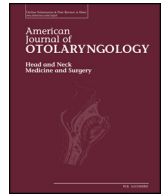




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## Clinical characteristics associated with persistent olfactory and taste alterations in COVID-19: A preliminary report on 121 patients



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#### To the Editor,

many patients infected by the Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) reported olfactory and taste dysfunction [1,2]. Anosmia and hypogeusia were recognized as presenting clinical symptoms of Coronavirus Disease 2019 (COVID-19) [3]. Sungnak et al. [4] investigated the expression of SARS-CoV-2 entry-associated genes in multiple tissues from healthy human donors. They found that these genes were expressed in nasal epithelial cells, highlighting the cells' potential role in initial viral infection. A multicenter European study enrolling 417 mild-to-moderate COVID-19 patients found olfactory/taste alterations in > 80% of cases [5]. The early follow up of these patients (14 days) showed that olfactory dysfunction persisted in 56% of cases [5]. In the present investigation, our primary aim was to evaluate olfactory/taste alterations one month after COVID-19 diagnosis. The secondary aim was to search clinical characteristics associated with the persistence of sensory dysfunctions.

Three international ethics committees (HAP2020-011; CHUSP20032020; EpiCURA-2020-2303) and the Italian committee of Veneto region (protocol n°: 0171064) approved the study protocol. Informed consent was obtained verbally during telephone interviews. Inclusion criteria were: i)  $\geq 18$  years old; ii) laboratory-confirmed COVID-19 infection (reverse transcription polymerase chain reaction on nasopharyngeal swab) at least one month before inclusion; iii) olfactory and/or taste dysfunction. Exclusion criteria: i) patients with olfactory/gustatory alterations before the epidemic; ii) patients who were in the intensive-care unit at the time of the study (due to their health status). Thus, we included mild-to-moderate COVID-19 patients, defined as patients without need of intensive cares.

During the telephonic survey, we used the questionnaire proposed by the COVID-19 Task Force of YO-IFOS<sup>5</sup>. We classified the outcome of olfactory/taste dysfunction as persistence (1) or resolution (0). We used Fisher exact test and Mann-Whitney *U* test as needed. For significant association at Fisher exact test, we calculated odds ratio (OR) and 95% confidence interval (CI). A multivariate logistic regression was calculated, adding only the clinical parameters with a *p* value  $\leq 0.05$ , as disclosed by Fisher exact test at univariate analysis. The results were expressed as ORs, *p* values, and 95% CI. A *p* value < 0.05 was

considered significant.

We included 121 COVID-19 patients with olfactory and/or taste alterations; the mean follow up time from diagnosis was 38.2 days (standard deviation [SD] 3.0 days). Table 1 summarized clinical characteristics and treatments. General symptoms resolved in all but 5 patients (3 had dry cough and 2 fatigue). Persistence of sensory dysfunction was reported by 26 subjects (21.5%). The duration of smell and gustatory symptoms was significantly longer ( $p < 0.00001$ ; Mann-Whitney *U* test) in patients with persistence (mean 39.1 days) when compared with those with resolution (mean 15.6 days). At univariate analysis, patients without fever (OR 6.26; 95% CI = 2.45–15.99;  $p = 0.0001$ ) and with olfactory/taste alterations before general symptoms (OR 3.36; 95% CI = 1.32–8.59;  $p = 0.01$ ) were at higher risk of persistent complaints. Only absence of fever (OR 5.29; 95% CI = 2.02–13.89;  $p = 0.0007$ ) was an independent prognostic factor (olfactory and taste dysfunction before general symptoms; OR 2.38; 95% CI = 0.86–6.58;  $p = 0.09$ ) at multivariate analysis.

Previous studies have already shown the ability of SARS coronavirus to cause neuronal death in mice by invading the brain via the nose close to the olfactory epithelium [1]. We could hypothesize that SARS-CoV-2 has a similar behavior, given the well-known genetic similarity with other coronaviruses [3]. In a recent clinical study, Vaira et al. [6] considering 72 COVID-19 cases, found in 34% a persistence of alterations in taste and olfaction. Also in our series of 121 COVID-19 patients olfactory and taste alterations lasted more than one month in 21.5% of cases. However, most of patients reported resolution of symptoms after a mean of 15 days, and this confirmed the data from previous survey [5]. In the present investigation, absence of fever was an independent prognostic factor of persistent olfactory/taste dysfunction in COVID-19 patients. A survey on 1420 COVID-19 patients found that fever was less frequent in patients with olfactory and taste dysfunctions [7]. Fever was considered a risk factor for severe COVID-19 [3]. Anosmia was recently associated with mild-to-moderate COVID-19 and outpatient care [6,8]. Considering our results and previous evidences, we could hypothesize that patients with olfactory/taste alterations and without associated fever would experience a mild-to-moderate COVID-19, but persistent sensory reduction. Our hypothesis was limited by the absence of severe COVID-19 in our case series.

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**Table 1**

Clinical characteristics and therapy of COVID-19 patients with resolved or persistent olfactory/taste alterations.

	Total	Resolution	Persistence	p value*
N.° of patients	121	95	26	
Female/male	72/49	55/40	17/9	0.65
Mean age	46.7	48.2	46.1	0.9
<b>Symptoms</b>				
Anosmia/Hyposmia	50/64	42/46	8/18	0.37
Ageusia/Hypogeusia	45/71	31/59	14/12	0.11
Nasal Congestion yes/no	19/102	14/81	5/21	0.55
Rhinorrhoea yes/no	27/94	20/75	7/19	0.6
Fever yes/no	89/32	78/17	11/15	0.0002
Cough yes/no	76/45	58/37	18/8	0.5
Fatigue yes/no	83/38	63/32	20/6	0.35
Myalgia yes/no	46/75	32/63	14/12	0.07
<b>Relationship between onset of olfactory/taste dysfunction and general symptoms</b>				
Before/together or after general symptoms	28/93	17/78	11/15	0.01
<b>Associated chronic medical illness</b>				
Allergic rhinitis yes/no	31/90	27/68	4/22	0.21
Hypertension yes/no	15/106	12/83	3/23	1.0
Asthma yes/no	11/110	8/87	3/23	0.7
Diabetes yes/no	3/118	3/92	0/26	1.0
<b>Therapy</b>				
Nasal saline irrigations yes/no	48/73	42/53	6/20	0.07
Nasal steroids yes/no	39/82	29/66	10/16	0.49
Hydroxychloroquine yes/no	7/114	7/88	0/26	0.34

\* Fisher exact test and Mann-Whitney U test as needed; Bold = p value inferior to 0.05.

In conclusion, olfactory and taste dysfunction may be persistent in COVID-19. There is an urgent need for randomized-controlled clinical trials focus on treatment of COVID-19 olfactory and taste alterations.

#### Conflicts of interest and source of funding

This was not an industry-supported study. The authors have no

conflicts of interest to disclose.

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