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Evaluation of olfactory dysfunction persistence after COVID-19: a prospective study

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Abstract. – OBJECTIVE: Alterations of the olfactory function in patients affected by COVID-19 often have an early onset and a variable duration ranging from a few weeks to months. The aim of this study was to evaluate olfactory dysfunction persistence after recovery from COVID-19, and potential related clinical-demographic conditions.

PATIENTS AND METHODS: A total of 76 patients recovered from COVID-19 from at least 20 days with olfactory dysfunction during the infection were included in the study. For the subjective evaluation of olfactory function, a visual analogic scale (VAS) was used. The objective evaluation was performed with the use of the Sniffin' Sticks test.

RESULTS: Objective assessment of olfactory function revealed that 48 (63.16%) patients were found to be normosmic (TDI ≥ 30.5), 26 (34.21%) were hyposmic (TDI from 30.5 to 16.5) and two (2.63%) were anosmic (TDI ≤ 16.5) at the time of the evaluation. These results did not show a significant difference between subjective and objective tests (p = 0.45). Most patients recovered their sense of smell within the first two months after recovery while a portion (22.2%) still experienced olfactory alterations 4-6 months after SARS-CoV-2 infection. Patients who had not recovered their sense of smell had a significantly longer period of SARS-CoV-2 positivity compared to patients that fully recovered (36.07 ± 7.78 days *vs.* 29 ± 7.89 days; p = 0.04).

CONCLUSIONS: Our results suggest that the duration of the infection negatively correlates with the recovery of olfactory function.

Key Words:
COVID-19, Olfactory dysfunction, Sniffin' Sticks Test, Hyposmia, Anosmia.

Introduction

The coronavirus disease 2019 (COVID-19) first appeared in December 2019 in the city of Wuhan, China. The disease was caused by a novel coronavirus called Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), and rapidly spread worldwide[1-5].

Bagheri et al[6] first described alteration of olfactory and gustatory functions in Iranian patients positive to SARS-CoV-2, suggesting that this symptomatology could have an early onset in the disease. Afterwards, many researchers studied the disturbance of smell and taste to define the incidence and prognostic significance, as well as to clarify its pathogenesis in COVID-19.

Studies available in the literature[7-11] report percentages of olfactory dysfunction ranging from 52% to 98%. These percentages, in most cases, are collected through questionnaires or telephone interviews; limited data are obtained through objective smell tests. In May 2020, the World Health Organization (WHO) added alterations in smell and taste to the symptoms of COVID-19.

Olfactory dysfunction appears to have an early onset, and a variable duration ranging from a few weeks to months[12,13]. The etiopathogenesis is not yet clear; hypotheses include nasal obstruction, damage to olfactory sensory neurons, damage to the olfactory cortex, damage to olfactory support cells, and damage to the olfactory epithelium related to inflammation[14-16].

The aim of this study was to evaluate, through subjective and objective tests, if and for how long the alteration of smell persisted at least 20 days after recovery from COVID-19, and potential related clinical-demographic conditions.

Patients and Methods

This prospective study was conducted at the Otolaryngology Clinic of the "Mater Domini" University Hospital of Germaneto, Catanzaro, Italy, from March to August 2021. The inclusion criteria were patients recovered from COVID-19 from at least 20 days that reported onset of olfactory dysfunction during the infection.

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The exclusion criteria were patients aged ≤ 18 years, patients who had not developed olfactory alterations during SARS-CoV-2 infection, patients with previous nasal disorders (such as previous facial trauma or nose/sinus surgery, or chronic or allergic rhinosinusitis), and patients with olfactory disorders prior to COVID-19 disease.

The study was approved by the Ethics Committee of the Calabria Region No. 111, March 2021. Patients were informed about the purpose and modalities of the study and signed informed consent to be included.

Demographic and clinical anamnestic data were collected for each patient. The duration of the disease was calculated on the time elapsed between the first positive nasopharyngeal swab and the first negative nasopharyngeal swab for COVID-19 using SARS-CoV-2 RNA quantitative reverse transcription polymerase chain reaction (RT-qPCR).

