Virologica Sinica (2020) 35:833–837
https://doi.org/10.1007/s12250-020-00272-9

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LETTER

Patterns of Gustatory Recovery in Patients Affected by the COVID-19 Outbreak

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Received: 28 June 2020 / Accepted: 15 July 2020 / Published online: 3 August 2020

Dear Editor,

Coronavirus disease 2019 (COVID-19) is a viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). From March 2020, several studies indicate that many subjects affected by mild-to-moderate COVID-19 presented olfactory/gustatory dysfunction (OD/GD) that appeared strongly correlated between them but not with the other symptoms suggestive of upper airway infection (Lechien *et al.* 2020a, b; Hopkins *et al.* 2020; Paderno *et al.* 2020).

Isolated OD and GD, without any other general or otolaryngologycal complaints like rhinorrhea or nasal obstruction, were also described as the main or unique symptoms of the infection in a variable percentage of cases; these patients, not initially identified as infected, could have represented a potential way to rapidly spread the infection among the population (Lechien *et al.* 2020b; Vaira *et al.* 2020).

Post-viral gustatory dysfunction is well established, has been shown to be a key symptom of the coronavirus diseases 2019 (COVID-19), with more than 50% European and U.S mild to moderate patients reporting some degree of loss of taste (Hopkins *et al.* 2020; Lechien *et al.* 2020b; Yan *et al.* 2020). We have apparently overcome the worst part of the initial outbreak. However, persistent GD appears to be commonplace and will drive the demand for general practitioner, otolaryngology or neurology consultation in the next months—evidence regarding recovery will be essential in counselling our patients.

In order to evaluate patterns of gustatory recovery, data from patients with confirmed mild COVID-19 were collected prospectively from four university hospitals. Inclusion and exclusion criteria were described in Fig. 1. All patients had at least 30-days of follow-up after their last negative subsequent COVID-19 test. Information was collected using an online questionnaire created with Professional Survey Monkey (San Mateo, California, USA). Informed consent was obtained. Data may be available upon a reasonable request and an approval from the originating university hospitals.

Relevant epidemiological and clinical features contained within the questionnaire were collected by the COVID-19 Study Group of Young Otolaryngologists of the International Federation of Oto-rhino-laryngological Societies (YO-IFOS), and consisted of four subsets (demographic data, medical background, ENT symptoms and olfactory and gustatory dysfunction). All patients completed the Short version of Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS) (Mattos *et al.* 2019). The remaining olfactory and taste questions were based on the smell and taste component of the National Health and Nutrition Examination Survey (Bhattacharyya and Kepnes

