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Short communication

The prognostic role of IL-10 in non-severe COVID-19 with chemosensory dysfunction

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ABSTRACT

Objectives: Olfactory and gustatory dysfunction (OD/GD) are now recognized as typical symptoms of COVID-19 infection. However, their pathogenesis remains unclear and no clear prognostic factors have been identified. We have analyzed a cohort of mild/moderate hospitalized patients to identify possible clinical or immunological predictors of recovery from OD/GD.
Methods: Clinical and biological parameters were reviewed along with associated comorbidities. Chemosensory Complaint Score was administered on admission and 30 days after the first negative swab. Unpaired Wilcoxon and chi-squared tests were used to compare the variables in the patients who recovered versus those who did not.
Results: From a cohort of 119 hospitalized patients, 43 (36%) reported OD/GD on admission. 60.6% had a full recovery from OD and 69.2% from GD. Only the concentration of IL-10 on admission emerged as significantly associated with recovery of taste ($p = 0.041$) while allergic respiratory disease was more prevalent in the group who did not recover from OD ($p = 0.049$) and GD ($p = 0.007$).
Conclusion: These findings suggest that COVID-19 associated OD/GD is an inflammatory-mediated condition and that clinical and immunological parameters could predict the evolution of these symptoms.

1. Introduction

It is now ascertained that a characteristic symptom of SARS-CoV-2 is olfactory and gustatory dysfunction (OD/GD) [1]. A recent *meta*-analysis estimated an overall prevalence of 41% and 38.2% for OD and GD, respectively [2]. While in the literature OD in COVID-19 seems to be associated with a mild clinical course in non-hospitalized patients, it is less clear if this symptom in an inpatient setting is linked to a different clinical course [3]. Despite the many limitations because of the subjective measurement of OD/GD, complete recovery seems to occur in less than 50% of patients while about 10.6% seems to report an unchanged or even worse dysfunction [4]. As the literature on the topic grows, only gender and nasal congestion have been identified so far as risk factors for persistent OD/GD [5,6].

The aims of this study are to quantify the OD/GD in a cohort of hospitalized COVID-19 patients, to have a more in-depth description of GD, to evaluate the recovery rate of these symptoms, and to identify possible clinical and/or laboratory predictors.

2. Methods

After Institutional Review Board approval (CEAVC 17104), we reviewed all the 119 patients hospitalized in the Department of Infectious and Tropical Diseases from 3 March to 1 April 2020 with laboratory-confirmed COVID-19. On admission, all patients had been screened for COVID-19 associated symptoms, and the subgroup reporting OD/GD was requested to compile the Chemosensory Complaint Score (CCS) [7]. In the absence of any specific tool, such a questionnaire was chosen because it was developed for monitoring another viral disease (AIDS) and it is straightforward to administer even by phone; there

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is a taste section (0–10 points regarding the change in sense of taste, the way food tastes, presence of a bad taste, the effect of medications, changes in quality of salt/sweet/sour/bitter, and overall taste dysfunction) along with a smell section (0–6 points investigating the change in the sense of smell, the way food smells, the effect of medications, change in the strength of odors, and a global severity of smell dysfunction) for a total CCS ranging from 0 (no OD/GD) to 16 (severe smell and taste disorder) [7,8]. Exclusion criteria were age < 18, a history of head injury or brain and/or nose operations, preexisting OD/GD because of other causes, severe clinical course (defined as the need to be transferred to ICU or death), and cognitive decline. Smoking status (coded as never vs. former/current), clinical comorbidities (cardiovascular diseases, diabetes mellitus, and allergic respiratory diseases including both allergic asthma and chronic rhinosinusitis), and several laboratory parameters (white blood cell count-WBC, C-reactive protein-CRP, and serum concentrations of IL-1β, IL-6, IL-8, and IL-10) taken on the day of admission were retrieved from electronic records. Measurement of human serum interleukins was performed by enzyme-linked immunosorbent assays (Thermo Fisher Scientific, Waltham, MA, USA).

Thirty days after the first negative swab all the patients were further contacted and CCS was again administered in order to assess those who recover (CCS = 0) from those who did not. Finally, clinical-laboratory values were compared between those who fully recovered and those who did not in order to identify possible predictors of recovery. Unpaired two-samples Wilcoxon test for continuous variables and Fisher's exact test for discrete variables were used to compare the two groups. P values < 0.05 were regarded as statistically significant. IBM® SPSS® Statistics v. 21 was used to perform the analyses.

