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Systemic steroids may enhance recovery from loss of smell and taste in hospitalized coronavirus disease 2019 (COVID-19) patients: an observational study

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INTRODUCTION

Chemosensory dysfunction (CD) is among the most frequent long-term consequences of coronavirus disease 2019 (COVID-19).[1] Management strategies for postviral CD remain disappointing and very little is known regarding risk factors for persistent CD.[2] We aimed to identify clinical predictors of persistent CD among hospitalized COVID-19 patients by 3 months upon admission.

METHODS

This is an observational study conducted on patients hospitalized for COVID-19 at the Infectious Diseases Unit of the Careggi University Hospital in Florence, Italy, from March 2020 to the end of December 2020. After institutional review board (IRB) approval (CEAVC 17104), patients were included if they complained of CD on admission for a virologically confirmed severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection, and they were alive and reachable by phone 3 months after admission. Informed consent was obtained from all individual participants included in the study. Exclusion criteria were any unwillingness to participate in the study, a history of previous sinonasal surgery, a known preexisting CD (brain injury, viral infection other than SARS-CoV-2), severe clinical course (defined as the need to be transferred to the intensive care unit [ICU], according to the National Institutes of Health [NIH] clinical criteria[3]), and cognitive decline.

The subjective CD was assessed on admission using a six-point scale, ranging from zero (absence of any CD) to five (complete loss of smell and taste function.) This question ("Compared to the period before the infection, how would you rate your current impairment of smell or taste?") was adapted from the 22-item Sino Nasal Outcome Test (SNOT-22), analogously to other recent publications in this field.[4] CD was then reassessed at the follow-up visits at 1 and 3 months after discharge when patients were reached during a formal in-hospital or telemedicine visit. Specifically, each patient was questioned if he/she perceived to have completely regained (i.e., a score of zero, otherwise they were considered to have a persistent CD) their sense of smell and taste, compared to the period before the infection with COVID-19. Data of those patients

whose CD was not quantified on admission were input only in a binary fashion (recovery from CD, yes/no), so as to avoid a recall bias.

In order to identify the factors associated with 3-month recovery, digital clinical records were reviewed to retrieve the clinical and biochemical covariates. Inflammatory parameters (e.g., C-reactive protein and interleukins) were routinely measured on the day of admission. Cutoffs for the laboratory values were set using either the median value or the upper reference limit of each measurement (when available). Indications for administering steroids followed the international recommendations of the need for supplemental oxygen therapy and it consisted of 4 to 8 mg of dexamethasone by mouth or intravenously (PO/IV) or an equivalent dose of IV methylprednisolone, as needed.

Standard descriptive statistics were used to describe the two groups by reporting mean ± standard deviation (SD) or median (range), as appropriate. Chi-square test, t test, and Mann-Whitney test were used to calculate the p values for categorical and continuous variables, respectively. A mixed-effects logistic regression model (with wave as higher-order level) was used in order to identify predictors of CD recovery. Analyses were conducted using Stata (version 14; Stata Corporation, College Station, TX, USA), and the significance value was set at alpha < 0.05.

RESULTS

A total of 141 patients were analyzed and a general description of the features and treatments received by the included population (separately for the first and second epidemic wave) is given in Table 1. The mean length of hospital stay was 11.1 ± 13.3 days (mean ± SD); 1 month after the discharge, 44 (31.2%) still complained of persistent CD, while, at the 3-month follow-up visit, 37 (26.2%) did not report a full subjective recovery. If we consider only the 117 patients with the quantitative evaluation, full recovery was more likely in the wave I than in the wave II subgroup (p = 0.008).

As shown in Table 2, tumor necrosis factor (TNF)-alpha was the only biochemical parameter to reach significance at the univariate analysis, along with the use of hydroxychloroquine and protease inhibitors. In the multivariable model, however, only administration of steroids during the hospitalization was significantly associated with a higher chance of 3-month recovery from CD (odds ratio [OR] 0.33; 95% confidence interval [CI], 0.12–0.92). Instead, protease inhibitors constituted a potential risk factor for persistent CD (OR 3.07; 95% CI, 1.06–8.87).

