, Turkey

observed in 5.1% of the patients [3]. As the COVID-19 pandemic was spreading rapidly around the World, more frequent symptoms of new-onset olfactory dysfunctions were reported as distinctive from the Wuhan series where the disease originated. In a study that was conducted in 12 centers in Europe, 417 patients were evaluated, and accompanying anosmia or hyposmia was reported in 79.7% [4]. As a consequence of these increasing numbers of clinical experiences, the Centers for Disease Control and Prevention (CDC) have acknowledged new-onset olfactory and gustatory dysfunctions as a symptom of COVID-19.

Olfactory dysfunction is a symptom that is difficult to standardize. In the literature, olfactory dysfunctions associated with COVID-19 are frequently based on the anamneses of the patients and observations [4–10]. This is why differing ratios are reported in different series. Also, data associated with the progression of olfactory dysfunctions are limited in the literature [11–16]. The purpose of the present study is to test the olfactory dysfunctions that occur in the course of COVID-19 with BSIT and to disclose its progress by time.

Materials and methods

This study was approved by the clinical research ethics committee (dated 19.08.2020 and no:318) and the Scientific Research Platform of the Ministry of Health. In our study, patients who were treated on an inpatient basis between March 20th and June 20th of 2020 in the COVID-19 Departments of our hospital were included. COVID-19 presence was demonstrated by PCR test for these patients and all described new-onset olfactory dysfunction. Patients with no cooperation, those under 18 years and over 60 years of age, patients with previous nasal surgery history, previous olfactory dysfunction, chronic sinusitis, or neurological or psychiatric diseases were excluded from the study. All patients who were included were invited to the study, their informed consent was taken and they were studied prospectively.

Clinical records

Age, sex, and health history of the patients and upper respiratory tract infection findings such as fever, cough, respiratory distress, nasal drip, and nasal congestion were recorded. Also, records on whether olfactory dysfunction was the first symptom and if so, the number of days it took for the other symptoms to occur were taken.

Detection of olfactory functions

All patients underwent the Brief Smell Identification Test (BSIT; Sensonics, Inc., Haddon Heights, NJ) to evaluate their olfactory functions. This test was designed by revising

the University of Pennsylvania Smell Identification Test (UPSIT), also known as the Cross-Cultural Smell Identification Test (CC-SIT). This is a test with proven validity and reliability and is not affected by ethnic roots [17]. In addition, it can be self-administered in less than 5 min by the patients. There are 12 different scent strips in the BSIT test kit and the odors are released when scratched with a pencil tip. It is a forced-choice test and the participants are asked to choose the right odor among 4 choices. While high BSIT scores indicate better olfactory functions, low scores demonstrate the presence of poor olfactory functions.

Patients who underwent tests for olfactory functions were followed up by monthly telephone calls and were reevaluated at the end of the third month and their new BSIT scores were recorded. According to the BSIT scores, 0–1–2 points were considered as severe olfactory dysfunction, 3–4–5 points were considered as moderate olfactory dysfunction, and 6–7–8 points were considered as mild olfactory dysfunction. Scores equal to or greater than 9 were evaluated as normal olfactory function [18, 19].

Statistical analysis

In data analysis, descriptive statistics are presented by frequency, percentage, mean, and standard deviation values. Because the expected value was higher than 20% and less than 5 Fisher's Exact Test was used. Independent samples *t* test was used to investigate the differences between the mean scores. *p* values smaller than 0.05 were considered to be statistically significant ($\alpha=0.05$). The analyses were conducted using the SPSS 22.0 software.

Results

A total of 104 patients who were hospitalized with the diagnosis of COVID-19 and met the study inclusion criteria were evaluated, and 42 (40.3%) of these were found to have the olfactory disorder. Of the patients included in the study, 23 were female and 19 were male, with a mean age of 41.2 ± 14.6 . The accompanying symptoms of the patients are shown in Table 1.

The mean BSIT test score of the patients at the time of the diagnosis was observed to be 5.2 ± 2.2 . There was severe olfactory dysfunction in 16.7% of the patients (0–2 points), moderate olfactory dysfunction in 31% (3–5 points), and mild olfactory dysfunction in 52.4% (6–8 points). The mean length of hospital stay of the patients included in the study was 8 days (1–23 days). It was found that the patients with the mild olfactory disorder had it for an average of 7 days (1–13 days), the patients with the moderate olfactory disorder had it for an average of 11 days (4–23 days), and the patients with the severe olfactory disorder had it for an

Table 1 Accompanying symptoms and their frequency in patients with olfactory dysfunction

Symptoms	Frequency
Fever	25 (59%)
Cough	26 (61%)
Dyspnea	12 (28%)
Diarrhea	15 (35%)
Sore throat	18 (42%)
Nasal drip	5 (11%)
Nasal obstruction	6 (14%)
Headache	19 (45%)