3. Results

After the application of the exclusion criteria, we selected 43 (36%) patients who reported OD/GD on admission, 19 (44.2%) males, and 24 (55.8%) females, with a mean age of 57.8 years. The median hospitalization time was 9.5 days. On admission, 33 referred OD and 39 GD (29 patients reported both, 4 only OD and 10 only GD). 12 and 14 of the 33 and 39 patients (36.4% and 35.9% respectively) reported OD/OG as the first symptoms. The mean value of the Smell Complaint Score was 3.72/6 (median 4), the mean value of the Taste Complaint Score was 6.51/10 (median 7), with a mean CCS of 10.23/16 (median 11) on admission. Regarding the specific alterations of taste, 33 patients (86.8%) reported an altered perception of salt, 24 (61.5%) an altered perception of bitter, 23 (59%), and 22 (56.4%) a change in sour and sweet taste, respectively.

Thirty days after the first negative swab, 20/33 (60.6%) patients referred complete recovery from OD and 27/39 (69.2%) full recovery from GD. Overall patients who have not recovered their sense of smell and/or taste were 16 (37.2%), with a mean CCS of 6.7/16: among them, 14 had an improvement in CCS, while none complained of a worsening in OD/GD. In those subjects with residual GD, an altered perception of bitterness was the most reported symptom (53.3%), followed by salt (34.8%), sweet (21.2%), and sour (8.1%). From all the clinical and laboratory parameters analyzed (Tables 1 and 2), a full recovery from GD only was significantly associated with a higher value of serum IL-10 concentration on admission (Table 2, p = 0.041); on the other hand, allergic respiratory disease was more prevalent in the group who did not recover from OD (Table 1, p = 0.049) and GD (Table 2, p = 0.007).

4. Discussion

To the best of our knowledge, this is the first study to analyze the relationship between immunological factors and the recovery of smell and taste after COVID-19. On admission the severity of chemosensory dysfunction was moderate/severe: as a comparison, the mean CCS of 10.2 is very similar to a recent survey using CCS in the population affected by chronic rhinosinusitis with nasal polyps where a mean of 10.4 was reported [8].

Table 1
Olfactory dysfunction (OD), comparison between the two groups in terms of clinical and laboratory features. Values are expressed as a proportion or mean as appropriate.

	Persistent OD (13)	Recovery group (20)	p-value
Clinical Features and Laboratory Parameters			
Age	60.23	59.85	0.944
Sex			
Male	7 (53.8%)	8 (40%)	
Female	6 (46.2%)	12 (60%)	0.435
Smoke	0 (0%)	1 (5%)	0.413
Cardiovascular diseases	6 (46.2%)	8 (40%)	0.727
Diabetes mellitus	2 (15.4%)	3 (15%)	0.976
Allergic Respiratory Disease	6 (46.1%)	3 (15%)	0.049
WBC	5.86	7.09	0.411
LDH (U/L)	380.83	260.24	0.108
CRP (mg/L)	105.67	80.94	0.389
IL-1beta (pg/mL)	0.60	0.52	0.811
IL-6 (pg/mL)	16.83	26.25	0.432
IL-8 (pg/mL)	30.29	58.29	0.222
IL-10 (pg/mL)	14.46	6.60	0.315
COVID-19 related symptoms			
Cough	10 (76.9%)	15 (75%)	0.900
Fever	12 (92.3%)	20 (100%)	0.208
Dyspnea	8 (61.5%)	11 (55%)	0.710
Nasal obstruction	2 (15.4%)	6 (30%)	0.399
Rhinorrhea	3 (23.1%)	4 (20%)	0.833
Asthenia	9 (69.2%)	19 (95%)	0.074
Headache	5 (38.5%)	5 (25%)	0.411
Gastrointestinal disorders	9 (69.2%)	13 (65%)	0.801

Abbreviations: See text for explanation.

Table 2
Gustatory dysfunction (GD), comparison between the two groups in terms of clinical and laboratory features. Values are expressed as a proportion or mean as appropriate.