Evaluation of olfactory function was performed with subjective and objective tests. For the subjective evaluation, a visual analogic scale (VAS) consisting of a centimeter scale showing values from 0 to 10, where 0 indicated the perception of completely compromised olfactory function, 5 indicated an average compromised olfactory function, and 10 indicated normal olfactory function, was used. The patient was asked to indicate the value corresponding to olfactory function at the time of the test. We considered a score of 0-3 as anosmia, a score of 4-8 as hyposmia, and a score of 9-10 as normosmia.

The objective evaluation with was performed with the use of the Sniffin' Sticks test (Burghardt®, Wedel, Germany) for smell threshold and odor discrimination tests. The Sniffin' Sticks test is a validated olfactory test that evaluates olfactory Threshold Discrimination and Identification (TDI) score by administering felt pens filled with odors to patients' nostrils[10]. For the olfactory threshold test, the threshold concentration at which the patient can identify n-butanol is established using a scale technique based on a forced choice of three alternatives. Among the pens presented, the patient must indicate the one that thinks contains the odorous substance. The odor discrimination ability is determined by 16 individual tests. In the triplet that is presented, the patient must identify the marker that contains an odorous substance different than the other two. The odor identification test is carried out using 16 common odors. The patient must identify the smell by choosing the image or term that identifies it from four variables presented. The numerical value obtained in the three tests is added to obtain the TDI score. TDI values ≥ 30.5 indicate normosmia, values of 16.6-30.5 indicate hyposmia, and values ≤ 16.5 indicate anosmia[17]. The test was performed in a large and airy room, and patients were asked not to eat or smoke at least 2 hours before the test. It was also recommended not to use body perfumes on the day they were tested. All patients had their eyes covered before starting the smell threshold and odor discrimination tests. The data collected was archived in special dedicated databases.

According to the Sniffin' Sticks test, normosmic patients were included in Group A and anosmic/hyposmic patients were included in Group B.

Statistical Analysis

Statistical analysis was performed with MedCalc software Version 19.4 (Mariakerke, Belgium). Means and standard deviations were calculated. A multivariate analysis was performed using multiple regression to determine independent prognostic factors. Fisher's exact test was used to identify differences between demographic and clinicopathologic data of the two cohorts of patients. Student's *t*-test was used for comparison of the means of the Sniffin' Sticks test between Group A and Group B. A *p*-value less than 0.05 was considered statistically significant.

Results

A total of 76 patients were included in the study; 36 were males (47.37%) and 40 were females (52.63%) with a mean age of 42.5 years ± 15.10 (range, 18-76).

Table I shows the clinical demographic characteristics of all patients included in the study. The most frequent symptoms reported by patients associated with SARS-CoV-2 infection were fatigue (78.9%), muscle pain (76.3%), and fever (68.4%) (Table I). None of the patients recruited had been hospitalized due to the disease. None of the patients had undergone therapy for the smell disorder. Forty-four (57.89%) patients reported that the smell disorder presented as the first symptom of the disease.

Subjective assessment was performed using the VAS scale: 56 (73.68%) patients reported a score between 9 and 10, 14 (18.42%) reported a score between 8 and 4, and 6 (7.89%) reported a score between 3 and 0.

Objective assessment of smell using the Sniffin' Sticks test revealed the following: 48 (63.16%)

Table I. Clinical-demographic characteristics of all patients.

Characteristics	Patients
Sample size	76
Age (mean ± SD)	42.50 ± 15.10
Gender	40 F (52.63%) | 36 M (47.47%)
Associated symptoms	***N (%)***
Fever	52 (68.4)
Headache	48 (63.2)
Muscle pains	58 (76.3)
Rhinorrhea	**12 (15.8)**
Nasal obstruction	24 (31.6)
Pharyngodynia	28 (36.9)
Vertigo	**22 (28.9)**
Diarrhea	24 (31.6)
Fatigue	60 (78.9)
Dyspnea	38 (50)
Cough	40 (52.7)
Comorbidities	***N (%)***
Cardiovascular	16 (21.1)
Respiratory	0 (0)
Diabetes	4 (5.2)
Allergies	18 (23.7)
Autoimmune diseases	6 (7.9)
Thyroid diseases	10 (13.1)
Hypercolesterolemia	4 (5.2)
Gastric diseases	2 (2.6)
Smoking habit	20 (26.3)
Duration of COVID-19	
Mean ± SD	31.1 ± 9.41 days
Range	11-46 days