Table 2 Accurate answer rates according to BSIT test parameters

Test parameters	Correct response rate
Cinnamon	14 (33%)
Turpentin	6 (14%)
Lemon	12 (28%)
Smoke	24 (57%)
Chocolate	18 (42%)
Rose	18 (42%)
Paint thinner	30 (71%)
Banana	10 (23%)
Pineapple	16 (38%)
Gasoline	32 (76%)
Soap	26 (61%)
Onion	28 (66%)

average of 6 days (1–15 days). After the 3-month follow-up, full recovery was observed in 36 patients (85.7%) and the mean test score rose to 9.9 ± 1.8 . Although olfactory dysfunction persisted in 6 patients, an increase in test scores was noted. The BSIT test results of the patients at the time of the diagnosis and in the third-month follow-up visit are shown in Fig. 1. When the patients with full recovery were inquired retrospectively, they stated that their olfactory dysfunction complaints recovered after an average duration of 3 weeks (1–8 weeks).

All the patients with mild olfactory dysfunction displayed full recovery in the follow-up. Patients with moderate or severe olfactory dysfunction had significantly lower rates of complete recovery compared to those with mild olfactory disorders ($p < 0.05$). Olfactory dysfunction was seen as the first symptom in 40% of the patients (17 patients). In patients whose first symptom was olfactory dysfunction, other symptoms showed up after an average of 2 days (1–6).

The smell that could be distinguished best was gasoline (76%), while the smell identified the least was turpentine (14%). Patient results according to test parameters are given in Table 2.

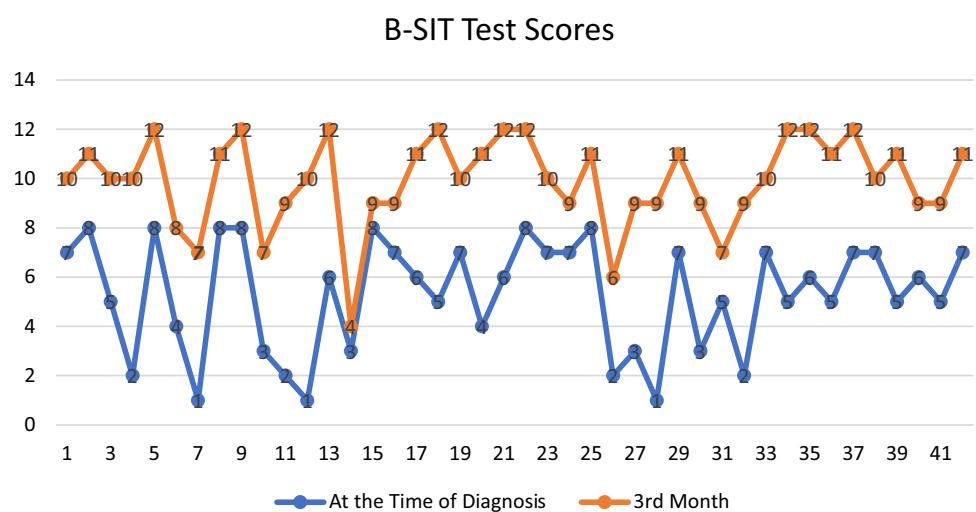
Age and lung involvement were observed to have no significant impact on olfactory functions ($p > 0.05$). While there

was no significant difference between the genders in terms of the severity of the olfactory dysfunction ($p > 0.05$), it was found that the recovery rate of the female patients was significantly lower than that of the male patients, considering the recovery rates in the 3 months of follow-up ($p = 0.04$).

Discussion

After the spread of SARS-CoV-2 to Europe, many olfactory dysfunction cases associated with COVID-19 began to be reported. This symptom has been reported at differing ratios in the literature; it can be the first symptom, or the only symptom in some cases [20]. This has been gaining importance gradually in breaking the chain of infection and isolating asymptomatic patients. However, a major part of the data reported in the literature (due to reasons such as difficulty describing olfactory dysfunction and infection risk) depends on subjective data such as patient questionnaires,

Fig. 1 BSIT test scores of the patients at the time of diagnosis and the third month



anamnesis data, telephone calls, etc.. The present study is one of the studies that objectively reveal olfactory dysfunctions that occur with COVID-19. Studies testing olfactory dysfunction in the literature are reported in Table 3.

Due to the difficulty in describing olfactory functions, there is a limited number of studies that test olfactory dysfunction occurring during the course of COVID-19 by quantitative tests and that display its severity objectively [13, 21]. There are many quantitative tests that test olfactory functions. In our study, we preferred the B-SIT test since it is easy to apply, less affected by intercultural differences, and can be performed in as little as 5 min and without close contact.

