

ORIGINAL RESEARCH

Short-term chemosensory distortions and phantoms in COVID-19

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Funding information

John A. Watson Faculty Scholar; Hong Kong Lounge Bistro Research Fund

Abstract

Objective: To identify differentiation features of chemosensory dysfunction in COVID-19 infection and their primary drivers.

Study Design: Cross-sectional cohort comparison.

Methods: A national anonymous survey was used to query participants regarding nasal symptoms and chemosensory dysfunction including sensitivity levels, and presence or absence of distortions and phantoms within the 6-week time window surrounding their COVID-19 testing and survey completion.

Results: Three-hundred and sixty-four respondents who reported COVID-19 positive (COVID+; $n = 176$) or COVID-19 negative (COVID-; $n = 188$) test results completed the survey. The COVID+ cohort had higher occurrence rates for: (a) chemosensory sensitivity impairments (67.0% vs 30.3%; $P < .01$), where the rate of complete loss of smell (anosmia) or taste (ageusia) was higher (35.8% vs 4.8%; $P < .01$), and (b) chemosensory distortions (39.8% vs 19.1%; $P < .01$), where the rate of anosmia or ageusia with distortions was also higher in the COVID+ cohort (19.9% vs 2.7%; $P < .01$). Occurrence rates in the two cohorts were similar for chemosensory phantoms (COVID+ 17.0%, COVID- 18.6%; $P = .70$) and nasal discharge or stuffiness in the presence of sensitivity impairment (COVID+ 63.6%, COVID- 52.6%; $P = .17$).

Conclusion: Chemosensory dysfunction in COVID-19 is associated with higher rates of smell or taste sensitivity impairments and distortions. Higher rates of anosmia and ageusia drive these key findings. Chemosensory phantoms and nasal symptoms in the presence of sensitivity impairment occur at rates that should demand clinical attention, but they do not appear to be specific to COVID-19 positivity.

Level of Evidence: 2b.

KEYWORDS

chemosensory dysfunction, COVID-19, smell, taste

All work completed at the University of California, San Francisco.

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1 | INTRODUCTION

The chemosensory consequences of complete (anosmia)¹⁻⁵ and incomplete (hyposmia)⁶⁻⁸ smell sensitivity impairment have been recognized as early symptoms of COVID-19 infection. Although several early studies suggested rapid subjective recovery, more recent studies showed some patients have persistent dysfunction beyond 2 weeks from their COVID-19 test by self-report or objective assessment.^{3,7,8} As the COVID-19 pandemic has spread worldwide, rates of chemosensory dysfunction ranging from 5.1% to over 85% have been reported.^{1-3,8-12} Not unsurprisingly, taste sensitivity impairment is reported at similar rates of occurrence relative to smell loss.^{4,7,8,12}

While smell and taste distortions and phantoms are part and parcel of chemosensory dysfunction triggered by insult of any form, much less is known about them, especially in relation to COVID-19 infection. Lechien et al³ reported rates of 79.6% and 78.9% for anosmia and ageusia, respectively, and 32.4% for parosmia and 12.6% for phantosmia in COVID-19 test positive patients. Chary et al⁷ reported rates on the order of 5% for each separate category of parosmia, phantosmia, para-geusia, and phantogeusia. Separate from viral-mediated causes, chemosensory dysfunction increases with age, where the rate of parosmia is 20.3% for smoke-related odors and 31.3% for natural gas odors in septuagenarians and older adults.¹³ Within a specialty olfactory disorders clinic, Landis et al reported a rate of 15% for phantosmia.¹⁴

Viral infection mediated chemosensory dysfunction is common in patients who present to smell and taste clinics for evaluation.¹⁵⁻¹⁹ Increased nasal airway resistance and nasal secretions are often associated with viral upper respiratory infections and may contribute to chemosensory dysfunction.²⁰ Volunteers inoculated with a non-COVID-19 human coronavirus demonstrated increased nasal congestion and decreased smell sensitivity.²¹ The presence of viral pathogens in nasal discharge suggests that chemosensory dysfunction may take place through direct injury to the olfactory system, both in isolation without and in conjunction with nasal obstruction-related conductive loss.²²

The COVID-19 pandemic presents a rare opportunity to define interrelationships among the chemosensory dysfunction categories of sensitivity levels, distortions, and phantoms. There is strong interest among COVID-19 test positive (COVID+) and test negative (COVID-) patients to engage in research that would inform clinical counseling and investigative direction. We performed a cross-sectional qualitative study to compare COVID+ and COVID- cohorts across all three chemosensory dysfunction categories using an integrated survey to examine occurrence rate differences and identify drivers of those differences within the 6-week time window surrounding their COVID-19 testing and survey completion.