patients were found to be normosmic (TDI ≥ 30.5) (Group A), while 26 (34.21%) were hyposmic (TDI from 30.5 to 16.5) and two (2.63%) were anosmic (TDI ≤ 16.5) (Group B). Fifty-six patients (73.68%) according to the subjective test and 48 (63.16%) according to the Sniffin' Sticks test appeared to have recovered olfactory function at the time of testing ($p = 0.45$). Contrarily, 20 (26.32%) and 28 (36.84%) patients according to the subjective and objective evaluations, respectively ($p = 0.61$), did not recover their sense of smell.

Of the 48 patients in Group A (Table II), 24 were males (50%) and 24 were females (50%) with a mean age of 42.3 years ± 14.42. In this group, the mean olfactory threshold value was 7.87 ± 1.42, the mean discrimination was 13.95 ± 1.44, and the mean identification was 13.79 ± 2.65 (TDI 35.61 ± 2.65). Twenty-four (50%) of them reported that the smell disorders appeared before the other symptoms. The mean duration of the self-reported disorder was 23.61 ± 22.67 days. The tests were administered in 10 patients after ≤ 30 days of healing, in 8 patients after 31-60 days, in 4 patients after 61-90 days, in 12 patients after 91-120 days, and in 14 patients after 121-180 days.

Table III shows the clinical-demographic characteristics and results of the Sniffin' Sticks test of the 28 patients in Group B (Table III). The average age was 43.5 years ± 17.27; 12 (42.86%) were males and 16 (57.14%) were females. In this group, the mean olfactory threshold was 4.76 ±

Table II. Clinical-demographic characteristics and results of Sniffin' Sticks test and VAS scale in Group A.

Characteristics	Patients
Sample size	48
Age (mean ± SD)	42.29 ± 14.42
Gender	24 F (50%) | 24M (50%)
Associated Symptoms	***N (%)***
Fever	32 (66.7)
Headache	30 (62.5)
Muscle pains	38 (79.2)
Rhinorrhea	6 (12.5)
Nasal obstruction	16 (33.4)
Pharyngodynia	18 (37.5)
Vertigo	12 (25.0)
Diarrhea	18 (37.5)
Fatigue	34 (70.9)
Dyspnea	18 (37.5)
Cough	28 (58.4)
Comorbidities	***N (%)***
Cardiovascular	12 (25)
Diabetes	0
Allergies	12 (25)
Autoimmune diseases	4 (8.4)
Hypercolesterolemia	0
Thyroid diseases	4 (8.4)
Gastric diseases	2 (4.2)
Smoking habit	10 (20.8)
Duration of COVID-19	
Mean ± SD	29 ± 7.89 days
Range	11-46
Sniffin' Sticks Test	
Mean ± SD	7.87 ± 1.42
OT	13.95 ± 1.05
OD	13.79 ± 1.44
OI	35.61 ±2.65
TDI	
VAS scale	
Score 0-3	0
Score 4-8	12
Score 9-10	36

Table III. Clinical-demographic characteristics and results of Sniffin' Sticks test and VAS scale in Group B.

Characteristics	Patients
Sample size	28
Age (mean ± SD)	43.50 ± 17.27
Gender	16 F (57.1%) | 12 M (42.9%)
Associated Symptoms	***N (%)***
Associated Symptoms	18 (64.3)
Fever	18 (64.3)
Headache	22 (78.6)
Muscle pains	6 (21.4)
Rhinorrhea	8 (28.6)
Nasal obstruction	8 (28.6)
Pharyngodynia	10 (35.7)
Vertigo	8 (28.6)
Diarrhea	26 (92.9)
Fatigue	16 (57.2)
Dyspnea	8 (28.6)
Cough	
Comorbidities	***N (%)***
Cardiovascular	4 (14.3)
Diabetes	4 (14.3)
Allergies	6 (21.4)
Autoimmune diseases	2 (7.2)
Hypercolesterolemia	4 (14.3)
Thyroid diseases	6 (21.4)
Gastric diseases	0
Smoking habit	10 (35.7)
Duration of COVID-19	
Mean ± SD	36.07 ± 7.78 days
Range	22-44 days
Sniffin' Sticks Test	
Mean ± SD	4.76 ± 1.06
OT	10.07 ± 1.86
OD	10.5 ± 2.41
OI	25.33 ± 5.01
TDI	
VADS scale	
Score 0-3	6
Score 4-8	2
Score 9-10	20

