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Long-Term COVID-19 Smell and Taste Disorders Differ Significantly from Other Post-Infectious Cases

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Introduction: COVID-19 is causing a wide range of clinical manifestations. Severe complications and long-lasting sequelae have been identified. Thus, olfactory disorders are reported in up to 86% of cases in mild and moderate COVID-19 infections. We present the first study comparing simple and complex post-COVID-19 cases with matched non-COVID-19 post-infectious smell and taste disorders.

Methods: A total of 328 patients were recruited from the University Clinic for Flavour, Balance and Sleep, Ear-nose-throat Department, Goedstrup Hospital, Denmark. A non-COVID -19 post-infectious population of 148 individuals was identified from the Redcap database, and was matched by duration of smell and taste disorders. Post-COVID-19 patients were divided into 99 patients with simple smell and taste disorders (only suffering from smell and taste disorders after COVID-19); and (81 patients with complex smell and taste disorder plus several other post-COVID-19 complaints). Besides patient-reported outcome measures (PROM) questionnaires and quality of life score (QoL), ear-nose-throat examination, Mini-Mental State Examination (MMSE), orthonasal smell test (Sniffing's sticks), retronasal quick test, and taste screening were performed.

Results: Cases with post-COVID-19-related smell and taste disorders deviated from non-COVID-19 post-infectious cases; the patients were younger, had a lower occurrence of anosmia/ageusia, and had higher overall smell test scores. In contrast, patients with post-COVID-19-related smell and taste disorders more frequently complained of distorted senses. Parosmia and phantosmia were more prevalent among patients with simple post-COVID-19 complaints than among complex cases and their QoL were more negatively affected.

Conclusion: Smell and taste function differ significantly between post-COVID-19 and other non-COVID-19 post-viral cases.

Key Words: COVID-19, long-term sequelae, smell and taste disorders.

Level of Evidence: 3

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INTRODUCTION

Since the World Health Organization (WHO) declared the SARS-CoV-2 infection a pandemic in March 2020, the COVID-19 pandemic has been ongoing for more than 18 months. As one of the first European countries, Denmark introduced lockdown measures on March 13, 2020. By November 2021, a total of 402,561 Danes had been infected with SARS-CoV-2 virus of whom 18,614 had been hospitalized. The mortality rate of SARS-CoV-2 virus infection is 0.7% (2,738) in Denmark as per November 7, 2021.[1]

Because of the successful national vaccination program, 76.5% of the Danish population aged 12 years or above has received one vaccine dose and 75.3% has received two doses. Furthermore, the national booster program was presented on October 15, 2021, and 3 weeks later (at the time of writing), 6.5% of the population had received the third dose.[1]

In the wake of the pandemic, several long-term sequelae of COVID-19 have been recognized. According to the guidelines from the Danish Health Authority, signs and symptoms that develop during or after acute COVID-19 infection and continue from four up to 12 weeks are considered ongoing symptomatic COVID-19, whereas long-term post-COVID-19 sequelae are defined as any symptoms persisting beyond 12 weeks.

The absolute number of patients suffering from long-term sequelae is accumulating due to the long-term nature of the condition. Knowledge about the entire course of COVID-19 has yet to be unraveled. Thus, the individual patient's prognosis remains unknown and unpredictable. Fatigue is one of the most commonly reported long-term post COVID-19 manifestations, but also pulmonary, cardiovascular, neurological, ear-nose-

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and throat (ENT), musculoskeletal, gastrointestinal, and dermatological long-term sequelae are rather frequent.[2–5]

Olfactory dysfunction is a very common symptom during acute COVID-19 infection with rates reaching 70.2%–85.9% in mild to moderate disease.[6,7] In more than two thirds (66.7%) of cases, patients suffer from parosmia.[8] Olfactory dysfunction is more frequently reported among younger females with non-critical COVID-19 symptoms than among other COVID-19 patients.[9,10] Overall, taste complaints during COVID-19 infection are less frequent than olfactory dysfunction.[11]