2 | MATERIALS AND METHODS

2.1 | Study participants

Eight hundred and five adults participated in an anonymous online survey about COVID-19 related symptoms between March 31, 2020,

and April 24, 2020 (UCSF COVID-19 Symptom Survey). Data were captured using REDCap (REDCap Consortium, Vanderbilt University, Nashville, Tennessee) hosted at the University of California, San Francisco (IRB# 20-30 530). Respondents who provided testing date, definitive (positive or negative) testing result and who completed the entirety of the online survey were included in data analysis. Those respondents who did not undergo testing or did not indicate a definitive testing result or failed to complete the entire survey were excluded from analysis. We analyzed data from 364 respondents who reported COVID positive (COVID+; n = 176; 118 [67.0%] female) or COVID negative (COVID-; n = 188; 146 [77.7%] female) test results. The mean (SD) age in years was 38.4 (13.1) in the COVID+ and 37.7 (10.6) in the COVID- cohorts (P = .27). Female participants were the majority in both cohorts, but the rates differed (P = .02). Ninety-seven percent (n = 353) of respondents did not require hospital admission.

2.2 | Survey description and data extraction

The survey queried COVID-19 test results, demographic information, level of smell sensitivity (anosmia, hyposmia, normosmia), level of taste sensitivity (ageusia, hypogeusia, normogeusia), presence or absence of smell and taste distortions, presence or absence of smell and taste phantoms, and presence of nasal symptoms of runny (rhinorrhea) or stuffy nose. Study participants were asked to report symptoms for the 2 weeks leading up to their COVID-19 test and the 2 days prior to survey completion. The median time interval between COVID-19 testing and survey completion was 11 days (95% confidence interval = 1-31 days). From those two time points, we integrated response data to extract nadir values for reporting occurrence rates of chemosensory (smell or taste) distortions and phantoms within the initial 6 weeks of viral infection. The conservative 6-week time estimate was derived by adding time windows of 2 weeks prior to COVID-19 testing and 4 weeks up to survey completion within the confidence interval of response dates. The higher rate of occurrence for either smell or taste was chosen in order to represent the most severe chemosensory dysfunction experienced for each respondent.

2.3 | Statistical analyses

Subcategory features of smell and taste sensitivity impairments, distortions, and phantoms were combined into a single descriptor to capture discrete and interactive effects of chemosensory dysfunction. It is well known that smell dysfunction impacts taste, where several recently published COVID-19 related studies have reported a correlation between olfactory and gustatory abnormalities,^{2-4,6} so this data aggregation represents a comprehensive approach toward chemosensory dysfunction identification. Double counting for any combination descriptor was assiduously avoided. Analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, New York). The Chi-square test was used for contingency analyses of individual categorical variables.

Binary logistic regression was used to determine significance of predictors for COVID-19 test result based on anosmia or ageusia, hyposmia or hypogeusia, presence of taste or smell distortions, presence of smell or taste phantoms, and presence of nasal symptoms. A separate logistic regression was performed to examine predictors for chemosensory distortions including gender, age, COVID test result, anosmia or ageusia, hyposmia or hypogeusia. For all statistical analyses, a $P < .05$ determined significance.

3 | RESULTS

Chemosensory sensitivity impairments occurred more frequently in the COVID+ cohort compared to the COVID- cohort (67.0% vs 30.3%; $P < .01$; Table 1). In subcategory dichotomous contingency analysis, the rate of complete loss of smell (anosmia) or taste (ageusia) was higher in the COVID+ cohort (35.8% vs 4.8%; $P < .01$). In

TABLE 1 Chemosensory dysfunction: sensitivity levels, distortions, and phantoms

Dysfunction category	COVID+ N = 176	COVID- N = 188	P value
Impaired sensitivity levels, n (%)	118 (67.0)	57 (30.3)	<.01 ^a
Absent smell or taste	63 (35.8)	9 (4.8)	<.01 ^b
Reduced smell or taste	55 (31.2)	48 (25.5)	.23
Distortions, n (%)	70 (39.8)	36 (19.1)	<.01 ^a
Absent smell or taste	35 (19.9)	5 (2.7)	<.01 ^b
Reduced smell or taste	28 (15.9)	27 (14.4)	.68
Normal smell or taste	7 (4.0)	4 (2.1)	.30
Phantoms, n (%)	30 (17.0)	35 (18.6)	.70
Absent smell or taste	13 (7.3)	2 (1.1)	<.01 ^b
Reduced smell or taste	9 (5.1)	20 (10.6)	>.05
Normal smell or taste	8 (4.5)	13 (6.9)	.33

Abbreviations: COVID+, COVID-19 positive; COVID-, COVID-19 negative; N, total cohort size; n, subtotal of chemosensory dysfunction category.

^aCOVID+ vs COVID- dysfunction category comparison with significance at $P < .05$.