DISCUSSION

SARS-CoV-2 is capable of directly infecting the nasal epithelial sustentacular cells with subsequent inflammatory-mediated disruption of the cytoarchitecture of the olfactory mucosa.[5] In the context of what is known as "long COVID syndrome," CD is considered, along with fatigue and dyspnea, as the main persistent symptom after virological clearance.[6]

Spontaneous recovery of CD is frequent but a small proportion of patients do not seem to fully regain their sense of smell; in addition, strategies such as olfactory training are the only treatment to have shown a sufficient level of evidence.[1,2,7] We have shown that the use of systemic steroids during hospitalization appears to be the only clinical predictor of recovery. Early administration of steroids seems to increase the length of hospitalization and viral shedding time of mild and non-hospitalized patients with COVID-19; however, in those patients who receive respiratory support, steroids were the only treatment to reduce the 28-day mortality.[7,8]

In the most recent literature, there is small yet increasing evidence that a significant improvement in CD can be obtained by a short course of oral methylprednisolone[9] or even intranasal fluticasone spray.[10] In these two studies, steroids were given within 6 weeks from the onset of CD,[9] or immediately during the hospitalization,[10] and in both studies only patients with mild-moderate disease were recruited. In conclusion, considering the conflicting results of systemic steroids and the low level of evidence available so far, a cautious use of systemic steroids is advised, especially outside controlled studies.[7]

Instead, we found protease inhibitors to constitute a possible negative factor for CD recovery. Although these drugs were progressively abandoned in favor of remdesivir during wave II, their neural toxicity is well-known and the damage to the small vessels of the brain and mitochondrial dysfunction are the two main mechanisms.[11] Intriguingly, there is increasing evidence for a SARS-CoV-2–associated injury to the olfactory bulb mediated by endothelial cell invasion,[3,5] and further studies are needed to explore a potential interaction in this regard. Our study has some limitations, such as the lack of psychophysical assessment of CD and the fact that a large proportion of home-based COVID-19 with CD present a mild clinical course, and, at present, steroid therapy remains contraindicated in this setting.[7] Finally, it should be considered that some of our findings associated with CD may actually represent a type II statistical error, or they can be unrelated to the clinical features (e.g., the use of low-molecular weight heparin [LMWH]).

TABLE 1 A detailed descriptive analysis of the cohort stratified according to the pandemic wave

Parameter	Wave I (March–August 2020, *n* 89)	Wave II (September–December 2020, *n* 52)	*p*
Features of chemosensory disturbances			
Severity of CD on admission, median (range)	4 (1–5)	4 (2–5)	0.522
Reported CD on admission (N.B., out of 117), *n* (%)			0.760
1	7 (9.2)	7 (17.1)	
2	7 (9.2)	4 (9.8)	
3	12 (15.8)	6 (14.6)	
4	20 (26.3)	8 (19.5)	
5	30 (39.5)	16 (39)	
Severity of CD after3 months, median (range)	0 (0–5)	0 (0–5)	0.048
Reported CD after 3 months (N.B., out of 117), *n* (%)			0.476
0	50 (65.8)	34 (83)	
1	8 (10.5)	3 (7.4)	
2	4 (5.3)	1 (2.4)	
3	6 (7.9)	1 (2.4)	
4	6 (7.9)	1 (2.4)	
5	2 (2.6)	1 (2.4)	
Patients complaining of persistent CD, *n* (%)	30 (33.7)	7 (13.5)	0.008
Clinical features and comorbidities on admission			
Age (years), mean ± SD	61.3 ± 14.2	56.9 ± 17.8	0.110
Sex, *n* (%)			0.861
Male	50 (56.2)	28 (53.8)	
Female	39 (43.8)	24 (46.2)	
Body mass index (kg/m^2), mean ± SD	27.3 ± 4.9	26.5 ± 4.8	0.419
Hypertension, *n* (%)	37 (41.6)	20 (38.5)	0.859
History of cardiovascular disease, *n* (%)	18 (20.2)	6 (11.5)	0.247
NOAC, *n* (%)	12 (13.5)	4 (7.7)	0.412
Diabetes mellitus, *n* (%)	8 (9)	14 (26.9)	0.007
Dyslipidemia, *n* (%)	7 (7.9)	11 (21.1)	0.035
COPD, *n* (%)	12 (13.5)	2 (3.8)	0.082
Immunosuppressive therapy, *n* (%)	6 (6.7)	1 (1.9)	0.261
Respiratory allergies, *n* (%)	7 (7.9)	2 (3.8)	0.485
Smoking history, *n* (%)	18 (20.2)	6 (11.5)	0.185
Clinical course and medical treatment of COVID-19			
Length of hospital stay (days), mean ± SD	11.9 ± 12.9	9.7 ± 9.7	0.288
Pneumonia on computed tomography, *n* (%)	77 (86.5)	37 (71.1)	0.044
Hydroxychloroquine, *n* (%)	78 (87.6)	0 (0)	<0.001
Protease inhibitors, *n* (%)	77 (86.5)	16 (30.8)	<0.001
Tocilizumab, *n* (%)	4 (4.5)	0 (0)	0.297
LMWH, *n* (%)	51 (57.3)	45 (86.5)	<0.001
Systemic steroids, *n* (%)	24 (27)	36 (69.2)	<0.001
Time elapsed from the admission and start of steroids (days), median (range)	1 (1–8)	0.5 (0–3)	0.001
Total duration of steroids therapy (days), mean ± SD	10.1 ± 5.8	9.9 ± 6.1	0.882
Cumulative equivalent dose of systemic steroids (mg), median (range)	650 (480–3060)	570 (320–1122)	0.545
Mean equivalent daily dose administered of systemic steroids (mg), mean (range)	59 (47–161)	53.1 (41–94)	0.476

