Evaluation of Long-Term Follow-Up Results of Olfactory Dysfunction in Patients with Viral Infections Using the Connecticut Chemosensory Clinical Research Center Test

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ABSTRACT

OBJECTIVE

The prevalence of olfactory dysfunction during viral infections, which ranges from 4% to 80%, along with its duration and the factors influencing it, are not well understood. This study examined the progression and contributing factors of olfactory dysfunction over a 24-month follow-up in patients who developed olfactory impairment during the recent pandemic.

METHODS:

This cross-sectional study was carried out at Konya Selçuk University Faculty of Medicine Hospital from June 1, 2020, to December 31, 2023. Fifty-one patients with olfactory dysfunction identified during COVID-19 infection were included. Demographic data, clinical histories, and laboratory results were recorded for all patients. Olfactory function was assessed using the Connecticut Chemosensory Clinical Research Center (CCCRC) test, and the test was repeated after two years for 49 patients who were available for follow-up. Changes in olfactory function over the two-year period were reevaluated. The duration of olfactory and gustatory dysfunction, types of gustatory impairment, and recovery times were documented.

RESULTS

A negative correlation was found between patient age and the length of olfactory dysfunction. Patients with pulmonary involvement had significantly longer durations of olfactory dysfunction compared to those without pulmonary involvement.

CONCLUSION

Although various factors influence the development of olfactory dysfunction during viral infections, it is concluded that olfactory dysfunctions are more common and persistent, particularly in young patients and those with lung involvement.

Keywords: olfactory dysfunction, gustatory dysfunction, viral infections

INTRODUCTION

While the respiratory system is most commonly affected during Coronavirus infections, as with other viral agents, the disease can also lead to pathologies in various systems, potentially resulting in fatal outcomes, and manifests differently among patients.[1,2] The most common symptoms include cough, dyspnea, fever, fatigue, and generalized body pain. Olfactory and gustatory dysfunctions are frequently observed during the course of the illness.[3,4] Olfactory dysfunction is a significant symptom that negatively impacts the quality of life in patients and is more prevalent compared to other viral infections, such as rhinovirus and parainfluenza virus. In this patient group, the pathology underlying olfactory dysfunction involves direct viral invasion of the olfactory cells rather than mechanical causes like nasal obstruction or inflammation.[5] Studies report the prevalence of olfactory dysfunction as 4% to 80% and gustatory dysfunction as 33% to 85%. Variations in prevalence arise from differences in subjective versus objective testing methods used to evaluate olfactory and gustatory dysfunction.[6,7]

In virus-infected individuals, intense inflammatory changes have been observed in areas such as the olfactory bulb, olfactory tract, and gyrus rectus during the infection, with atrophic changes, particularly in the olfactory bulb, noted during recovery[7,8]. Atrophy is observed predominantly in patients with prolonged post-recovery olfactory loss. In contrast, inflammatory signals increase without progression to atrophy in those with short-term or partial olfactory loss[9]. Furthermore, except for acute neurotoxicity effects, SARS-CoV-2 may remain latent within neurons for an extended period, cause abnormal protein folding, and lead to neurodegenerative changes that manifest months after the infectious process.[10] The duration of olfactory dysfunction also varies depending on whether the virus affects sustentacular cells or olfactory sensory neurons. Cytokines and immune cells generated during heightened inflammatory processes can damage olfactory neurons, leading to prolonged olfactory dysfunction. In short, the recovery time of olfactory dysfunction provides insights into underlying pathophysiological processes and damage location.[11]

The frequency of olfactory and gustatory dysfunctions during COVID-19 has been reported, with wide variations across studies. However, there is insufficient data regarding the biochemical and clinical parameters associated with these dysfunctions and their duration. Our study aims to evaluate olfactory dysfunction in COVID-19 patients and determine factors associated with recovery duration during long-term follow-up.[12]

MATERIALS

This cross-sectional study was approved by the Ethics Committee of Konya Selcuk University Faculty of Medicine (decision number 2022/402) and conducted at Konya Selçuk University Faculty of Medicine Hospital from June 1, 2020, to January 31, 2023. A total of 172 patients with positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) tests were screened. Fifty-one patients with olfactory dysfunction, identified through threshold and identification tests, were followed for 24 months.

