

Neurology: Clinical Practice Publish Ahead of Print
DOI: 10.1212/CPJ.0000000000001029

Hyposmia and Dysgeusia in COVID-19: Indication to Swab Test and Clue of CNS Involvement

Authors: Francesco Bax, MD¹; Carlo Tascini MD²; Mariarosaria Valente, MD¹; Alessandro Marini, MD¹; Andrea Surcinelli, MD¹; Gaia Pellitteri, MD¹; Chiara De Carlo, MD²; Valentina Gerussi, MD²; Gian Luigi Gigli, MD¹.

Affiliations:

¹University of Udine, Clinical Neurology Unit, Udine, Italy

²University of Udine, Clinical Infectious Diseases Unit, Udine, Italy

Neurology® Clinical Practice Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

Search terms: Hyposmia. Dysgeusia. Covid-19. Prevalence studies.

Publication history: none

Submission type: Research article

Title Character count: **87**

Number of Tables: **2**

Number of Figures: **1**

Word count of Abstract: **248**

Word Count of Paper: **1190**

Corresponding Author:

Francesco Bax

e-mail: francesco@francescobax.it

Statistical Analysis conducted by Francesco Bax, MD, Clinical Neurology Unit, Udine.

Study Funding:

No targeted funding reported.

Disclosures: The authors report no disclosures relevant to the manuscript.

Abstract

Objective/Background: To evaluate the prevalence of hyposmia and dysgeusia in patients with SARS-CoV-2 infection and their temporal relationship with the onset of other symptoms.

Methods: We performed a retrospective analysis of patients admitted during the month of March 2020 to the non-intensive Covid unit of Udine University Hospital on the basis of a positive swab test and/or of clinical-radiological signs of SARS-CoV-2 infection. Patients were interviewed with a standardized questionnaire. Clinical and laboratory data were collected. Data were analyzed with descriptive statistics and results expressed as point estimates and 95% confidence intervals.

Results: Of 141 patients admitted, 93 were interviewed. Hyposmia and dysgeusia were present in 58 cases (62.4%). In 22.4% of them, olfactory and gustatory impairment clearly preceded systemic symptoms. The presence of active smoking was very limited in both groups: 8.6% in hyposmic vs 2.9% in normosmic patients [OR= 3.2 CI 95% (0.3 to 28.6)]. Moreover, total leukocytes and neutrophils count were respectively 23% [effect estimate 1.23 CI 95% (1.06 to 1.42)] and 29% [effect estimate 1.29 CI 95% (1.07 to 1.54)] lower in the hyposmic cohort. No difference was found for other inflammatory biomarkers.

Conclusions: Hyposmia and dysgeusia are common in SARS-Cov-2 infection and can precede systemic symptoms. They should be actively searched and prompt close monitoring and isolation until infection is confirmed or disproven. The lower number of total leukocytes and neutrophils in hyposmic patients might indicate an early phase virus-induced cytopenia.

INTRODUCTION

Hyposmia and dysgeusia have been described in association with SARS-CoV-2 infection, with recent studies ranging from 33.9% to 85.6%¹⁻⁴. This high variability may reflect the different populations considered: in fact, low severity of disease, low comorbidity burden, female sex and younger age all seem to be associated with a higher prevalence of these symptoms^{1,5,6,7}. On the other side, these manifestations may not be recognized when dealing with acute respiratory complications or cannot be evaluated in those who are in intensive care unit. However, these symptoms could represent an early marker of disease that precedes systemic symptoms.

In our non-intensive care “Covid Unit”, we observed that hyposmia and dysgeusia were frequently reported as initial symptoms, typically prior to the onset of systemic symptoms, which typically followed these sensory alterations by 24-48 hours. Based on this observation, we conducted a retrospective study of symptom onset and initial laboratory values. Our study extends the clinical observations on hyposmia and dysgeusia in SARS-Cov-2 infection and evaluates the frequency of their presentation as first symptoms of this condition.

METHODS

Study design and patient population

We retrospectively analyzed the patients who had been admitted to the non-intensive “Covid unit” of “Santa Maria della Misericordia” University Hospital (Udine, Italy) in the period March 1st -31st, 2020, on the basis of a positive swab test and/or of clinical and radiological signs of lung involvement (Chest X-Ray or CT scan). Patients who could not be interviewed due to mechanical ventilation, cognitive impairment or death were excluded from these analyses. The presence of cognitive impairment was identified by evaluating if patient was alert and oriented in space, time and self. Patients who had an initial negative swab and persistence of swab test negativity throughout the hospital stay were excluded from the analysis, although infection was suspected based on clinical and radiological findings.

