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ORIGINAL CONTRIBUTION

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Persistent olfactory complaints after COVID-19: a new interpretation of the psychophysical olfactory scores*

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Abstract

Background: Sudden olfactory loss is a major symptom of SARS-CoV-2 infection and has a negative impact on daily life quality. Almost 80% of disorders regress spontaneously. No precise characterization of the medium- and long-term olfactory symptoms has been carried out yet, apart from self-assessments. The main objective of this work was to characterize persistent smell disorders in this population.

Methodology: Consecutive patients consulting to the ENT department with post-Covid19 olfactory loss were included. The clinical examination included an analog scale for the self-assessment of olfactory recovery), a nasofibroscopy, the Sniffin' Stick Test and the short version of the Questionnaire of olfactory disorders.

Results: Among the 34 patients included, based on the Sniffin' Sticks Test, 29.4% (n=10) could be classified as normosmic, 55.9% (n=19) as hyposmic and 14.7% (n=5) as functional anosmic). Only olfactory identification impairment was significantly correlated with olfactory complaint and daily anxiety and annoyance related to lack of olfaction recovery. This identification disorder seemed to worsen over time.

Conclusions: It is crucial to assess odor identification disorders in case of persistent olfactory complaints after COVID-19. It is fundamental to target this disorder, as it does not improve spontaneously and negatively impact quality of life.

Key words: olfactory dysfunction, olfaction, sniffin sticks test, COVID-19, quality of life

Introduction

COVID-19 infection symptoms initially described were fever and cough in respectively 44 and 65% of cases[(1)]. Currently, many studies report the frequency of anosmia preceding or during COVID19 seroconversion[(2–5)]. Anosmia can be the only COVID-19 symptom[(6)]. So, sudden olfactory loss must lead to a COVID-19 screening[(7)]. Olfactory and taste loss are respectively reported, with great heterogenicity, in 25% to 98% and 15% to 85% of cases in COVID-19 patients[(2,8,9)], especially because physicians used auto-questionnaires sent by e-mail, apps and mobiles to avoid obvious contagious situations. They are severe in 50% cases (22 to 80% of anosmia and 20% of ageusia[(8,10)]) and is more common in women over 50[(2,3,11–13)]. Psychophysical testing these acute COVID-19 patients allowed Lechien et al.[(14)] to specify the extent of the acute olfactory loss to 80% of patients, 50% and 20% of them being respectively anosmic and hyposmic.

A patient with anosmia and loss of taste would be 6 times more likely to be infected with COVID-19[(8)], which in this specific case,

would more frequently be a "mild" form that doesn't require hospitalization[2].

The long-term anosmia can cause an alteration in the quality of life and psychiatric disorders such as depression[15,16], anxiety, anorexia[17] and its nutritional consequences[18], social interaction disorders[19,20] and cognitive impairment[19,21,22]. So, the diagnosis of olfactory disorders and their management is essential.

Spontaneous olfactory recovery between the first and third year after loss is observed in 32 to 66%[23] of other post-viral olfactory loss, not related to COVID-19[23]. The early recovery rate (at 2 months) of post-viral olfactory loss post-COVID-19 is approximately 44% to 79% (of which 73% of patients recover within 8 days)[2,23,24]. So, spontaneous olfactory recovery rate is better in of post- COVID-19 olfactory loss that in other post-viral olfactory loss such as Rhinovirus, Influenza, Respiratory syncytial virus or other Coronavirii. However, post- COVID-19 olfactory disorders appears to persist after 6 months in 60%[25] of patients (including 50% hyposmia and 10% anosmia with sometimes parosmia[26]).

The principal aim of this study was to analyse the characteristics of persistent olfactory disorders post-COVID-19. The secondary aim was to measure their effects on olfaction-related quality of life.

Materials and methods

Population

The study was approved by the institutional review board of the Nice University Hospital (CNIL number: 412). This study is part of a large work registered under a ClinicalTrials.gov number (ID: NCT04799977). Since March 2020, we retroprospectively recruited at ENT department of Nice University Hospital all patients infected by COVID-19 with persistent olfactory disorders from two to nine months. Patients where self-referred or referred by colleagues, general practitioners or advised by the infectiology department that managed all COVID-19 declared patients (city guidelines). Patients had either an olfactory complaint for over 6 weeks and a molecular-proven SARS-CoV-2 diagnosis or a CT-proven SARS-CoV-2 diagnosis secondarily confirmed by serology. The patients' demographic data and clinical characteristics were recorded. Nasofibroscopy was performed to evaluate state and nasal cavity patency. The clinical examination included a visual analogue scale (VAS) for the subjective assessment of olfactory recovery (ranging from 0% to 100%), an objective evaluation of olfactory loss using Sniffin' Sticks Test®[27–29] and the completion of a short version of Questionnaire of Olfactory Disorders (Short-QOD-NS)[30].