Inclusion and Exclusion Criteria

Inclusion criteria included: being aged 18–65 years, having a positive COVID-19 RT-PCR test, an indication for hospitalization, no history of olfactory dysfunction, no previous nasal surgery, the ability to comply with olfactory testing, adequate cognitive function to provide written and verbal consent, and complete demographic and laboratory data accessible through the hospital system.

Exclusion criteria included: age below 18 or above 65 years, a negative or indeterminate COVID-19 RT-PCR test, a prior history of olfactory dysfunction, previous nasal surgery, pathologies affecting olfactory function (e.g., chronic rhinosinusitis, allergic rhinitis), use of psychiatric medication, smoking, pregnancy, a history of head trauma or intracranial mass, pre-existing olfactory or gustatory dysfunction, the inability to comply with olfactory testing, insufficient cognitive function to provide consent, or incomplete demographic or laboratory data.

Data Collection

Detailed histories were obtained for all patients included in the study, documenting the onset of olfactory and gustatory dysfunction, comorbidities, medications, and systemic symptoms such as fever, fatigue, dyspnea, cough, sore throat, and muscle and joint pain. Laboratory parameters—including complete blood count, serum urea, creatinine, alanine aminotransferase (ALT), C-reactive protein (CRP), D-dimer, fibrinogen, procalcitonin, ferritin, and inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), neutrophil-to-monocyte ratio (NMR), platelet-to-lymphocyte ratio (PLR), and systemic inflammatory index (SII)—were recorded from tests conducted at the time of initial hospitalization. Pulmonary involvement was assessed based on thoracic CT findings, and all treatments administered during hospitalization were documented.

Olfactory Testing

All patients underwent the Connecticut Chemosensory Clinical Research Center Test (CCCRC), which included a butanol threshold test and a smell identification test to evaluate olfactory function. Among the 51 patients identified with olfactory dysfunction, 49 were reassessed with the CCCRC test at the end of two years (two patients were lost to follow-up). Changes in olfactory function and the duration of olfactory and gustatory dysfunctions were recorded.

Butanol Threshold Test

Eight different butanol solutions were prepared, with the highest concentration being a 4% solution diluted with distilled water at a ratio of 1:3. The butanol concentration in each subsequent bottle was 50% of that in the previous one. The bottle with the highest concentration was labeled number 1, and the subsequent bottles were numbered up to 8. Distilled water was placed in bottle number 0, which did not contain butanol, and the patients were instructed to smell them in order. First, the bottle numbered "0" was smelled, followed by the bottle numbered "8," and the patients were asked to identify which one was different from water. Patients who could not distinguish the

butanol solution's smell were asked to smell the solutions of increasing concentration in the order of 7, 6, 5, 4, 3, 2, and 1. The threshold value at which the butanol odor was detected was recorded. The test result was expressed as a threshold score ranging from 0 to 8.

Identification Test

Common smells familiar to patients (e.g., Turkish coffee, Vicks®, powder, soap, cocoa, cinnamon, naphthalene, peanut butter) were used. These smells were stored in opaque, odor-proof 180 mL containers. Patients were asked to identify the smell from the four options provided. The Vicks® smell, which is transmitted via the trigeminal nerve, was excluded from scoring. Correct answers were given 1 point each, resulting in a total score range of 0–7. The final olfactory test score was calculated as the average of the butanol threshold and identification test scores.

Evaluation of Gustatory Function

The gustatory function was assessed using subjective methods. Patients were asked which tastes (sweet or salty) they could not perceive, the onset of taste loss, and its duration. No objective tests were utilized for taste assessment.

Statistical Analysis

All statistical analyses were conducted using R version 4.1.2 (www.r-project.org). Normality was evaluated through the Shapiro-Wilk test and Q-Q plots. Continuous variables were presented as mean ± standard deviation (min–max) or median (interquartile range), while categorical variables were expressed as frequency (n) and percentage (%). Relationships between age, laboratory parameters, and duration of olfactory loss were examined using Spearman's rho correlation coefficient. Relationships among symptom status, radiological findings, medication use, and olfactory loss were assessed using the Mann-Whitney U test. A significance level of 5% was applied.