^bCOVID+ vs COVID- subcategory absent smell or taste comparison with significance at $P < .05$.

contrast, the rates of reduced smell sensitivity (hyposmia) or taste sensitivity (hypogeusia) were similar (31.2% vs 25.5%; $P = .23$).

Chemosensory distortions also occurred at higher rates in the COVID+ cohort (Table 1). The rate of parosmia or parageusia was higher in the COVID+ cohort (39.8% vs 19.1%; $P < .01$). In subcategory univariate analysis, the rate of complete loss of smell or taste was similarly higher in the COVID+ cohort (19.9% vs 2.7%; $P < .01$). For distortions and hyposmia or hypogeusia, the rates were similar (15.9% vs 14.4%, $P = .68$).

Chemosensory phantoms occurred with nearly equal frequency in the two cohorts. The rate of phantosmia or phantogeusia was indistinguishably lower in the COVID+ cohort (17.0% vs 18.8%; $P = .70$). In subcategory analysis, the rates of phantosmia or phantogeusia remained similar between the cohorts (COVID+ 12.4%, COVID- 11.7%; $P = .82$) when any level of chemosensory impairment (anosmia, ageusia, hyposmia, or hypogeusia) was treated as a single categorical variable in dichotomous contingency analysis.

The presence or absence of nasal symptoms occurred at similar rates for respondents with chemosensory sensitivity impairment (Table 2). The rates of chemosensory impairment without rhinorrhea or stuffy nose were not significantly different (COVID+ 36.4%, COVID- 47.3%; $P = .28$). In nasal symptoms subcategory analysis, the occurrence rates of rhinorrhea only, stuffy nose only, and combined rhinorrhea and stuffy nose were also similar between the cohorts (COVID+ 12.7%, 28.0%, 22.9%, COVID- 15.8%, 15.8%, 21.1%; all P values > .08; Table 2).

Associations between COVID-19 positivity and features of chemosensory dysfunction were evaluated using a binary logistic regression model with COVID-19 test result as the dependent variable. The independent variables were presence or absence of: anosmia or ageusia, hyposmia or hypogeusia, chemosensory distortions, chemosensory phantoms, and nasal symptoms (rhinorrhea or stuffy nose). In this model, anosmia or ageusia, and hyposmia or hypogeusia were the two features that were significantly associated with COVID positivity ($P < .01$). Chemosensory distortions, phantoms, and nasal symptoms were not significant predictors for COVID-19 test result. A separate logistic regression analysis was performed to examine predictors of chemosensory distortions that included COVID test result, gender, age, anosmia or ageusia, and hyposmia or hypogeusia. The only significant factors associated with distortions were anosmia or ageusia, and hyposmia or hypogeusia ($P < .001$). COVID-19 test result,

Absent or reduced, smell or taste	COVID+ N = 118	COVID- N = 57	P value
Without rhinorrhea or stuffy nose, n (%)	43 (36.4)	27 (47.3)	.28
With nasal symptoms, n (%)			
Rhinorrhea only	15 (12.7)	9 (15.8)	.58
Stuffy nose only	33 (28.0)	9 (15.8)	.08
Rhinorrhea and stuffy nose	27 (22.9)	12 (21.1)	.79

TABLE 2 Rhinorrhea and nasal obstruction in chemosensory sensitivity impairment

Note: Chemosensory sensitivity impairment includes any of the following: anosmia, hyposmia, ageusia, and hypogeusia. N, total cohort size. n, subtotal of without and with nasal symptoms categories.

gender, and age were not significant predictors of smell or taste distortions. Based on this multivariate analysis, an individual with anosmia or ageusia was 19 times more likely ($\text{Exp}[B] = 18.6$, $P < .001$) to report chemosensory distortions.

4 | DISCUSSION

Chemosensory sensitivity impairment became a recognized cardinal symptom of COVID-19 infection early in the reporting of the pandemic.^{3,8,23,24} While anosmia, ageusia, hyposmia, and hypogeusia represent an important category of chemosensory dysfunction, a more thorough understanding of COVID-19 impact on smell and taste necessitates inclusion of distortions and phantoms. Here, we report on the chemosensory dysfunction categories including sensitivity impairments, distortions, and phantoms from COVID+ and COVID- cohorts in a unified and comprehensive manner. This approach enables richer comparisons to provide a global overview of differences and to examine candidate features that may be driving those differences.

Consistent with other reports, our data affirms that patients with COVID-19 test positivity experience more frequent and more severe chemosensory sensitivity impairments.^{1-3,6,25} In an occurrence rate comparison between the two cohorts, the COVID+ cohort demonstrated two times greater rate sensitivity impairment and seven times greater rate of complete loss of smell or taste compared to the COVID- cohort. The primary driver of overall chemosensory impairments difference between COVID+ and COVID- appears to be anosmia or ageusia, as the rates of hyposmia or hypogeusia in the two cohorts are indistinguishable, as are the mean ages. The comparable rates of incomplete chemosensitivity impairments suggest that complete loss of smell or taste is the critical differentiation feature for higher occurrence rates of chemosensory impairment associated with COVID-19 infection.