In our study, the olfactory disorder was detected in 42 (40.3%) of 104 patients between the ages of 18–60 years. Different rates have been reported in different studies for COVID-19 related olfactory dysfunction in the literature. Angelo VL et al. evaluated 72 patients with olfactory dysfunction and performed the Connecticut Chemosensory Clinical Research Center orthonasal olfaction test (CCCRC). They detected mild-moderate hyposmia in most patients, but total anosmia was detected only in 2 patients [13]. In a study conducted by Moein et al., the olfactory functions of 60 patients were evaluated using the UPSIT test. When the results were compared with the control group matched by age and sex, advanced olfactory dysfunction was detected at a high rate of 58% [21]. No information on smell recovery was provided in either of the studies. In this study, in accordance with the study by Angelo L. et al., mild function

loss was detected in most patients (52.4%) and severe function loss was detected in a smaller group (16.7%). Hornuss et al. [12] studied 45 patients, and reported an olfactory dysfunction rate of 84% with the Sniffin's Sticks test. Using the same test method, Altin et al. [16] examined 81 patients and reported an olfactory disorder rate of 61%. In their studies, Vaira et al. [22] and Petrocelli et al. [15] administered the test which they defined as the Patient Self-Administered Olfactory Psychophysical Test. In this test, olfactory thresholds were determined by smelling denatured ethyl-alcohol at rising concentrations. For the odor discrimination threshold, patients were asked to group and differentiate odors that are commonly found in the home environment. Although it is stated as an objective method in these studies, the patient factor is in the foreground in these tests and the margin of error will be high.

Given the B-SIT test results, it appears that the rate of identifying odorants that cause trigeminal stimulation by the patients was higher. (Paint thinner 71%, gasoline 76%, smoke 57%, etc.) Nevertheless, as an exception to this, turpentine was the least identified odor although it also stimulates the trigeminal pathways (14%). This may be due to the fact that the turpentine odor is less recognized by the patient population. Our experience during the test application process was in this direction. Indeed, Altundag et al. [23] revised the UPSIT test for the Turkish population and recommended that the odor of turpentine be changed due to the low recognition in the population. Our experience also supports Altundag's study.

Table 3 Olfactory dysfunction rates and test methods in different studies

Authors	Country	Patients	Olfactory dysfunction rate	Testing methods
Giacomelli et al. [5]	Italy	59	5.1%	Subjective
Klopfenstein et al. [6]	France	114	47%	Subjective
Lechien et al. [4]	Multicenter in Europe	1420	70.2%	Subjective
Levinson et al. [7]	Israel	42	35.7%	Subjective
Tostmann et al. [8]	Netherland	79	47%	Subjective
Yan et al. [9]	USA	128	28%	Subjective
Wee et al. [10]	Singapore	154	22.7%	Subjective
Moein et al. [21]	Iran	60	98%	UPSIT
Moein et al. [11]	Iran	100	96%	UPSIT test
Hornuss et al. [12]	Germany	45	84%	Sniffin's stick
Vaira et al. [32]	Italy	345	70%	CCCRC and patient self-administered olfactory psychophysical tests
Vaira et al. [33]	Italy	138	67%	CCCRC and patient self-administered olfactory psychophysical tests
Vaira et al. [22]	Italy	106	67%	CCCRC and patient self-administered olfactory psychophysical tests
Prajapati et al. [14]	USA	81	67%	BSIT
Petrocelli et al. [15]	Italy	300	63%	Chemosensitive psychophysical test
Altin et al. [16]	Turkey	81	62%	Sniffin' stick
Vaira et al. [13]	Italy	72	61%	CCCRC

American Academy of HNS established the system of “COVID-19 Anosmia Reporting Tool for Clinicians” to detect olfactory dysfunctions and many doctors from various departments supplied data input to this system. As a result of the data obtained, it was reported that olfactory dysfunction was present before COVID-19 diagnosis in 172 of the 237 patients (73%) and that olfactory dysfunction contributed to the diagnosis process for 94 patients (40%) [24]. In our study, when we analyzed the clinical course, we too detected that olfactory dysfunction was the first symptom with a high rate (40%) and the other symptoms were observed after an average of 2 days (1–6 days) in these patients. This is in parallel with the data in the literature.