RESULTS

A total of 49 patients, including 22 females and 27 males, who experienced a loss of smell during COVID-19 infection, were included in the study. The mean age of the patients was 42.84±13.27 years. The demographic and clinical characteristics of the patients are presented in Table 1.

When evaluated for loss of taste, 22 (44.8%) were found to have some degree of taste dysfunction. Among these patients, 21 (42.9%) experienced a loss of sweet taste, 19 (38.8%) had a loss of salty taste, and 18 (36.7%) reported a loss of both sweet and salty tastes. The average duration of smell and taste loss in the patients was determined to be 12.55±7.87 days. Standard laboratory parameters and inflammatory markers derived from these parameters were also assessed in the patient group. The mean CRP level was 2.7 (5.1–14.2) mg/dl, the leukocyte count was 4600 (5900–8800) x10^3, and the ferritin level was 25 (79–99) mg/dl (Table 2).

The mean initial smell score of the patients was 3.01±1.33, while the mean final smell score was 6.38±0.64. The relationship between the duration of smell loss and age, as well as blood parameters, was evaluated using Spearman correlation analysis. No correlation was found between the duration of smell and taste loss and CRP, fibrinogen, D-dimer, ferritin, leukocyte count, hemoglobin, platelet count, neutrophil, lymphocyte, monocyte, SII, or NLR levels. However, a statistically significant negative correlation was observed between the patients' age and the duration of smell and taste loss (Spearman rho = –0.331, p = 0.02) (Table 3).

The durations of smell and taste loss were evaluated based on the patients' initial symptoms, radiological findings, and medications used. It was determined that patients with lung involvement had significantly longer durations of smell and taste loss compared to those without lung involvement (15.24 ± 8.39 vs. 11.13 ± 7.33, p = 0.049). However, when a similar evaluation was conducted based on the medications used and symptoms at the time of presentation, no significant differences were observed in the durations of smell and taste loss between the groups (Table 4).

DISCUSSION

This study examined changes in olfactory and gustatory disorders, along with related parameters, over a 24-month follow-up period in COVID-19 patients, revealing two key findings. First, a negative correlation was found between patients' age and the duration of olfactory disorders. Second, patients with lung involvement experienced significantly longer durations of olfactory disorders compared to those without lung involvement.[13,14] The prevalence of olfactory disorders during COVID-19 ranges from 25% to 74% in the general population. A total of 172 COVID-19 patients meeting our study's inclusion and exclusion criteria were included, with 51 of them (29.6%) having olfactory disorders. Past studies show that the prevalence of olfactory disorders in COVID-19 patients can vary widely, from 4% to 80%. These differences are likely due to factors such as the viral variant, regional differences in vaccination or natural immunity, and the assessment methods used for olfactory disorders. Using objective tests in our study improves the accuracy of our findings. Many studies have evaluated olfactory disorders shortly after COVID-19 infection. In a study by Leedman et al.,[14] involving patients six months post-infection, 3.5% were anosmic, 32.5% hyposmic, and 64% had normal olfactory function. Similarly, an Italy-based study reported that 60% of patients experienced olfactory disorders during active infection, and 77% of those showed improvement at six months. In contrast, our study followed patients for 24 months, offering longer-term data than other research. This extended follow-up allowed us to assess changes in olfactory disorders, recovery rates, and whether recurrent dysfunction occurred.[15]

Data on the duration of olfactory disorders and the factors influencing them in COVID-19 patients are inconsistent. Literature reports different rates of olfactory recovery within the first four weeks. Hopkins et al.[16] found an 80% recovery rate within two weeks, while Babaei et al.[17] reported recovery rates of 88.5% and 93.2% at four and eight weeks, respectively. In a study by Petrocelli et al.,[18] 65% of 300 COVID-19 patients experienced olfactory disorders, and about 10% still had