Before the COVID-19 pandemic, other types of upper respiratory tract viruses such as common cold, influenza, and so forth were observed to damage the human olfaction system. Thus, the prevalence of non-COVID-19 post-infectious olfactory disorders in clinical settings has been found to vary between 18%–45%.[12–14] More than half (56%) of these patients were suffering from parosmia in the post-infectious period.[15] In other words, distortion of smell is a phenomenon in post-infectious olfactory disorders. Smell disorders were typically more frequently associated with female gender and higher age.[16] Post-infectious taste complaints were also reported in rare cases.[17]

When it comes to long-term smell and taste disorders after COVID-19, current literature is yet quite sparse. Questions that warrant investigation include: (1) What are the differences between patients suffering simple versus complex post COVID-19 complaints? (2) What are the differences between patients with COVID-19 smell and taste dysfunction and patients with non- COVID-19 post-infectious smell and taste dysfunction? (3) Is it possible to identify specific risk factors/patient characteristics to establish the prognosis and predict the severity of smell and taste dysfunction?

Risk factors for developing such disorders and the spontaneous course remains to be substantiated. Furthermore, it remains unknown whether differences exist between patients with smell and taste disorders as the only long-term effect of COVID-19 (simple post-COVID-19) and those with several other long-term complaints (complex post-COVID-19).

Based on the literature we hypothesize that patients suffering from COVID-19 smell and taste dysfunction may deviate in more aspects from patients with non-COVID-19 post-infectious smell and taste dysfunction. Therefore, the present study aimed to add further knowledge to our understanding of long-term post-COVID-19 smell and taste disorders, specifically compared with non-COVID-19 post-infectious smell and taste disorders to achieve a more solid basis for patient counselling and prognostication.

MATERIALS AND METHODS

Populations

A total number of 328 patients were recruited from the Smell and Taste Clinic, University Clinic for Flavour, Balance, and Sleep, ENT Department, Goedstrup Hospital, Denmark. Patients suffering from post-COVID-19 were separated into two groups: (1) simple post-COVID-19 patients, that is smell and taste disorder as the only long-term post-COVID-19 complaint; and (2) complex post-COVID-19 patients, that is, more long-term post-COVID-19 complaints in addition to smell and taste disorders. The simple post-COVID-19 patients were referred from practicing ENT specialists, whereas the complex post-COVID-19 patients were referred from the two regional long-term post-COVID-19 hospital clinics. All post-Covid-19 patients had smell and taste disorders at least 4 months at the moment of assessment. Patients with persisting smell and taste symptoms including other long-term post-COVID-19 sequelae, that is, meeting the complex post-COVID-19 patient criteria, were referred to the Smell and Taste Clinic for further assessment. Thus, 81 of these complex post-COVID-19 patients had been examined at the Smell and Taste Clinic by September 30, 2021. A total of 99 patients with simple post-COVID-19 smell and taste disorders were referred from practicing ENT specialists before October 2021.

For comparison, a non-COVID-19 post infectious population of 146 patients with smell loss was identified from the Flavour Redcap Database. The database became operational on January 1, 2017; and by October 2021, it contained more than 2,000 patients with various etiologies underlying smell and taste disorders. The database entails all patients seen in our Smell and Taste Clinic, with minor exceptions as a few patients did not wish to sign the consent form for the database, see [12]. A total of 146 pre-COVID cases were selected from three criteria: post-infectious etiology of smell loss, smell loss debut before January 1st 2020, duration of smell loss below longest duration of smell loss in the COVID group (308 days).

Questionnaires and Testing

All patients completed questionnaires comprising demographics, patient-reported outcome measures (PROMs), the Sinonasal Outcome Test (SNOT-22),[18] and the Major Depression Inventory (MDI).[19] In the PROM questionnaire, the assessment of QoL was made by asking the patients "How severely is your quality of life affected by your smell loss?", which was rated on a scale from 1 (no affection of QoL) to 10 (Worst possible affection of QoL). Furthermore, a cutaneous allergy test and an objective ear-nose-throat (ENT) examination with flexible rhino-pharyngo-laryngo-scopy were performed. In addition, the following psychophysical tests were conducted in all patients: orthonasal smell test (Sniffing Sticks): threshold (T), discrimination (D), identification (I), resulting in an overall T D I score[20]; retro-nasal quick test[21]; taste screening for bitter, salt, sweet and sour tastes[22]; and the Mini- Mental State Examination (MMSE).