After the studies on the prevalence of olfactory dysfunction, researchers also began to report recovery times. Hopkins et al. reached COVID-19 patients, with olfactory dysfunction via e-mail, and asked them to fill out a questionnaire, where 80.1% of the participants reported that they had better olfactory functions after one week. 17.6% of the patients stated that there was no change in their olfactory dysfunction, while deterioration was observed in 1.9% [25]. In their study, T. Klopfenstein et al. observed the average anosmia time of 54 patients as 8.9 days. Recovery time was equal to or longer than 7 days in 24 patients (55%) and equal to or longer than 14 days in 9 cases (20%), but no recovery was observed in one case after 28 days [6]. Sufficient data has not been obtained yet for long-term follow-ups. However, in a study where smell recovery was investigated, it was reported that of 621 patients with total smell loss and 130 patients with partial smell loss, full recovery was observed in 367 patients (49%) and partial recovery was observed in 107 (14%) after an average of 47 ± 7 days from the first consultation. However, the persistence of olfactory dysfunction was reported for 277 patients (37%). The data obtained was subjective, since information on patients was acquired by questionnaires and follow-up was carried out via telemedicine [26]. In their study, Gelardi et al. [27] reported that sensory symptoms lasted an average of 16.1 days (range 7–22 days), and of the patients, 37% completely recovered, 33% partially recovered, and 30% did not recover. In their study, Boscolo-Rizzo et al. [28] examined the course of olfactory disorder in mildly symptomatic COVID-19 patients and reported partial or complete recovery in 89% of cases after 4 weeks. Although the patients were followed up for a short time, the high rate of recovery suggested that the cause of the olfactory disorder may be due to neurotoxic or cytopathic damage. Contrary to this opinion, in their study, Huart C. et al. [29] compared 10 COVID-19 and 10 common cold patients who described olfactory disorders with 10 healthy controls and reported that the mechanism of olfactory disorder in COVID-19 may be different from the common cold and that the COVID-19-related olfactory disorder could be associated with the central nervous system, at least to some

extent. In our study, a high rate of full recovery was observed after a follow-up of 3 months, in parallel with the literature. Interview with patients who displayed full recovery revealed that recovery time was 3 weeks on average (1–8 weeks). The olfactory dysfunction of 6 patients did not display full recovery, but significant improvement was observed in the test scores found in the third month ($p < 0.05$). These results are in line with the high recovery rates in the literature.

When olfactory dysfunction was compared between patients with lung involvement and those with no lung involvement, no significant difference was observed. However, since the patients who required intensive care and those with mild clinical pictures who were followed up on an out-patient basis could not be included in the study, these data need to be supported by studies of greater scope. There is a need in the literature for standardized studies that demonstrate the correlation between the severity of olfactory dysfunction and the severity of the disease.

In a systematic review by Agyeman et al. [30] analyzing 24 different studies from 13 countries, 8,438 patients diagnosed with COVID-19 were examined, and the prevalence of olfactory dysfunction and its relationship with variables such as age and sex were investigated, and a downward trend was observed in the prevalence of olfactory dysfunction with increasing age. The author suggested that this may be related to the severe course of the disease in elderly patients and COVID-19-related olfactory disorder may be related to the mild form of the disease. But, considering the studies using psychophysical methods as a test method, it was seen that this declining trend in the prevalence of olfactory disorders in the elderly disappeared. In our study, there was no significant difference when the severity of olfactory disorder was compared between patients under 40 and over 40 years of age ($p > 0.05$). Likewise, there was no significant difference between age and recovery rates at the end of the 3rd month. However, since patients over 60 and under 18 years of age were not included in our study, a limited population was studied. This is the negative aspect of our study.

In their systematic review, Agyeman et al. [30] reported that 58.7% of the patients with olfactory dysfunction were female and there was no significant relationship between sex and olfactory dysfunction. Meini et al. [31] investigated the course of the olfactory disorders by calling 42 patients who were hospitalized and had olfactory disorders and reported that both genders had a high rate of recovery, but that females had a longer recovery compared to males (an average of 26 days in females, 14 days in males $p = 0.009$). In our study, there was no significant difference in the test scores when male patients ($n:19$) with the olfactory disorder were compared with female patients ($n:23$). However, 5 of the 6 patients who did not achieve recovery in the 3rd month of follow-up were female and the test scores of female patients were lower than male patients in the 3rd-month test

results ($p=0.04$). Considering the quite high rates of complete recovery, similar to the study by Meini et al. [31], it can be speculated that recovery may take longer in females.

Conclusion

When olfactory dysfunction in COVID-19 was tested through quantitative tests, a high rate of mild-moderate level symptoms was observed and it was seen that the rate of recovery was high in the 3-month follow-up. The finding revealing that olfactory dysfunction was the first symptom in 40% of the patients demonstrates the significance of inquiry on olfactory functions in early diagnosis.

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Compliance with ethical standards

Conflict of interest There is no conflict of interest.

Ethics approval The study was conducted after the approval of Hilit University Clinical Research Ethical Committee (Date: 29.08.2020—Decree no: 318).

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