Nasofibroscopy

Using a flexible endoscope and a high-definition camera, a nasofibroscopy was performed without local anesthesia (to avoid transient olfactive disorders) in order to assess the permeability of the olfactory cleft (presence of polyps, surgical adhesions, tumor or mucus was being sought).

Objective olfactory disfunction

Olfactory function was assessed using Sniffin' Sticks test, a validated psychophysical test that include an odor Threshold detection (T), an odor Discrimination (D) and an odor Identification (I) tests[28,31–34]. During the test, subjects were blindfolded. Odor thresholds were determined for N-butanol (BUT), using a three-alternative forced choice task. Three sticks were presented to the patient in an alternating order, one containing the odorant, the other two containing solvents only. The subject's task was to find out which of the three pens smelled of the odorant. The odor discrimination test was performed using 16 triplets of odorants sticks. Subjects were presented with three sticks, two containing the same odorant, and one a different odorant. Through a forced choice, the patient's task was to identify the stick that smelled differently. For odor identification, 16 odorant sticks were presented once, separated by an interval of at least 20 seconds to prevent olfactory desensitization. Each stick presentation was accompanied by a written list containing the correct odorant and 3 semantic distractors. Results from the three tests, odor threshold (T), odor discrimination (D), and odor identification (I) were summed up to a composite score, the so-called "TDI-score."

Olfactory quality of life

The olfactory quality of life was assessed using the Short-QOD-NS which is based on the Questionnaire of Olfactory Disorders (QOD) related to the consequences of an olfactory and taste loss such as the pleasure of sharing a meal, of creating social interactions or even of creating close bonds with others[35]. The original version was divided into 52 items regarding negative and positive social consequences of olfactory loss[36]. The "negative consequences" subdomain of QOD (QOD-NS[37]) has been shown to be more correlated with the results of psychophysical olfactory tests (Sniffin 'sticks tests)[38]. So, shorter versions have been developed to be more suitable for daily clinical practice [30,39,40]. These shorter versions increase the response rate and reduce the patient's mental load when completing the questionnaire[30]. The QOD-NS is a validated test[41] which includes 17 questions with answers go from 0 to 3 for a total score of 0 to 51 (51 meaning there is no disorder). Finally, Mattos et al. [30] developed an even shorter version (Short-QOD-NS) with the 7 most relevant questions with the different aspects such as social aspect (n = 3), eating (n = 2), anxiety (n = 1) and annoyance (n = 1) following an olfactory loss. We have decided to use this version for this study, with score ranging from 0 to 21(21 meaning there is no disorder).

Statistical analysis

Data are presented as mean (SD) for quantitative variables and

Table 1. Demographic and clinical characteristics.

	mean	SD
Age (years)	41.6	12.9
Months post-COVID-19	5.0	2.8
	n	%
Total	34	100
Sex		
Women	16	47
Men	18	53
COVID19 testing		
Molecular PCR test	24	82.8
Chest CT	6	20.7
Serology (antibody test)	10	34.5
COVID-19 dedicated treatment		
Oral corticosteroids	5	14.6
Nasal corticosteroids	4	11.7
Inhaled corticosteroids	1	2.9
Azithromycin alone	4	11.7
Azithromycin + Hydroxychloroquine	2	5.9
Amoxicillin alone	1	2.9
Amoxicillin + Azithromycin	2	5.9
Others (vitamins, zinc)	9	26.5

SD=standard deviation; CT=computed tomography; PCR=polymerase chain reaction

Table 2. Smell and taste disorders, olfactory quality of life.

	mean	SD
VAS (subjective % of recuperation)	37.2	26.5
Short-QOD-NS – Total	11.1	5.0
Short-QOD-NS-Eating	3.1	2.2
Short-QOD-NS-Anxiety	2.0	1.0
Short-QOD-NS-Annoyance	1.2	1.2
Short-QOD-NS-Social	4.8	2.6
Sniffin' Sticks test - scores		
Threshold detection	5.4	4.0
Discrimination	10.9	2.6
Identification	10.2	2.7
	n	%
Sniffin' Sticks test - classification		
Normosmic	10	29.4
Hyposmic	19	55.9
Anosmic	5	14.7
Taste disorders	30	88.2
Retro-olfaction alone	22	73.4
Retro-olfaction + taste	7	23.3
Taste alone	1	3.3

Short-QOD-NS =Short version of Questionnaire of Olfactory Disorders[30]

as frequency and percentage for qualitative variables. In order to investigate correlations between subjective reports (VAS), objective disorders in the different dimension (threshold detection, T; odor discrimination, D; odor identification I), and Short-QOD-NS, we performed bivariate correlation analyses. As data were not normally distributed (as suggested by Kolmogorov-Smirnov test), non-parametric Spearman's correlations were employed.