Data collection and interview structure

At admission all patients underwent a comprehensive blood panel, including total blood count, C-reactive protein (C-RP), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), interleukin 6 (IL-6), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (GGT). PaO₂/FiO₂ ratio was calculated from the results of the arterial blood gas analysis at admission.

Patients were personally interviewed at bedside, if still admitted, or by phone call, if transferred to other hospital units or at home. Interviews were all conducted by Neurology Residents (F.B., A.M., A.S., G.P.) using a structured interview with open questions including the development of hyposmia and/or dysgeusia, the time of their appearance and temporal relationship with other symptoms, their duration and persistence, smoking habits, history of asthma, allergic rhinitis and other nasopharyngeal conditions. Interview model form is available as a supplemental file (Figure e-1, <http://links.lww.com/CPJ/A240>). The time span from the beginning of symptoms and the time in which patients were interviewed has been reported. In order to have synthetic measure of the disease burden in our population, we calculated the Charlson Comorbidity Index⁸ using the information obtained from the clinical history and from all the available records. In order to evaluate the role of pre-existing conditions associated with hyposmia, we recorded whether the patients had a history of Parkinson's disease and/or traumatic brain injury.

Statistical analysis

Data were analyzed with descriptive statistics. Kolmogorov test and histogram were used to control for normal distribution of variables. Continuous variables were analyzed by the two-sample t test, while categorical variables were analyzed using χ^2 test. Since we did not account for a prespecified method for error control, summary statistics is limited to point estimates and 95% confidence intervals. The widths of the intervals have not been adjusted for multiplicity and the inferences drawn may not be reproducible. Estimate of effect for normally distributed variables were calculated using Cohen's d test (d). Logarithmic transformation was applied to non-normal distribution and estimate of effect was calculated as a raw mean

difference (D) for continuous variables. Raw mean differences were re-transformed by means of antilogarithm and thus expressed as a ratio. Odds ratio (OR) was calculated for categorical variables.

Standard Protocol Approvals, Registrations, and Patient Consents

Due to the urgent need of data on the new Covid-19 infection and the situation of emergency at the peak of the pandemic, it was impossible to ask for a preliminary approval of the regional ethics committee. All patients, however, at the time of the admission gave written general consent to the anonymous use of their clinical data for research purposes. In addition, at the time of the interview, verbal informed consent was obtained on the phone.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

RESULTS

We reviewed 141 consecutive patients, with mean age of 62.6 ± 15.8 years (range 19-91). 66.7% of the study population was male (n=94). 34 % of patients (n= 48) were excluded from the study (see Figure 1). Interviews were completed for 66% of patients (n= 93) with results from this cohort presented in Table 1. Among 141 patients only one was affected by Parkinson's disease, but was not interviewed due to concomitant cognitive decline. No patient reported a history of traumatic brain injury. Charlson Index for the entire group of interviewed patients is reported as a supplemental file (Figure e-2, <http://links.lww.com/CPJ/A240>), no differences in the score were found in the two groups [mean score for hyposmic patients 2.2 vs. mean score for normosmic patients 1.72; mean difference 0.48 CI 95% (-0.27 to 1.23); $d = 0.28$ CI 95% (-0.15 to 0.71)].

Among the interviewed patients, hyposmia and dysgeusia were present in 58 cases (62,4%). Age and sex distribution of the hyposmic group were not different from those of the entire interviewed population [mean difference 0.91 years, CI 95% (-6.1 to 7.9); $d = .06$ CI 95% (-0.4 to 0.5)]. The presence of active smoking was very limited in both groups, 6.5 8.6% in hyposmic vs 2.9 % in normosmic patients [OR= 3.2 CI 95% (0.3 to 28.6)].

Considering only the group of 58 patients affected by olfactory and gustatory symptoms, hyposmia and dysgeusia often appeared along with systemic symptoms, but in 13 cases (22.4%) clearly preceded them. The interview took place at a variable time interval from onset of symptoms [(mean 26.6 ± 7.3 days (range 12-50)] and, at the time of the interview, 25.9% of patients reported persisting olfactory and/or gustatory symptoms. Persistence of symptoms was not associated with a shorter time interval from their onset and the moment of interview [mean interval for patients with persisting symptoms 30.9 days vs. mean interval for patients without persisting symptoms 25.0 days; mean difference 5.9 days, CI 95% (1.6 to 10.2); $d = .81$ CI 95% (0.22 to 1.40)].