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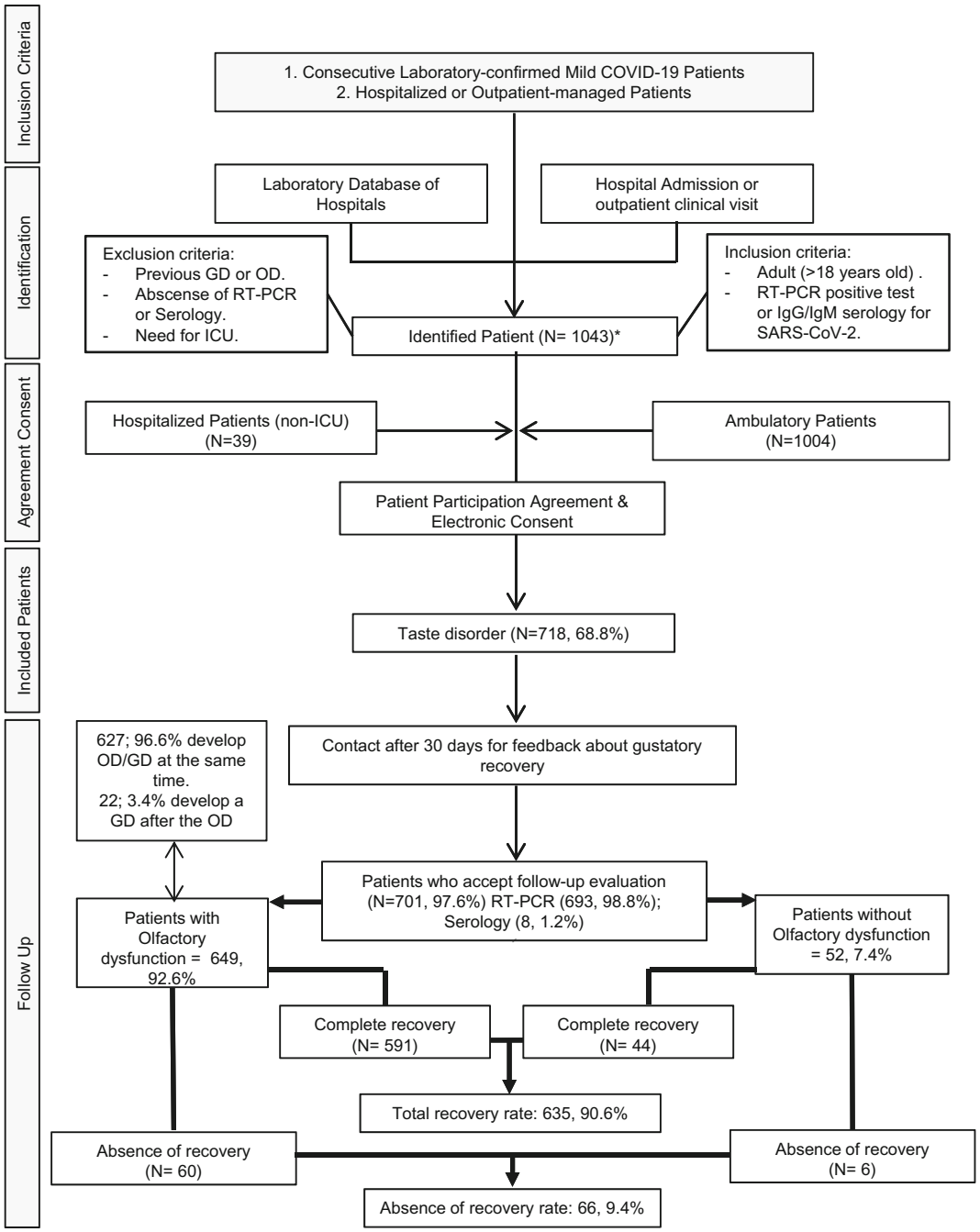

Fig. 1 Gustatory dysfunction flowchart. * Those patients with symptom duration < 14 days were tested with a nasopharyngeal swab; in the case of three negative RT-PCR or patients with symptoms for ≥ 14 days, serology testing was performed.

2015). Physical examination (rhinoscopy, nasal endoscopy or objective olfactory or gustatory testing) was not performed in this study due to the risk of nosocomial infection.

Statistical Package for the Social Sciences for Windows (SPSS version 21,0; IBM Corp, Armonk, NY, USA) was used to perform the statistical analyses. The potential associations between epidemiological, clinical and gustatory outcomes have been assessed through cross-tab generation between two variables (binary or categorical variables) and Chi square test. Incomplete responses were excluded from analysis. A level of $P < 0.05$ was used to determine statistical significance. A multivariate analysis (MA) was performed to address possible confounders. Part of this data was previously published in other papers (Lechien *et al.* 2020a, b, c; Chiesa-Estomba *et al.* 2020).

All told, 1043 patients identified in the emergency room or primary care consultation were invited and agreed to

Table 1 Demographic and clinical data.

Characteristics	All patients = 701	%	*P*	M.A.
Median age (Years)	40 ± 13 (range: 18–78).			
Sex			0.001	0.003
Male	230	32.8		
Female	471	67.2		
Ethnicity			0.791	0.346
European	558	79.6		
Latin-American	136	19.4		
North American	2	0.3		
North-African	2	0.3		
Sub-Saharan African	2	0.3		
Current Smoker	83	11.8	0.334	0.291
History of seasonal allergy	121	17.2	0.276	0.301
Comorbidities				
Diabetes	18	2.6	0.271	0.683
Heart problems	15	2.1	0.555	0.511
COPD	6	0.9	0.767	0.871
Hypertension	47	6.7	0.654	0.391
Asthma	41	5.8	0.433	0.213
Hypothyroidism	44	6.3	0.267	0.379
Autoimmune disease (LES, RA)	27	3.9	0.301	0.411
General symptoms				
Headache	539	72.6	0.001	0.009
Myalgia	494	66.6	0.411	0.395
Cough	373	51	0.062	0.008
Loss of appetite	418	56.6	0.598	0.541
Dyspnea	39	5.8	0.911	0.934
Diarrhea, Abdominal pain	281	39.3	0.466	0.093
Fever (> 38C)	261	36.2	0.051	0.035
Arthralgia	359	49.5	0.467	0.402
Nausea, vomiting	140	19.7	0.541	0.387
Sticky mucus/phlegm	121	17.3	0.219	0.314
Ear, nose and throat Symptoms				
Nasal obstruction	108	15.4	0.413	0.367
Olfactory dysfunction	649	92.6	0.001	0.001
Sore throat	189	26.2	0.404	0.635
Rhinorrhea	79	12.5	0.433	0.391
Postnasal drip	90	13.4	0.212	0.566
Face pain/heaviness	103	16.6	0.133	0.418
Ear pain	30	4.1	0.871	0.793
Dysphagia	64	9.2	0.398	0.501