Results

Demographic and clinical features

Thirty-four patients consulting the ENT department of Nice University Hospitals (CHU) for olfactory complaints after a COVID-19 infection were included in the study. The demographic and clinical features are reported in Table 1. 47% of whom were female (n=16), with a mean age of 41±12 years. They were seen after 5±2,8 months after the COVID-19 infection. Twenty-eight patients received a COVID-19 related treatment.

Loss of smell and taste

Descriptive analyses for the loss of smell and taste are reported in Table 2. The day of consultation, patients reported to have recovered 37±27% of their olfaction (ranging from 0% to 90%). The global results of the Sniffin' Sticks Test (TDI) suggested that 29,4% (n=10) of the patients could be classified as normosmic (TDI≥30.75), 55,9% (n=19) as hyposmic (16.25≤TDI≤30.5) and 14,7% (n=5) as anosmic (TDI≤16). Eighty eight percent of the patients (n=30) reported taste disorders, including retro-olfaction (food flavors) alone (73,4%, n=22), retro-olfaction associated to taste (23,3%, n=7, 66% concerning sweet and salty, 33% concerning sour and bitter), or taste alone (3,3%, n=1 concerning sweet and salty).

Links between self-reported and objective olfactory disorders

Correlations between subjective reports (VAS) and the T, D and I scores of the Sniffin' Stick Test suggested a significant, positive correlation between percentage of subjective olfactory recovery (VAS) and odor identification (I, $rho_{(32)}$= 0.36, p=0.034). Correlations with odor threshold detection and discrimination were not-significant (T, rho(32)= 0.23, p= 0.193;D, $rho_{(32)}$= 0.23, p= 0.184). Correlations between the three Sniffin' Sticks Test subscales and the months after the first COVID-19 infection were not statistically significant. However, while objective disorders in odor detection seemed not to improve over time ($rho_{(32)}$= 0.20, p= 0.260), disorders in odor identification showed an alternative pattern. A longer timeframe from the first infection was associated a non-significant trend towards decrease of identification

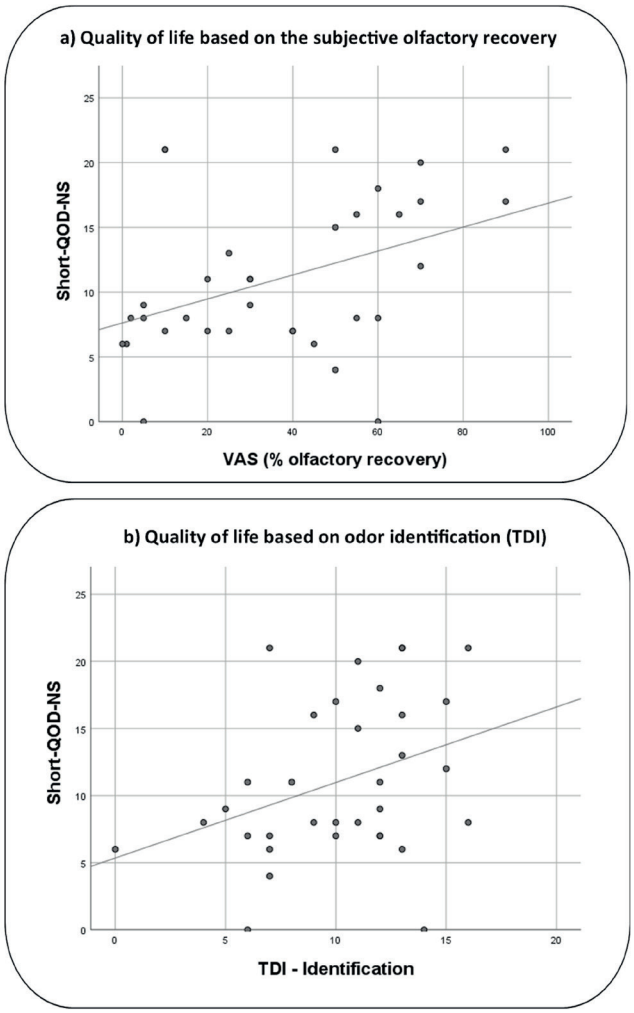

Figure 1. Correlations between quality of life (Short-QOD-NS) and percentage of subjective odor recovery (VAS; a), and objective odor identification scores (TDI-I; b).

performance ($rho_{(32)}$= -0.24, p= 0.177).