Notably only 6 out of 58 hyposmic patients (10.3%) reported rhinorrhea and/or nasal congestion. Similarly, asthma was reported only by 2 of our hyposmic patients (3.4%) in their medical history, while history of allergic rhino-conjunctivitis was present in 6 patients (10.3%). Moreover, one patient affected by pre-existing hyposmia reported worsening of his problem 2 days prior to the onset of systemic symptoms and this worsening persisted at the time of interview. Among non-hyposmic patients, one had a history of nasal polyposis. Comparative prevalence of medical history elements between hyposmic and normosmic patients is shown in Table 1.

The results regarding biomarkers of inflammation are reported in Table 2. Comparing the group of 58 patients with hyposmia with that of 34 non-hyposmic patients (for one more patient data about leukocytes are missing) we observed that total leukocytes and neutrophils count were respectively 23% (effect estimate 1.23 CI 95% [1.06 to 1.42]) and 29% (effect estimate 1.29 CI 95% [1.07 to 1.54]) lower in the

hyposmic cohort. No differences were found in any of the other indexes examined (CRP, IL-6, LDH, lymphocytes). Similarly, no differences were found between the two groups for the presence of dyspnea [46.6% in hyposmic vs 48.6% in normosmic patients; OR=1.08 CI 95% (0.4 to 2.5)] or the PaO₂/FiO₂ ratio [mean PaO₂/FiO₂ ratio in hyposmic 351 vs mean PaO₂/FiO₂ ratio in normosmic 327; mean difference 24, CI 95% (-10.5 to 59.3); $d = .31$ CI 95% (-0.14 to 0.77)]. Arterial blood gas analysis was performed in 87% of the interviewed patients at a mean time interval of 6.5 ± 4.3 days from systemic symptoms onset.

DISCUSSION

Our results suggest that olfactory symptoms are prevalent among patients with mild-moderate COVID-19 infection. The observed rate of 63% is consistent with previously published reports. This frequency appears independent of smoking given our cohort had only 8.6% of smokers.

Although olfactory symptoms are encountered in other upper respiratory viral infections (e.g. rhinovirus, influenza virus, adenovirus and other coronaviruses) their prevalence is higher in SARS-CoV-2 infection⁹. Moreover, to our knowledge, a single case of olfactory dysfunction following SARS-CoV-1 infection has been reported¹⁰. It would be difficult to attribute hyposmia and dysgeusia only to upper airways involvement, at least for patients with olfactory symptoms preceding systemic symptomatology. On the other side, rhinorrhea and/or nasal congestion were infrequent, while only a small proportion of hyposmic patients reported in their medical history the presence of nasal problems preceding the development of olfactory symptoms and of the Covid infection⁴. For these reasons, we think that an “obstructive” mechanism in the pathogenesis of hyposmia is unlikely.

In our study, we found that 22.4% of patients with hyposmia and dysgeusia recalled that these symptoms were their initial complaints. Given this, we suggest that these symptoms should be considered as a sentinel of an incumbent infection. At the very least, hyposmia and dysgeusia should be symptoms that prompt close monitoring of patients for subsequent symptoms of Covid infection and consideration for isolation or quarantine until infection is confirmed or disproven.

Recently, it has been reported that 44% of secondary cases of laboratory confirmed Covid-19 are infected during the index case's presymptomatic stage¹¹. This important observation underlines the usefulness in detecting early signs of infection and should be re-evaluated in the light of the possible presence of olfactory dysfunction.

The temporal presentation of olfactory symptoms raises some questions: could they represent a clinical correlate of a central nervous system (CNS) entry of SARS-Cov-2, alternative to the pulmonary or intestinal ones? Are olfactory nerves uniquely susceptible to SARS-Cov-2 infection? Could asymptomatic viral spread through cerebrospinal fluid or glymphatics explain some of the symptoms of this new infection?

In addition, the lower number of total leukocytes and neutrophils in hyposmic patients, compared to non-hyposmic ones could be suggestive of an earlier viral induced cytopenia. It is not possible the moment to infer that this represents a damage of the cellular immune system, but its association with hyposmia could at least help in identifying patients at risk.

As of today, a pre-clinical evidence of CNS invasion in SARS-Cov-2 infection does not exist and viral RNA isolation in cerebrospinal fluid has been published just for one case¹², in addition to the case reported by the press¹³. Nevertheless, clinical and laboratory evidence exists that beta-coronaviruses¹⁴ related to SARS-Cov-2 (i.e. MERS and SARS-CoV-1) have access to CNS and may damage nerve cells. Murine models of MERS infection demonstrated viral entry via olfactory neurons and then spread through thalamus to brainstem structures, while in SARS-CoV-1 murine models neuronal damage may exist without encephalitis evidence and may drive disease outcome¹⁵.