(Continues)

TABLE 1 (Continued)

Parameter	Wave I (March–August 2020, *n* 89)	Wave II (September–December 2020, *n* 52)	*p*
Laboratory parameters			
IL-6 (pg/ml), median (reference values)	17.7 (8.4–257.8)	14.6 (2.7–78.7)	0.019
IL-10 (pg/ml), median (range)	7 (0–28.6)	4.9 (1.1–16.9)	0.606
IL1- beta (pg/ml), median (range)	0 (0–2)	1 (1–2)	0.011
IL-8 (pg/ml), median (range)	70.5 (123.4)	25.2 (22.6)	0.043
Fibrinogen (mg/dl), median (range)	537 (160.5)	597.9 (234.5)	0.112
D-dimer (ng/ml), median (range)	1360 (950–3126)	1393 (299–5031)	0.770
White blood cells (1 × 109/L), mean ± SD	5497.3 ± 3392	7479 ± 4675.6	0.005
TNF-alpha (pg/ml), median (range)	13.1 (0.6–55.2)	3.9 (1.3–7.8)	0.053
Ferritin (μg/L), median (range)	1104 (55–1879)	1100 (403–1350)	0.678
CRP (mg/L), mean ± SD	85.1 ± 80.3	61.6 ± 56.6	0.051

Note: Chi-square test and Mann-Whitney test were used to calculate the *p* values for categorical and continuous variables, respectively.

Abbreviations: CD, chemosensory dysfunction; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; IL, interleukin; LMWH, low-molecular weight heparin; N.B., nota bene; NOAC, novel oral anticoagulants; SD, standard deviation; TNF, tumor necrosis factor.

TABLE 2 Univariate and multivariate analysis of factors associated with the 3-month incomplete recovery from CD

Univariate analysis					
Clinical, laboratory, and treatment-related factors	*n*	OR	Lower 95% CI	Upper 95% CI	*p*
Hypertension	134	0.47	0.20	1.10	0.081
Hydroxychloroquine	134	3.92	1.57	9.81	0.004
Protease inhibitors	134	3.58	1.28	10.04	0.015
Steroids treatment	134	0.52	0.21	1.34	0.176
Age (+1 year)	134	1.02	0.99	1.04	0.247
Age (above median)	134	1.29	0.58	2.84	0.531
IL-8 (above median)	61	2.28	0.58	8.92	0.237
Fibrinogen (above median)	102	0.81	0.31	2.16	0.675
Fibrinogen (above 400 mg/dl)	102	0.49	0.15	1.60	0.239
Neutrophil cell count (above median)	128	0.53	0.22	1.26	0.152
TNF-alpha (above median)	43	2.48	0.54	11.28	0.240
TNF-alpha (above 15 pg/ml)	43	10.50	2.09	52.85	0.004
Ferritin (above median)	110	0.52	0.21	1.29	0.158
Ferritin (above 150 μg/L)	110	0.76	0.17	3.36	0.720
Multivariate analysis					
Factors included in the logistic model	*n*	OR	Lower 95% CI	Upper 95% CI	*p*
Hypertension	134	0.42	0.17	1.06	0.067
Age (+1 year)	134	1.03	1.00	1.06	0.052
Steroids treatment	134	0.33	0.12	0.92	0.033
Protease inhibitors	134	3.07	1.06	8.87	0.039

Note: The number of included values for each covariate considered into the model, limits of the 95% CI, and the *p* values are shown in the columns.

Abbreviations: CD, chemosensory dysfunction; CI, confidence interval; IL, interleukin; OR, odds ratio; TNF, tumor necrosis factor.

CONFLICT OF INTEREST
All authors declare they have no conflict of interest.

ETHICS STATEMENT
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

AUTHOR CONTRIBUTIONS
Luca Giovanni Locatello: Conceptualization, data curation, formal analysis, investigation, resources, and writing - review and editing. Benedetta Trotta: Conceptualization, data curation, formal analysis, investigation, resources, and writing - review and editing. Chiara Bruno: Conceptualization, data curation, formal analysis, investigation, resources, and writing - review and editing. Michele Trotta: data curation, supervision and editing. Giandomenico Maggiore: Conceptualization, supervision and writing - review and editing. Laura Rasero: data curation, supervision and editing. Saverio Caini: data curation, supervision and editing; Oreste Gallo: Conceptualization, supervision and writing - review and editing.

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