Links between olfactory disorders and quality of life

Descriptive analyses of the Short-QOD-NS are reported in Table 2. Spearman's correlations revealed that the global Short-QOD-NS was positively correlated to self-reported percentage of olfactory recovery (VAS, $rho_{(32)}$= 0.42, p= 0.014, see Figure 1a). When considering the different Short-QOD-NS subscales, the only significant correlation was found for the Short-QOD-NS-eating ($rho_{(32)}$= 0.45, p= 0.008). Concerning correlations between Short-QOD-NS and the Sniffin' Sticks Test scores, odor identification was positively correlated with the global Short-QOD-NS scale ($rho_{(32)}$= 0.36, p= 0.037, see Figure 1b). Specifically, significant correlations were found for the Short-QOD-NS-anxiety ($rho_{(32)}$= 0.39, p= 0.025) and the Short-QOD-NS-Annoyance question ($rho_{(32)}$= 0.37, p= 0.031). No significant correlation was found between Short-QOD-NS (global score and subscales) and the detection and discrimination scores (all ps > 0.13).

Discussion

This is the first study that evaluates quantitatively olfactory disorders and their influence on the quality of life of 34 patients after five months on average from their olfactory loss due to a SARS-CoV-2 infection. This study is also the first to show a mismatch between subjective olfactory complaints of post-COVID-19 patients and the results of objective psychophysical tests. In fact, half of the patients had a persistent olfactory complaint whereas, based on the Sniffin Test, only 15% (n = 5) of them were classified as functional anosmic. In the same way, 30% of normosmic at Sniffin' Stick test (TDI) patients reported only partial recovery of their previous olfaction (VAS = 40% [5% -70%]). A previous study showed that 6% of patients infected with COVID-19 who presented an olfactory complaint after 12 days from onset of symptoms were normosmic on the Sniffin' Stick test [14].

Subdomain Sniffin' Stick test analyses employing recent normative data[33] highlights a predominant disorder on the identification (I) of the odorant, which is more important than the odor discrimination (D) or the detection threshold (T). Also, normosmic patients (TDI> 30.75)[33] had more altered scores in odor identification (I) than in detection (T). The results of this study raise the question of an unrecognized central involvement of olfaction, compatible with an olfactory agnosia type[34,42]. Indeed, Whitcroft et al.[42] have shown that the impairment of odor identification compared to the impairment of threshold detection, was more frequently found in central damage sequelae of neuronal lesions of infectious, traumatic or degenerative origin. On the contrary, it has been shown that the isolated impairment of detection is mainly the consequence of sinonasal pathologies [42]. These sinonasal symptoms[43,44] reduce olfactory perception (obstruction of the olfactory cleft, mucous edema) but decrease significantly only the olfactory threshold and not the identification, as we observed in our study. This observation highlights the independence of the central processing of the olfactory message in relation to the peripheral perception of the odorant at the level of the olfactory epithelium. Our results are in line with previous studies, which hypothesized a central impairment of olfaction due to contact of the membrane viral glycoprotein S1 with ACE2 facilitated by TMPRSS2[45–48]. Indeed, more and more reports suggest the penetration of SARS-CoV-2 into the central nervous system [49,50] through the olfactory cleft through the olfactory epithelium, and more particularly through sustentacular and / or trans-cribriform sheath cells[47,51,52], through a rupture of the blood-brain barrier [53,54] or by trans-axonal feedback [50,55] within the peripheral nerves coming from the respiratory tree (Vagus nerve). Finally, previous SARS-CoV-1 studies results [56] and the olfactory identification impairment found in neurodegenerative diseases, raised questions about the pathophysiological similarities and consequences of SARS-CoV-2 cells and the mechanisms involved in the origin of neurodegenerative

diseases [57].

This study did not show any significant correlation between the olfactory disorder duration and the severity of the olfactory impairment. However, we observed a non-significative tendency for identification disorders to increase over time, rather than to reduce. This pattern has to be confirmed using longitudinal data. If this observation will be confirmed by other authors, two hypotheses can be put forward. The first is an early progressive deafferentation [58] of central olfactory projections, which negatively influences the cognitive performance of these patients. In this way, Lu et al. [59] found an alteration in cerebral trophicity on MRI at the level of the olfactory cortex, the hippocampus, the Insula, the left Rolandic operculum, the Heschl gyrus, left and right cingulate about 3 months from the end of COVID-19 symptoms. The second is the emergence of new variants of SARS-CoV-2 in which the Spike S1 protein is said to have an increasing affinity in vivo with ACE2. This physiopathological mechanism described by Butowt et al. [60,61] is thought to have its origin in a mutation of an aspartic acid to glycine at position 614 of the code for the Spike S1 protein (D614G). This mutation, associated with a genetic and geographic polymorphism of ACE2[62], could potentially cause an increase in the prevalence of olfactory damage, specifically in Europe[61].