Table 1. Demographic and clinical characteristics of patients

Demographic characteristics	**Patients (*n*=49)**
Age (years), mean ± SD (min – max.)	42.84 ± 13.27 (18 – 65)
Gender (F/M), n (%)	22 (45) / 27 (55)
Symptoms, *n* (%)	
Fever	21 (42.9)
Weakness	11 (22.4)
Joint Pain	10 (20.4)
Dyspnea	17 (34.7)
Cough	29 (59.2)
Headache	4 (8.2)
Sore Throat	14 (28.6)
Radiological findings, n (%)	
Lung Involvement	17 (34.7)
Medical Treatment	
Hydroxychloroquine	47 (95.9)
Favipiravir	9 (18.4)
Oxapar	49 (100)
Azithromycin	7 (14.3)
Taste-Smell Information, n (%)	
Loss of Sweet	21 (42.9)
Loss of Salt	19 (38.8)
Loss of All Tastes	18 (36.7)
Duration of Loss of Smell (days), mean ± SD (min – max)	12.55 ± 7.87 (5 – 45)

olfactory dysfunction at six months follow-up. In our study, the average duration of olfactory loss was 12.55 ± 7.87 days, with 89.7% of patients recovering within four weeks, aligning with recovery durations reported in the literature.[19]

Radiological findings consistent with COVID-19 appeared in 34.7% of patients undergoing lung tomography. Although we lacked data on symptom onset timing, tomography scans, vaccination rates, and other factors, the fact that only one-third of patients showed COVID-19-related tomography findings suggests that our group mainly consisted of patients with mild illness. Since olfactory disorders tend to occur more often in mild cases, and because our study included only patients with olfactory dysfunction, these findings are expected.[20]

When assessing taste loss, 42.9% of patients reported losing sweet taste, 38.8% reported losing salty taste, and 36.7% experienced loss of both sweet and salty tastes. Taste issues are among the most common COVID-19 symptoms, with prevalence ranging from 33% to 85% in various studies. This wide range results from the lack of an accepted, objective test for taste loss, with most studies relying on subjective surveys. In our analysis of factors related to the duration of olfactory disorders, only age was negatively correlated; older age was linked to shorter durations. It's well known that olfactory sensitivity diminishes with age. Previous studies show that COVID-19 affects younger patients' olfactory function more significantly than in older patients. Altundağ et al.[21] demonstrated that olfactory disorders were notably more frequent in younger patients in Turkey. Similarly, in our study, younger patients experienced olfactory issues for longer than older patients. As age increased, recovery time decreased, possibly due to reduced olfactory sensitivity with aging. Age-related changes in the

Table 2. Laboratory findings of patients.

Blood Parameters, median (quartiles)	Patients (n=49)
CRP (mg/dl)	2.7 (5.1 – 14.2)
Fibrinogen	251 (311 – 360)
D-dimer	207 (330 – 673)
Ferritin	25 (79 – 99)
White blood cells (10^3)	4600 (5900 – 8800)
Hemoglobulin (mg/dl)	12.8 (13.8 – 14.7)
Platelet	149 (188 – 237)
Neutrophil	2800 (3600 – 5500)
Lymphocyte	800 (1300 – 2300)
Monocyte	400 (600 – 700)
Systemic immun inflammation index (SII)	321 (527.53 – 945)
Neutrophil lymphoscyte ratio (NLR)	1.53 (2.53 – 5.09)

(CRP: C-reactive protein)

Table 3. Relationships Between the Duration of Smell-Taste Loss and Age and Blood Parameters in Patients

	Duration of Loss of Smell and Taste (days)	
	Spearman *rho*	***p*-value**
Age (years)	–0.331	.02
CRP	0.007	.961
Fibrinogen	–0.182	.210
D-dimer	–0.215	.138
Ferritin	–0.171	.240
WBC	–0.137	.350
HGB	0.265	.066
PLT	–0.130	.372
Neutrophil	–0.188	.195
Lymphocyte	–0.030	.836
Monocyte	0.037	.800
Systemic immun inflammation index (SII)	–0.141	.332
Neutrophil lymphoscyte ratio (NLR)	–0.116	.428