This study has several limitations. First of all, only the patients still admitted in the ward have been personally interviewed. This may have created a difference with the information obtained on the phone from the already discharged patients, although we used a standardized questionnaire. Secondly, we cannot exclude

the possibility of recall biases, although we performed the interviews in the shortest possible time. For the same reason, all the patients with evidence of cognitive decline have been excluded from the study. Moreover, detection of olfactory and gustatory symptoms was performed by means of a questionnaire which has a lower sensitivity compared to olfactory tests². This may have led to an underestimation of symptom prevalence. Finally, we cannot rule out that our results might have been different if we had been able to interview the patients who had severe course, leading to ICU admission or fatal outcome.

Although preliminary, our findings suggest that hyposmia and dysgeusia should be considered evidence of Covid infection and should prompt a cross-specialty approach to diagnosis, bearing in mind that there could be more at play than what the lung can tell us.

APPENDIX 1: Authors

Name	Location	Contribution
Francesco Bax MD	Santa Maria della Misericordia University Hospital, Udine, Italy	Design and conceptualized study; acquisition of data; analyzed the data; performed statistical studies; drafted the manuscript for intellectual content
Carlo Tascini MD	Santa Maria della Misericordia University Hospital, Udine, Italy	Design and conceptualized study; revised the manuscript for intellectual content
Mariarosaria Valente MD	Santa Maria della Misericordia University Hospital, Udine, Italy	Revised the manuscript for intellectual content
Alessandro Marini MD	Santa Maria della Misericordia University Hospital, Udine, Italy	Major role in the acquisition of data; analyzed the data
Andrea Surcinelli MD	Santa Maria della Misericordia University Hospital, Udine, Italy	Major role in the acquisition of data; analyzed the data
Gaia Pellitteri MD	Santa Maria della Misericordia University Hospital, Udine, Italy	Major role in the acquisition of data; analyzed the data
Chiara De Carlo MD	Santa Maria della Misericordia University Hospital, Udine, Italy	Acquisition of data
Valentina Gerussi MD	Santa Maria della Misericordia University Hospital, Udine, Italy	Acquisition of data
Gian Luigi Gigli MD	Santa Maria della Misericordia University Hospital, Udine, Italy	Design and conceptualized study; drafted the manuscript for intellectual content; revised the manuscript for intellectual content

References

1. Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clinical Infectious Diseases*. Epub 2020 Mar 26.
2. Moein ST, Hashemian SMR, Mansourafshar B, Khorram - Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID - 19. *International Forum of Allergy & Rhinology*. Epub 2020 Apr 17.
3. Vaira LA, Deiana G, Fois AG, et al. Objective evaluation of anosmia and ageusia in COVID - 19 patients: Single - center experience on 72 cases. *Head & Neck*. Epub 2020 Apr 29.
4. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *European Archives of Oto-Rhino-Laryngology*. Epub 2020 Apr 6.
5. Klopfenstein T, Kadiane-Oussou NJ, Toko L, et al. Features of anosmia in COVID-19. *Médecine et Maladies Infectieuses*. Epub 2020 Apr.
6. Beltrán - Corbellini Á, Chico - García JL, Martínez - Poles J, et al. Acute - onset smell and taste disorders in the context of Covid - 19: a pilot multicenter PCR - based case - control study. *European Journal of Neurology*. Epub 2020 Apr 22.
7. Yan CH, Faraji F, Prajapati DP, Ostrander BT, DeConde AS. Self - reported olfactory loss associates with outpatient clinical course in Covid - 19. *International Forum of Allergy & Rhinology*. Epub 2020 Apr 24.
8. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *Journal of Chronic Diseases*. 1987;40:373–383.
9. Wee LE, Chan YFZ, Teo NWY, et al. The role of self-reported olfactory and gustatory dysfunction as a screening criterion for suspected COVID-19. *European Archives of Oto-Rhino-Laryngology*. Epub 2020 Apr 24.
10. Hwang CS. Olfactory neuropathy in severe acute respiratory syndrome: report of A case. *Acta Neurol Taiwan*. 2006;15(1):26 - 28.
11. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nature Medicine* [online serial]. Epub 2020 Apr 15. Accessed at: <https://www.nature.com/articles/s41591-020-0869-5.pdf>. Accessed April 20, 2020.
12. Moriguchi T, Harii N, Goto J, et al. A first Case of Meningitis/Encephalitis associated with SARS-Coronavirus-2. *International Journal of Infectious Diseases*. Epub 2020 Apr.
13. Beijing hospital confirms nervous system infections by novel coronavirus - Xinhua | English.news.cn [online]. www.xinhuanet.com. Accessed at: http://www.xinhuanet.com/english/2020-03/05/c_138846529.htm.
14. Li K, Wohlford-Lenane C, Perlman S, et al. Middle East Respiratory Syndrome Coronavirus Causes Multiple Organ Damage and Lethal Disease in Mice Transgenic for Human Dipeptidyl Peptidase 4. *Journal of Infectious Diseases*. 2015;213:712–722.
15. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe Acute Respiratory Syndrome Coronavirus Infection Causes Neuronal Death in the Absence of Encephalitis in Mice Transgenic for Human ACE2. *Journal of Virology*. 2008;82:7264–7275.