1.06, the mean was discrimination 10.07 ± 1.86, and the mean identification was 10.5 ± 2.41 (TDI 25.33 ± 5.01). Of these patients, only two were found to be anosmic with a TDI ≤ 16.5. Twenty patients (71.43%) reported that the smell disorder appeared before the other symptoms. The tests were administered in 6 patients after ≤ 30 days, in 12 patients after 31-60 days, in 4 patients after 61-90 days, in 2 patients after 91–120 days, and in 4 patients after 121-180 days.

The comparison of olfactory function evaluated by the Sniffin' Sticks test showed a significant difference between Group A and B in odor threshold ($p < 0.0001$), odor discrimination ($p < 0.0001$), odor identification ($p < 0.0001$), and TDI ($p < 0.0001$) (Figure 1).

In Group A, the time of positivity to the virus evaluated by RT-qPCR (date of positivity - date of negativity) was on average 29 ± 9.73 days while in the Group B the average duration of virus positivity was 36.1 ± 7.78 days ($p = 0.04$). The duration of the disease in multivariate analysis was the only independent variable related to the recovery of smell; no significant correlations were found for other clinical-anamnestic variables taken into consideration.

According to the period of examination of normosmic patients, 10 of 16 (62.5%) patients were evaluated in the first 30 days after healing, 8 of 20 (40%) patients were evaluated after 31-60 days, 4 of 8 (50%) patients were evaluated after 61-90 days, 12 of 14 (85.71%) patients were evaluated after 91-120 days, and 14 of 18 (77.78%) were patients evaluated at 121-180 days.

Discussion

Olfactory alteration is an early symptom of COVID-19 infection, most often observed in cases of mild and moderate infections that do not require hospitalization; for this reason, it is considered a prognostic factor of non-serious disease[18-20]. In the early periods of the pandemic, the alteration of smell was assessed through subjective tests such as questionnaires administered by telephone or through surveys to limit the risk of contagion. These studies indicated that smell disorders were reported by 33.9%-85.6% of the infected population[13,21-24]. Thanks to the help of personal protective equipment, some study groups have begun to submit their hospitalized patients to objective smell tests using tests[25-27].

The objective of our study was to evaluate the recovery of the sense of smell in patients recovered from SARS-CoV-2 from at least 20 days using both a subjective and objective test to detect olfactory function. Our results did not show a significant difference between the responses to the subjective and objective tests; however, other researchers, such as Gozen et al[28], observed differences between the results of the objective and subjective tests (52.5% *vs.* 83.0%, respectively).