Statistics

Data are presented as absolute numbers and percentages. Mean values and 95% confidence intervals (CIs) are listed. Proportions and frequencies were compared by means of odds ratios (ORs) and 95% CIs. The Student's *t*-test was applied for comparison of normally distributed variables, whereas the Kruskal-Wallis rank sum test and the Chi-squared (X^2) test were used for categorical data and not normally distributed variables.

RESULTS

Demographics

Patient demographics are listed in Table I. A female preponderance was observed in all three groups, but no significant between-group differences were observed. Post-COVID-19 patients were significantly younger than non-COVID-19 patients ($t > 8.4646$, $p < 0.0001$). Fewer patients in the simple post-COVID-19 group were

TABLE I.
Demographics.

	Simple post COVID-19 group ($n = 99$)	Complex post COVID-19 group ($n = 81$)	Non-COVID-19 post infectious group ($n = 146$)
Gender (female)	74.7%	70.3%	67.1%
Age (years)	**39.9 (36.7–43.0)** **	**44.5 (41.7–47.2)** **	59.2 (57.1–61.4)
Duration of smell and taste dysfunction (days)	287 (266–308)	272 (250–295)	285 (270.1–300.1)
Other COVID-19 long-term sequelae			
Fatigue		80.3%	
Headache		54.3%	
Cognitive		46.0%	
Dyspnoea (% of patients)		45.7%	
Smokers			
Non-smokers	***86%****	72%	69%
Previous smokers	***12%****	21%	25%
Current smokers (% of patients)	***2%****	7%	6%
Allergy (% of patients)	35.4%	34.6%	27.4%

Note: Bold types indicate significant difference from non-COVID-19 post-infectious. *Bold italics* indicates significant difference from both complex post-COVID-19 and non-COVID-19 post-infectious.
*$0.002 < p < 0.02$;
**$p < 0.0001$.

current or previous smokers than in the other two groups (OR: 0.4153; 95% CI: 0.1975–0.8736 and OR = 0.3581; 95% CI: 0.1842–0.6959; Z = −2.3161, and Z = −3.0295; $0.002 < p < 0.02$). In addition to smell and taste disorders, the complex post-COVID-19 patients indicated several other long-term sequelae, in particular fatigue, headache, and cognitive problems (concentration and short-term memory).

Table II presents PROMs. Subjective anosmia was less frequent in the post-COVID-19 groups than in the non-COVID-19 group (OR = 2.4389 and OR = 2.7787; 95%CI: 1.3788–4.3141 and 95% CI: 1.4837–5.2041; Z = 3.0640 and Z = 3.1924; $p = 0.0022$ and $p = 0.0014$). In contrast, distorted smell was more prevalent among simple post-COVID-19 patients compared to non-COVID-19 cases (OR = 3.2042; 95%CI:1.6250–6.1804; Z = 3.3617; $p = 0.00078$).

Though not as pronounced, the same pattern was seen for subjective taste: less ageusia and more distorted taste. Only the simple post-COVID-19 group deviated

TABLE II.
Patient-Reported Outcome Measures (PROMs).

	Simple post COVID-19 group ($n = 99$)	Complex post COVID-19 group ($n = 81$)	Non-COVID-19 post infectious group ($n = 146$)
Smell			
Anosmia	**23.2%****	**20.5%****	42.1%
Hyposmia	47.5%	60.3%	46.9%
Distorted (% of patients)	**28.3%*****	15.4%	11.0%
Taste			
Ageusia	**8.1%***	10.4%	18.8%
Hypogeusia	56.6%	62.3%	56.9%
Distorted (% of patients)	**26.3%****	19.5%	13.2%
Quality of life QoL (mean, 95% CI)	*6.90 (6.53–7.26)**	**6.21 (5.70–6.71)****	7.08 (6.67–7.50)
SNOT 22			
Total score (mean, 95% CI)	*21.94 (19.35–24.52)*****	**30.71 (27.75–33.68)*****	20.84 (18.52–23.16)
MDI (mean, 95% CI)	*11.30 (9.74–12.85)*****	**17.62 (15.32–19.93)*****	9.68 (7.91–11.45)