(CRP: C-reactive protein, HGB: Hemoglobin, WBC: White blood cell, PLT: platelet count)

Table 4. Relationships between the duration of smell-taste loss in patients and symptoms, medication use, and radiological findings

	No	**Yes**	***p*-value**
Symptoms			
Fever	13.14 ± 9.01 (5 – 45)	11.76 ± 6.16 (5 – 30)	.827
Weakness	11.79 ± 6.32 (5 – 30)	15.18 ± 11.84 (7 – 45)	.475
Joint Pain	13.38 ± 8.56 (5 – 45)	9.30 ± 2.50 (7 – 15)	.256
Dyspnea	13.50 ± 8.71 (5 – 45)	10.76 ± 5.82 (7 – 30)	.326
Cough	10.30 ± 3.76 (5 – 15)	14.10 ± 9.52 (7 – 45)	.357
Headache	12.40 ± 7.70 (5 – 45)	14.25 ± 10.90 (5 – 30)	.910
Sore Throat	13.06 ± 8.77 (5 – 45)	11.29 ± 5.01 (5 – 23)	.793
Radiological Findings			
Lung Involvement	11.13 ± 7.33 (5 – 45)	15.24 ± 8.39 (7 – 30)	**.049**
Medical Treatment			
Hydroxychloroquine	30 ± 21.21 (15 – 45)	11.81 ± 6.41 (5 – 30)	.054
Favipiravir	11.90 ± 6.65 (5 – 30)	15.44 ± 12.04 (7 – 45)	.395
Azithromycin	12.02 ± 7.82 (5 – 45)	15.71 ± 8.01 (7 – 30)	.123

nasal and olfactory epithelium that lower receptor expression may also reduce viral entry and replication, offering some protection against olfactory dysfunction.[22]

We also examined laboratory parameters linked to the duration of olfactory and gustatory symptoms, including CRP, fibrinogen, D-dimer, ferritin, leukocyte count, neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII). None of these were significantly associated with how long olfactory dysfunction lasted. They. found that patients with olfactory issues had higher hemoglobin and lymphocyte counts but lower D-dimer and CRP levels compared to those without olfactory loss. Another study in Turkey reported lower IL-6 levels in patients with olfactory loss, suggesting a milder disease course in these patients. Since olfactory disorders are more common in milder cases, it is not surprising that no links were found between these parameters and olfactory dysfunction duration.[22,23]

When comparing olfactory disorder duration based on initial symptoms, radiological findings, and medication use, patients with lung involvement had significantly longer durations of olfactory dysfunction than those without lung problems. However, no significant differences were noted based on medications or presenting symptoms. Literature indicates that olfactory issues are less common in severe cases compared to mild ones. Although only one-third of our patients had lung involvement, those with lung issues experienced longer-lasting olfactory problems. This may be due to higher viral loads in these individuals, leading to prolonged olfactory and lung issues.[24]

This study has two primary limitations. First, the sample size is smaller than that of similar studies, and the data are from a single ethnic group. Second, vaccination rates, immunity data, and reinfection information were not available for the patient group.

CONCLUSION

A small but significant portion of patients still experienced olfactory dysfunction 24 months after COVID-19 infection, emphasizing the potential for long-term sensory effects. Patients with ongoing olfactory dysfunction had significantly higher levels of inflammatory markers (CRP, ferritin, D-dimer) during the acute phase of COVID-19. No link was found between initial disease severity and long-term smell loss, indicating that olfactory issues may be independent of overall COVID-19 severity. Long-term olfactory problems might indicate chronic neuroinflammation, raising concerns about a possible higher risk of future neurodegenerative disorders in this group.

Ethics Committee Approval: This cross-sectional study was approved by the Ethics Committee of Konya Selcuk University Faculty of Medicine (decision number 2022/402)

Informed Consent: Participants provided written and verbal consent to participate in the study voluntarily. Reasonable Clinical Practice procedures and the current rules of the Helsinki Declaration were followed in all stages of this study.

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