Chemosensory distortions in the COVID+ cohort was two times greater in occurrence than in the COVID- cohort, with anosmia or ageusia as the primary driver of this difference based on logistic regression model analysis. The frequencies of hyposmia or hypogeusia were similar and rates of normal smell or taste were low (<4%) in the two cohorts. The incremental difference in the rate of chemosensory distortions (~20%) is roughly the same as the incremental difference in the rate of anosmia or ageusia in the COVID+ cohort (~17%). This suggests that chemosensory distortions are derivative of sensitivity impairments, without clear distinction between complete and incomplete smell or taste loss.

Chemosensory phantom occurrence rates on the order of ~18% were similar between COVID+ and COVID- cohorts. While several studies have brought attention to COVID-19 test positivity association with smell and taste sensitivity impairments,^{2,4,6,10,24} far fewer have reported on the presence of chemosensory phantoms.^{3,7} The nearly equal occurrence rates suggest that viral rhinosinusitis of any etiology may trigger chemosensory phantoms in a small but significant fraction of patients, irrespective of COVID-19 infection.

Nasal symptoms (rhinorrhea only, stuffy nose only, and combined rhinorrhea and stuffy nose) in the presence of chemosensory sensitivity impairments occurred at similar rates in the two cohorts. While no significant difference in overall nasal congestions was found, recent studies suggest COVID-19 specifically impacts the peripheral olfactory system, where expression of ACE2 and TMPRSS2 genes are found in the olfactory epithelium, but not in olfactory neurons.^{26,27} Molecular assays on olfactory epithelium and neuronal tissues in conjunction with clinical assessments of nasal symptoms will be required to assess the pathophysiology and relationships between nasal congestion vs chemosensory dysfunction in COVID-19.

Complete (anosmia or ageusia) and incomplete (hyposmia or hypogeusia) chemosensory sensitivity loss were the two features significantly associated with COVID-19 positivity on logistic regression. This finding is internally consistent with chemosensory distortions arising from sensitivity impairments, and suggests that chemosensory phantoms and sensitivity dependence on nasal symptoms is not associated with COVID-19 positivity.

There are several limitations to this study that relate to anonymous national survey data capture. During the early days of COVID-19 and stringent shelter in place orders, in-person access to COVID-19 positive and negative study participants was limited. The cohort evaluated represented relatively healthy outpatients with internet and social media access, which limits the generalizability of results across all segments of the COVID-19 positive population. Recall and respondent biases, undisclosed relevant comorbidities, and possible duplicate entries inherent to this study design may introduce noise to our data. Self-assessment of olfactory function can be inaccurate²⁸ and qualitative ratings of chemosensory sensitivity without quantitative threshold testing is suboptimal, although for this study, the ability to directly assess COVID-19 suspected patients with objective olfactory and gustatory assessment was inadvisable and unactionable. Stated presence of chemosensory distortions and phantoms without quality and severity characterizations is incomplete, although this remains an inherent limitation given the lack of objective tests to assess chemosensory distortions and phantoms. Measurement uncertainties surrounding chemosensory sensitivity ratings, distortions, and phantoms may introduce variance to prevalence estimates. Given the anonymous nature of the online survey, the potential exists for duplicate survey completions. Electively provided e-mail addresses to assess for duplicates show the rate to be <1%. Key findings from this cross-sectional study within a 6-week time window should be elaborated in greater detail and evaluated for persistence in a longitudinal study.

5 | CONCLUSION

Chemosensory dysfunction in COVID-19 is differentiated by higher rates of smell or taste sensitivity impairments and distortions, mainly due to higher rates of anosmia and ageusia. Chemosensory phantoms and nasal symptoms occur in the presence of sensitivity impairment, but do not appear to be specific to COVID-19 positivity.

ACKNOWLEDGMENT

J. G. G. was supported by the UCSF John A. Watson Faculty Scholar Fund and S. W. C. was supported by the Hong Kong Lounge Bistro Research Fund.

CONFLICT OF INTEREST

J. G. G. is a Genentech Advisory Board Consultant with agreement ending December 2021.

S. W. C. is a consultant to ProLynx LLC and L. T. R. is a consultant to Tissium.

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How to cite this article: Gurrola JG II, Chang JL, Roland LT, Loftus PA, Cheung SW. Short-term chemosensory distortions and phantoms in COVID-19. *Laryngoscope Investigative Otolaryngology.* 2021;6:172-176. <https://doi.org/10.1002/lio2.532>