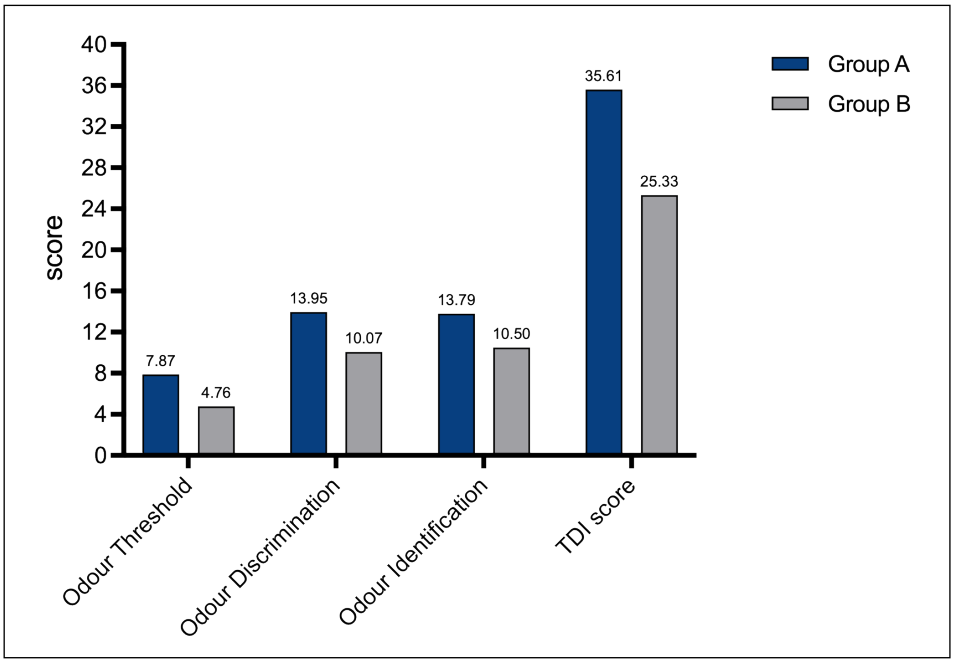

Figure 1. Comparison of Odour Threshold, Odour Discrimination, Odour Identification and Threshold Discrimination and Identification scores between Group A and Group B.

In our sample, we found that most patients recovered their sense of smell within the first two months of healing, while recovery for the remaining patients took much longer; 22.2% had not recovered functionality after 4-6 months after healing.

The recovery time of the sense of smell seems to be related to the duration of the disease; patients who had not recovered their sense of smell had a significantly longer period of virus positivity compared with patients that had recovered their sense of smell (36.07 ± 7.78 days *vs.* 29 ± 7.89 days; $p = 0.04$).

Other clinical-anamnestic variables, such as age, sex, smoking habits, and comorbidities, do not appear to have influenced the recovery of the sense of smell, which is consistent with previous reports[9,29].

It is thought that in most cases, the recovery of olfactory function occurs in the first few weeks[8,26,30]. In a multicenter study, Niklassen et al[29] tested 111 patients 3–28 and 169 days after infection with the Sniffin' Sticks test. While most people recovered function within the first 28 days, 27% showed persistent dysfunction. Again, using the Sniffin' Sticks test, Otte et al[31] evaluated 91 patients previously infected with COVID-19 and found 45.1% were hyposmic almost 8 weeks after infection.

The studies conducted so far agree that recovery occurs within the first 60 days; however, no evaluation of the sense of smell after more than 6 months has been described to allow us to evaluate what percentage and how seriously this disorder persists after healing

This is the first study to show that recovery of olfactory function depends on the duration of the disease and that the loss of smell can persist even 6 months after healing. The correlation between disease duration and the pathophysiology of olfactory damage from COVID-19 could be due to several reasons. The spike protein of the SARS-COV-2 virus binds the Angiotensin-Converting Enzyme 2 (ACE2) receptor to enter the host, and this interaction requires splitting of the Spike protein by the protease TMPRSS2 on the cell surface. The cell surface protein ACE2 and TMPRSS2 are expressed in sustentacular cells of the olfactory epithelium but not in the olfactory sensory cells, which could explain the transience of the disorder[32].

An alternative pathway for virus entry to the central nervous system is via by Neurolipin 1 receptor (NRP-1). NRP-1 is a cell surface receptor that plays an essential role in angiogenesis, regulation of vascular permeability, and development of the nervous system, and is expressed in the respiratory and olfactory epithelium and can bind

the spike protein[33,34]. This link could facilitate virus entry and damage of olfactory sensory neurons with consequent loss of smell in a persistent manner[35]. Therefore, the persistence of the virus on the epithelium of the nasal cavities could create greater and more consistent damage to sustentacular cells or directly to the olfactory neurons and the bulb. One limitation of our study is the small sample investigated but one strength is the use of the three components of the Sniffin' Stick test, thus allowing an evaluation of complete olfactory function in a homogeneous group of patients. We were also able to evaluate patients 4-6 months after healing, allowing us to highlight the small number of patients who had not recovered their sense of smell several months after healing.

Conclusions

The recovery of olfactory function after COVID-19 appears to be independent of the patient's clinical and demographic characteristics. Instead, it appears that the duration of the infection negatively correlates with the recovery of olfactory function. Further studies on larger patient samples are needed to understand the mechanisms underlying the correlation between the duration of the disease and the recovery of smell.

Conflict of Interests

The authors declare that they have no conflict of interests.

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