In addition, this study shows an isolated taste disorders (sweet, salty, sour, bitter and umami) in 3.3% of cases. This is in line with the results of Hopkins et al.[25], that found 2.8% of persistent taste disturbances 6 months after COVID-19 infection. Taste loss can be explained by the tantalizing effect of ACE2 involvement on the taste buds[63], which remains the main receptor targeted by SARS-CoV-2. However, the intricacy of primary taste and retrognathic olfaction in patient complaints makes its interpretation difficult. Taste loss disappears mainly within the first 15 days after the onset of symptoms, in particular thanks to the fast turnover of taste buds in the average time of 10 days [63]. Their persistence beyond 10 days suggests a possible role of the retrognathic olfaction in the perception of a taste disorders by the patients, which confirms the significant impact of an olfactory loss on the quality of food life showed in this study.

Finally, this study highlights the need of further studies on central consequences of post-COVID-19 olfactory loss, especially regarding impaired semantic memory of odours in patients with persistent olfactory complaints. Moreover, these patients, considered to be normosmic in olfactory tests but nevertheless symptomatic, underline the limits of psychophysical tests and suggest the need to adapt them, specially concerning the central processing disorders of olfactory diagnosis.

Olfaction assessment is most important as olfaction impairments can be the cause of domestic accidents (gas, burning smell)[17], can testify the emergence of psychological[19], psychiatric[15,16,19], or eating disorders[64,65], as well as loss of taste pleasure[66] and social isolation for fear of one's own body odor, or even eating spoiled or undercooked food.

Smell loss will therefore cause a significant deterioration in the quality of life[35,39,67], especially since the loss occurs before the age of 30[67]. In ENT studies, 22-item Sinonasal Outcome Test (SNOT-22)[68] is commonly used for quality-of-life assessment but is not focused on smell and taste impairment. QOD and specifically QOD-NS[37,40,67,69] is rather used for this specific olfaction assessment. However, QOD-NS 17-item questionnaire length can be a problem in clinical and scientific research as patients' mental burden can be important. In order to improve efficiency and the quality of collected data, Mattos et al.[30] suggested to use a Short-QOD-NS, reporting an strong correlation with QOD-NS total and domain-specific scores. Even if it is not internationally validated, we have chosen this quality-of-life assessment because it fit betters with the constraints of the routine clinical assessment. In our study, Short-QOD-NS results allowed us to underline a negative correlation between olfactory loss and quality of life, and more particularly on the pleasure of eating, which is often the predominant patient's complaint. Specifically, an odor identification disorder generates anxiety and concern for patients regarding the lack of smell recovery. In a previous study, Lechien et al.[62] already showed, at about 10 days of the onset of symptoms of COVID-19, a degradation of Short-QOD-NS, which is more significant in anosmic patients and predominant in their daily worry about habituation to this disorder. Their results showed a deterioration in the overall quality of an olfactory life with the duration of olfactory deprivation[62].

Despite these interesting results, this study suffers from some limitations. The main limitation concerns the small cohort of 34 patients, with no follow up reported, who spontaneously consulted our university hospital, which represents the risk of a recruitment bias. The small sample size may have contributed to a limited strength of correlations ($rho_{(32)}MAX = 0,45$), and therefore our results cannot be directly generalized to all patients with a post-covid olfactory disorder.

Conclusion

This work analyzes long term olfactory disorders occurring after COVID-19 infection. Sniffin' Stick Tests results are mismatching with self-reported complains in olfactory loss. Indeed, the Sniffin' Stick Tests evaluated 30% of subjectively affected patients as normosmic. We highlighted the presence of a significant impairment in odor identification that should be targeted by a specific olfactory training added to these patients' care, especially because it significantly worsens quality of life and does not seem to spontaneously recover over time.

Authorship contribution

CV, MP, LED, VMF, AG contributed to study design, data collection, interpretation of results, drafting and critical evaluation of the final manuscript. AP, DC, ED, KR, NG and LC contributed

to study design, interpretation of results, drafting and critical evaluation of the final manuscript. VM contributed to biostatistics, interpretation of results and critical evaluation of the final manuscript.

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