Note: Bold types indicate significant difference from non-COVID-19 post-infectious. *Italics* indicates significant differences between simple and complex post-COVID-19.
Abbreviations: MDI, Major Depression Inventory (range 0–50, higher score indicates more depressive symptoms); QoL, Quality of life (range 1–10, higher score indicates more negative impact on QoL); SNOT 22, Sino-nasal Outcome Test (range 0–110, higher score indicates worse symptoms).
*$p < 0.05$;
**$p < 0.01$;
***$p < 0.001$;
****$p < 0.0001$.

TABLE III.
Results (Mean, 95% CI) of Smell and Taste Tests, Including the Mini-Mental State Examination (MMSE).

	Simple post COVID-19 group ($n = 99$)	Complex post COVID-19 group ($n = 81$)	Non-COVID-19 post infectious group ($n = 146$)
Smell			
T	**4.19 (3.72–4.67)****	**4.00 (3.45–4.55)****	2.83 (2.48–3.18)
D	**10.38 (9.95–10.81)** ****	**10.02 (9.44–10.61)*****	8.79 (8.73–9.22)
I	**10.87 (10.17–11.57)***	**11.46 (10.75–12.16)*****	10.01 (9.49–10.52)
TDI score	**25.45 (24.14–26.75)****	**25.47 (24.00–26.96)****	21.56 (20.56–22.56)
Retronasal	*4.84 (3.65–6.04) ($n = 45$)***	2.82 (1.88–3.76) ($n = 67$)	
Taste			
Screening	3.89 (3.79–3.99) ($n = 85$)	***3.71 (3.54–3.87)***/****	3.96 (3.92–3.98)
MMSE	28.77 (28.49–29.05)	*28.05 (27.49–28.61)**	28.40 (28.11–28.70)

Note: Bold types indicate significant differences from non-COVID-19 non-infectious. *Italics* indicates significant differences between simple and complex post-COVID-19.

Abbreviations: MMSE, Mini Mental State Examination (range 0–30, scores below 24 indicate various degrees of cognitive impairment). Retronasal test: (range 0–10; number of correctly identified odorants out of 10 transorally presented odorants).

*$p < 0.05$;
**$p < 0.01$;
***$p < 0.001$;
****$p < 0.0001$.

significantly from the non-COVID-19 post-infectious group (OR = 0.38746 and OR = 2.3807; 95% CI: 0.16812–0.89290 and 1.23306–4.5964; $Z = -2.22595$ and $Z = 2.58414$; $p = 0.02602$ and $p = 0.0098$).

All MDI scores were within normal limits. However, scores among complex post-COVID-19 patients were generally higher than among simple post-COVID-19 and non-COVID-19 patients ($t = 4.5336$ and $t = 5.4303$; $p < 0.0001$). Quality of life (QoL) was negatively affected by a factor of almost seven out of 10 due to smell and taste disorders. The complex post-COVID-19 group was significantly less affected than the other two groups ($t = 2.6576$ and $t = 2.1999$; $p = 0.0043$ and $p = 0.0147$).

The complete scores obtained by the SNOT-22 were significantly higher in the complex post-COVID-19 group than in the simple post-COVID-19 and non-COVID-19 cases ($t = 5.2057$ and $t = 4.4363$; $p < 0.0001$). The SNOT-22 questions regarding "tiredness" and "waking up as tired" ($44.674 < X^2 < 79.409$, $p < 0.0001$) were significant drivers of this difference.