Abbreviations: MA: multivariate analysis; SEL: systemic lupus; RA: Rheumatoid arthritis.

participate in the study. Among them 718 (68.8%) described a GD. 701 patients completed the study (Fig. 1). The mean age of patients was 40 ± 13 (range: 18–78). There were 471 females and 230 males. Patients were grouped according the presence or absence of olfactory dysfunction. Both groups were comparable according to age, sex ratio, comorbidities and addiction ($P = 0.273$, Wilcoxon). Of those patients who reported GD, there were 649 patients (92.6%) who subjectively report a partial or total loss of smell. By contrast, 52 (7.4%) did not report OD. About general symptoms, headache, cough and fever were the most common in those patients who develop a GD. After a mean follow-up of 63 ± 9 days (range: 60–76) from the first consultation, 66 (9.4%) of patients still reported a

persistent subjective GD and 635 (90.6%) reported complete recovery. There was a statistical correlation between GD and OD ($P = 0.001$). However, no difference in the rate of gustatory recovery according to the presence or absence of olfactory dysfunction was encountered ($P = 0.952$). The mean duration of the GD was 11 ± 5 days (range: 3–36) in those patients who recovered (Fig. 1). There was no significant association between comorbidities and the development or persistence of GD. Other possible confounders rather than OD were identified according to our MA (Table 1).

Taste sense correspond to an integrative experience that involves the correlation of information from oral cavity mucosal surfaces through numerous peripheral cranial nerves and other sensory modalities, such as olfaction and somatosensation (Daly *et al.* 2012). The prevalence of self-reported gustatory dysfunction in our study was similar to those previously reported in COVID-19 patients (Lechien *et al.* 2020a, b; Hopkins *et al.* 2020; Paderno *et al.* 2020; Vaira *et al.* 2020). However, the frequency of residual GD after 60 days of follow-up was significantly low. According to our results and similarly to previous report, GD is related to OD. Despite the rate of recovery was higher in those patients without OD, we were not able to find statistical differences among groups. According to our findings, we consider highlighting the presence of isolated GD in at least 7% of our patients.

At this moment, the molecular mechanisms of GD in COVID-19 patients remain still unclear. Regarding taste, it depends on the activity of specialized epithelial cells and taste cells, which are located mainly in the tongue mucosa. Shigemura *et al.* recently found that renin-angiotensin system (RAS) components as well as angiotensin-converting enzyme- 2 (ACE-2) are expressed in mouse taste organs and are present in the taste buds of fungiform and circumvallate papillae with ENaC (epithelial sodium channel -subunit, a salt taste receptor) or T1R3 (taste receptor type 1 member 3, a sweet taste receptor component). These preliminary results indicate the existence of a local RAS in the taste organ and suggest that taste function may be regulated by both locally-produced and circulating angiotensin II (Shigemura *et al.* 2019).

It is well known that SARS-CoV-2 binds directly to the ACE2 cell receptors to infect humans and it has been reported that ACE2 is the main host cell receptor of SARS-CoV-2, playing a crucial role in the entry of virus inside the cell to cause the final infection (Hoffmann *et al.* 2020). ACE2 receptors were also identified in brain and have been detected over glial cells and neurons (Netland *et al.* 2008). However, more evidence is necessary to elucidate the real mechanism for the GD.

Limitations of this study are the exclusion of patients with severe disease, the small proportion of older patients, the higher proportion of female respondents, loss to follow-up and recruitment from ENT-Clinics, potentially introducing a selection bias. Lack of objective testing to confirm GD is also a limitation. Also, the fact that retro-olfaction is essential for taste. However, at this relatively early point in the pandemic, subjective patterns of recovery of GD in COVID-19 patients are valuable for our patients, hypothesis generation and treatment development.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Animal and Human Rights Statement Four ethics committees approved the current study protocol (HAP2020-011; CHUSP20032020; EpiCURA-2020-2303; CHU-Charleroi:B32522020).

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