Table 1: Demographics of patients with Covid-19 infection interviewed for olfactory and gustatory symptoms.

	Interviewed	Normosmic	Hyposmic and Dysgeusic	Difference between groups - Cohen's d/OR (CI 95%)*
Number of patients	93 (100%)	35 (37.6%)	58 (62.4%)	n.a.
Sex (Male)	61 (65.5%)	22 (62.9%)	39 (67.2%)	1.2 (0.5 to 2.9)
Mean age \pm S.D. (range)	58.0 \pm 15.0 (19-87)	58.6 \pm 18.3 (19-87)	57.7 \pm 12.7 (33-87)	0.06 (-0.4 to 0.5)
Hyposmia and dysgeusia as heralding symptoms	13 (14.0%)	n.a.	13 (22.4%)	n.a.
Active smokers	6 (6.5%)	1 (2.9%)	5 (8.6%)	3.2 (0.3 to 28.6)
Rhinorrhea or nasal congestion	9 (9.7%)	3 (8.6%)	6 (10.3%)	1.2 (0.2 to 5.2)
Pre-existing sinusitis	10 (10.8%)	4 (11.4%)	6 (10.3%)	0.9 (0.2 to 3.4)
Asthma	4 (4.3%)	2 (5.7%)	2 (3.4%)	0.5 (0.07 to 4.3)
Parkinson's disease	1 (1.1%)	1 (2.9%)	0 (0%)	n.a.

Legend: OR= Odds Ratio; n.a. = not applicable

* differences between hyposmic and normosmic groups are expressed as point estimates and 95% confidence intervals. Cohen's *d* was calculated for continuous variables and OR was calculated for categorical variables.

Table 2: Association between olfactory symptoms (OS) and inflammatory biomarkers obtained at hospital admission.

	Patients without OS (median; IQR)	Patients with OS (median; IQR)	Effect Estimate and unadjusted CI (95%)
Leucocytes (n/μL)	6010.0 (3117.5)	4695.0 (2255.0)	1.23 [1.06 to 1.42]
Neutrophils (n/μL)	3960.0 (2835)	3250.0 (2192.5)	1.29 [1.07 to 1.54]
Lymphocytes (n/μL)	920.00 (425)	925.00 (350)	1.01 [0.84 to 1.21]
C-RP (mg/L)	36.82 (76.8)	41.15 (68.6)	1.05 [0.58 to 1.92]
IL-6 (mg/mL)	35.5 (45.4)	27.0 (50)	1.05 [0.65 to 1.70]
LDH (IU/L)	453.0 (231)	475.0 (285)	0.91 [0.77 to 1.07]

* IQR = interquartile range.

Figure 1: Flow chart of the study. Patients with a negative swab test were excluded from the study.



Neurology® Clinical Practice

Hyposmia and Dysgeusia in COVID-19: Indication to Swab Test and Clue of CNS Involvement

Francesco Bax, Carlo Tascini, Mariarosaria Valente, et al.
Neurol Clin Pract published online December 9, 2020
DOI 10.1212/CPJ.0000000000001029

This information is current as of December 9, 2020

Updated Information & Services	including high resolution figures, can be found at: http://cp.neurology.org/content/early/2020/12/09/CPJ.0000000000001029.full.html
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): COVID-19 http://cp.neurology.org/cgi/collection/covid_19 Prevalence studies http://cp.neurology.org/cgi/collection/prevalence_studies Viral infections http://cp.neurology.org/cgi/collection/viral_infections
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://cp.neurology.org/misc/about.xhtml#permissions
Reprints	Information about ordering reprints can be found online: http://cp.neurology.org/misc/addir.xhtml#reprintsus

Neurol Clin Pract is an official journal of the American Academy of Neurology. Published continuously since 2011, it is now a bimonthly with 6 issues per year. Copyright © 2020 American Academy of Neurology. All rights reserved. Print ISSN: 2163-0402. Online ISSN: 2163-0933.