	Persistent GD (12)	Recovery group (27)	p-value
Clinical Features and Laboratory Parameters			
Age	56.42	57.15	0.900
Sex			
Male	6 (50%)	12 (44.4%)	
Female	6 (50%)	15 (55.6%)	0.748
Smoke	1 (8.3%)	2 (7.4%)	0.920
Cardiovascular diseases	4 (33.3%)	11 (40.7%)	0.661
Diabetes mellitus	2 (16.6%)	2 (7.4%)	0.379
Allergic Respiratory Disease	6 (50%)	3 (11.1%)	0.007
WBC	5.98	5.88	0.914
LDH (U/L)	342.18	286.40	0.204
CRP (mg/L)	79.64	87.17	0.788
IL-1beta (pg/mL)	1.02	0.73	0.559
IL-6 (pg/mL)	40.84	15.49	0.170
IL-8 (pg/mL)	32.87	64.83	0.190
IL-10 (pg/mL)	3.72	16.33	0.041
COVID-19 related symptoms			
Cough	9 (75%)	21 (77.7%)	0.849
Fever	12 (100%)	25 (92.6%)	0.333
Dyspnea	7 (58.3%)	15 (55.5%)	0.872
Nasal obstruction	4 (33.3%)	10 (37%)	0.761
Rhinorrhea	3 (25%)	9 (33.3%)	0.603
Asthenia	8 (66.6%)	25 (92.6%)	0.083
Headache	5 (41.6%)	11 (40.7%)	0.957
Gastrointestinal disorders	9 (75%)	16 (59.3%)	0.344

Abbreviations: See text for explanation.

The recovery rates of smell and taste were slightly higher than those reported by other authors but this is probably due to the longer follow-up time between discharge and revaluation of symptoms [9]. While initial reports had suggested a direct neuroinvasive potential, now OD/GD is being attributed to a generalized inflammatory disruption of the

cytoarchitecture of the nasal mucosa: in particular, SARS-CoV-2 seems to invade the $ACE2^{+}$ $TMPRSS2^{+}$ sustentacular cells that are crucial for signal transduction and neural regeneration after damage [10]. Our results may indirectly support this concept: on the one hand, subjects with allergic conditions are less prone to be infected with SARS-CoV-2, yet the inflammatory remodeling in their airways may hamper successful mucosal healing [11]. On the other hand, the role of IL-10 in this context is intriguing because high levels of this cytokine were reported in severe COVID-19 patients requiring critical care support in what is called the "cytokine storm syndrome" [12]. IL-10 is classically designated as immunosuppressive (it was formerly called "cytokine synthesis inhibitory factor"), and, to this regard, some years ago a very interesting study was conducted on mice that were infected with the J2.2-V-1 variant of a betacoronavirus (murine hepatitis virus) that produces encephalomyelitis [13]. The authors showed that nearly 50% of IL-10–producing cells in the infected brain were actually murine hepatitis virus-specific cytotoxic CD8 T cells; furthermore, the levels of IL-10 were related to the clinical disease in acute encephalomyelitis with the net effect of reducing the immunopathological disease to the neural structures [13].

However, IL-10 under certain clinical conditions that reflect a specific cellular context (*e.g.*, the septic microenvironment) was recently proven to be immune-stimulatory [14,15]. For instance, Mazer and coworkers used blood samples from critically ill septic patients and age-matched healthy controls in order to show a differential action of IL-10: while in the former group the inhibition of this cytokine had a positive effect on the stimulation of both the innate and adaptive responses (by increasing the production of interferon-gamma and tumor necrosis factor-alpha), this was not seen in the control group [15]. In our cohort of mild-moderate patients, outside the setting of the generalized disrupted systemic response during the cytokine storm, we believe that the high production of this molecule should be viewed as a marker of recovery and future prospective studies will eventually solve the issue.

In conclusion, the presence of an elevated serum concentration of IL-10 on admission is associated with the 30-day recovery of gustatory dysfunction while respiratory allergic disease seems to be a risk factor for persistent dysfunction suggesting that immunological parameters are also useful to monitor the course of chemosensory impairments in non-severe COVID-19 patients.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Ethical approval

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.

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CRediT authorship contribution statement

Luca Giovanni Locatello: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Writing - review & editing. **Chiara Bruno:** Conceptualization, Data curation, Formal analysis, Investigation, Resources, Writing - review & editing. **Giandomenico Maggiore:** Conceptualization, Data curation, Formal analysis, Investigation, Resources, Writing - review & editing. **Maria Cilona:** Data curation, Resources. **Pietro Orlando:** Data curation, Resources. **Giuseppe Fancello:** Data curation, Resources. **Matteo Piccica:** Resources, Supervision, Writing - review & editing. **Iacopo Vellere:** Data curation, Supervision. **Filippo Lagi:** Data curation, Supervision. **Michele Trotta:** Data curation, Supervision. **Oreste Gallo:** Conceptualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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