Psychophysical Chemosensory Tests

The results of the psychophysical tests are presented in Table III. In general, all scores were significantly higher in the two post-COVID-19 groups than in the non-COVID-19 group ($1.9690 < t < 5.2008$; $0.0001 < p < 0.0252$) and no differences between the two post-COVID-19 groups were recorded. The retronasal test was introduced only to the post-COVID-19 patients as from February 2021. The retronasal scores were significantly better among patients in the simple post-COVID-19 group ($t = 2.6712$; $p = 0.0045$). The number of correctly identified basic tastants was significantly lower in the complex post-COVID-19 group ($2.2774 < Z < 3.0864$; $0.0020 < p < 0.0295$).

Finally, MMSE scores were within the normal range; but even so, the scores in the complex post-COVID-19 group were significantly lower than the scores in the simple post-COVID-19 group ($Z = 2.1774$; $p = 0.0295$). The results of the MMSE tended to be better in the simple post-COVID-19 group than in the non-COVID-19 group ($Z = 1.7466$; $p = 0.0807$).

DISCUSSION

The present study is the first to compare simple and complex post-COVID-19 smell and taste disorders; and to compare these two groups with non-COVID-19 post-infectious cases. We found that patients suffering from long-term smell and taste disorders related to COVID-19 differed from non-COVID-19 post-infectious cases in several aspects; they were younger, had a lower occurrence of anosmia/ageusia, more often experienced distorted senses, and generally had higher TDI scores. Furthermore, parosmia and phantosmia were more frequent among patients with simple post-COVID-19 complaints than among complex cases, and their QoL scores were more negatively affected by their distorted senses. Finally, the complex post-COVID-19 group had higher SNOT-22 scores, mainly due to sleep- and pain-related complaints.

It is unique that physicians have the opportunity to follow the temporal development of smell and taste disorders in COVID-19 patients. Previous experience is that post-infectious smell and taste complaints are reported months to years after their onset, reflecting the general and occasionally neglecting attitude toward chemosensory problems. In general, approximately 70% of all patients in the present study were female and no inter-group differences were observed. Whereas several studies have reported a positive association between female gender and the risk of subjective olfactory loss after COVID-19, a resent multi-center study of 774 patients with PCR-test

verified COVID-19 found no association between gender and the prevalence of measured olfactory loss.[23] Similarly, the present study found no association between age and post-COVID-19 olfactory loss. However, women have been shown to report their symptoms more often than men.[24]

To eliminate the influence of symptom duration, we matched the COVID-19 cases with non-COVID-19 post-infectious cases from before the COVID-19 era and recognized several significant differences. The much younger age of the post-COVID-19 patients may not only be caused by selection, that is, younger patients have more resources to contact health care systems, whereas the elderly have other and more serious complaints. Thus, if other non-COVID-19 infections caused smell and taste disorders among the young generations to the same extent as COVID-19, we would have expected the average age to have been lower. Therefore, we conclude that post-COVID-19 patients are younger than the non-COVID-19-post-infectious group. On the other hand, selection may occur especially in complex post-COVID-19 patients as they suffered from a total of three or more long-term sequelae that could not be explained by other conditions than COVID-19, and possibly only the youngest had the resources to accept referral to the Smell and Taste Clinic.

Overall, smell and taste dysfunction had a rather heavy impact on all patients irrespective of the underlying etiology as 7–10 on the applied QoL scale indicates a severe to extremely severe impact. Only patients with persisting complaints of smell and taste disorders were referred from the two regional long-term post-COVID-19 hospital clinics, which implies selection bias. However, the patients with simple long-term COVD-19 sequelae were more negatively affected by the problem than the complex cases were - a finding that may also reflect selection as patients with the most annoying symptoms tend to seek help in the health care system. This was further substantiated by the markedly lower smoking status among those with simple post-COVID-19, which is indicative of a healthier lifestyle.

In line with the inclusion criteria, the group of patients with complex long-term sequelae complained of fatigue and headache. This also explains their significantly higher SNOT-22 scores (worse symptoms). Most of the patients in the complex post-COVID-19 group had indicated the highest scores in relation to questions about sleep disorders, tiredness, and pain, whereas scores related to the upper airways and sinuses were extremely low. Thus, none of the patients in the three groups suffered from chronic rhinosinusitis, which is supported by the fact that the majority of the patients had completely normal sino-nasal computed tomography scans.

Surprisingly, almost all MDI and MMSE scores were within normal limits. It would be expected that those suffering from complex long-term sequelae were more emotionally affected, resulting in higher MDI scores. However, MMSE is a rather week test of light cognitive impairment. Unfortunately, we did not register anxiety scores—though it seems highly relevant. PROMs obtained in the regional long-term post-COVID-19 hospital clinics have revealed that more than a fourth of patients with complex long-term sequelae indicate scores above five in the Symptom Check List (SCL)-13, that is, were severely worried about their symptoms and prognosis (unpublished data).

Furthermore, almost half of the patients with long-term sequelae also complained about cognitive dysfunction, which, however, was not reflected in the MMSE scores. The PROMs obtained in the regional long-term post-COVID-19 hospital clinics have demonstrated that approximately 80% of patients complain of moderate to severe cognitive difficulties (concentration and short/long-term memory) (unpublished data), that is, significantly more than recorded in the present study. The reason for this discrepancy may possibly be the mentioned selection of the more resourceful patients or the time lag between the consultation in the regional long-term post-COVID-19 hospital clinics and the Smell and Taste Clinic. In addition, several patients had received advice/assistance from occupational therapists before being examined at the Smell and Taste Clinic.

The PROMs revealed that subjective complete loss of smell and/or taste was significantly more frequent in the non-COVID-19 post-infectious group of patients than in the other groups. In contrast, distorted senses were more prevalent among patients with post-COVID-19 long-term sequelae. Several theories may contribute to explaining the underlying mechanism of parosmia. Parosmia may occur due to ephaptic firing in demyelinated neurons—a form of short circuiting[25] or as a result of mis-wiring of olfactory sensory neurons.[26] Although the clinical presentations may be heterogeneous, Parker et al. recently demonstrated that distortions are more likely to occur in relation to certain odorants, which is in line with our clinical experience with these patients. From earlier studies on post-viral olfactory loss, parosmia has been identified as a good prognostic factor for olfactory recovery.[27]

In accordance with the PROMs, TDI scores were significantly higher among post-COVID-19 patients, that is, qualitative complaints were characteristic of post-COVID-19, whereas quantitative problems were less prominent. Interestingly, patients with complex long-term COVID-19 sequelae had lower retronasal scores and taste scores than patients with simple long-term COVID-19 sequelae. These findings may be the result of more extensive viral damage to the peripheral sensory system in patients with complex long-term post-COVID-19 sequelae. The retronasal test is, in fact, a multi-sensory test, that is, trigeminal as well as olfactory and gustatory functions may be involved. SARS-CoV-2 virus may affect the angiotensin-converting enzyme (ACE) receptors on type 2 taste cells and thereby disturb the gustatory function.[28] Furthermore, tiredness and reduced cognitive capability may have influenced the test results. In the acute phase of COVID-19 there is an increased risk for thromboembolism.[29] Evidence of neuroinflammation is reported in the acute phase of COVID-19 as well.[30,31] Yet, few studies guide the establishment of a pathophysiological explanation for the long-term post-COVID-19 sequelae. We previously found electrophysiological abnormalities long after the acute infection and suggest the lower retronasal scores in patients with complex symptoms despite less subjective complaints should be taken into consideration when looking for explanations for long-term post-COVID-19 sequelae.[32] After 18 months

with COVID-19, it remains an open question how many patients should be characterized as patients with chronic or permanent sequelae. The chances of recovery from post-viral olfactory loss are higher than for other etiologies of olfactory loss such as head trauma.[33] However, even in post-traumatic olfactory loss, recovery may occur years after symptom debut,[34] so defining when olfactory loss may be classified as a chronic condition is difficult. Some studies have defined post-COVID olfactory loss as chronic when it has lasted 6 months or more.[35] However, more recent studies have indicated that recovery may occur later,[36] which underlines that more long-term follow-up studies are needed to accurately establish the prognosis and definition of chronic olfactory loss.

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