Objective Olfactory Findings in Hospitalized Severe COVID-19 Patients.

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To The Editor

Since the onset of the coronavirus disease 2019 (COVID-19) pandemic, many patients reported sudden loss of smell (SLS).*1* However, due to the sanitary situation, only a few studies investigated SLS with objective testings, which remains essential to confirm the olfactory dysfuntion.*2-4* All these studies involved outpatients with mild COVID-19 forms. The mean age and the prevalence of comorbidities were low,*2-4* leading some authors to suspect that SLS could be more specific to mild COVID-19 forms.*5* In this study, we investigated the prevalence of self-reported and objective SLS in severe COVID-19 patients.

Methods:

Adults (33-88 years old) with severe COVID-19 were recruited from the Department of Medicine of the EpiCURA Hospital (Hornu, Belgium; Ethics Committee: EpiCURA-2020-2303). The disease was confirmed through nasopharyngeal swab (RT-PCR). Patients were defined as severe COVID-19 if they required continuous care (oxygenotherapy, blood pressure monitoring) in internal medicine or intensive care units.

Patients with neurological disorder, chronic rhinosinusitis or history of nasal surgery prior the pandemic were excluded. Epidemiological and clinical data were collected at the hospital discharge. Details of the patient-reported outcome questionnaire used for data collection are reported in a previous study.*3* Briefly: 1) olfactory and gustatory questions were based on the smell and taste component of the National Health and Nutrition Examination Survey; 2) symptoms were evaluated through a 4-point scale ranging from 0 (no symptom) to 4 (severe symptoms);*3* 3) nasosinusal symptoms were evaluated through the French sino-nasal outcome test-22 (SNOT-22).*6*Patients benefited from psychophysical olfactory evaluation through sniffin'stick tests (Medisense, Groningen, Netherlands): 16 pens were presented to patients every 30 seconds. The patient had to choose the adequate term describing the smell between 4 given options. The test was scored on a total of 16 points and allowed categorization into in 3 groups: normosmia (score between 12-16), hyposmia (score between 9-11) and anosmia (score <9).*3* Moreover, the following hospitalization outcomes were recorded: duration of hospitalization (days); admission biology (D-dimer; hemoglobin; leucocyte count; lymphocyte count; CRP; creatitin; bilirubin; platelet count; LDH; Na^+; K^+; Cl^-); 1-month serology (IgG) and chest computed tomography findings. Subjective and objective evaluations were made meanwhile.

The relationship between clinical and olfactory outcomes was analyzed through multiple linear regression between scale variables and through Mann-Whitney test and boxplot representation for groups versus scale variables (SPSS, v22,0; IBM-Corp, Armonk, NY, USA).

Results:

Complete evaluation was performed in 47 patients, including 25 females. Patients were hospitalized in EpiCURA hospital from March, 20th, 2020 to April, 16th, 2020. Evaluations were conducted 41.0±10.3 days after the onset of symptoms, corresponding to 1-2 weeks after the end of the hospitalization. Clinical outcomes are reported in Table 1. The most prevalent symptoms were: fever, asthenia and anorexia. The mean duration of symptoms before hospitalization was 10.7±5.0 days. Eight patients were hospitalized in

intensive care unit (ICU) for a mean duration of 8.5±5.6 days. The CT-scan and blood tests features are reported in Table 1.

Psychophysical olfactory evaluations indicated that 4 (8.5%) and 9 (19.1%) patients reported anosmia and hyposmia (in the entire cohort), respectively (Table 2). Note that three hyposmic patients reported in the patient-reported outcome questionnaire that they have hyposmia prior the infection. Excluding these three patients, the prevalence of objective SLS in our cohort was 21.3%.

Eight and 10 patients experienced -subjective- total and partial loss of smell, respectively, over the clinical course of the disease; accounting for 38.3% of individuals. Among them, only 3 and 4 were anosmic and hyposmic (38.9%), respectively. The three patients who experienced hyposmia prior the pandemic were not included in the subjective SLS patients. According to subjective evaluations of olfaction, 38.3% of patients complained from SLS. Additional olfactory outcomes are reported in Table 2.

Patients with diabetes had lower sniffin'sticks test results compared with those without diabetes (Mann Whitney U test; p=0.045). The linear regression analyses revealed significant negative associations between the sniffin'sticks test and age (r_s=-0.339; p=0.032). Symptom duration was significantly correlated with the severity of fever (r_s=0.395; p=0.046) and dysphonia (r_s=0.572; p=0.002). Duration of hospitalization was significantly correlated with age (r_s=0.402; p=0.008). Serum IgG concentration measured by the SARS-CoV-2 LIAISON? test (Diasorin, Centralino, Italy) was negatively correlated with the severity of nasal burning (r_s=-0.407; p=0.029).

Discussion:

Olfactory disorder is undoubtedly a key symptom of mild COVID-19 patients, affecting more than 70% of patients.*4,5* However, its prevalence remains uninvestigated in severe forms of the disease. In this study, we found that 38.3% of patients with severe disease experience SLS. Among them, 38.9% had abnormal objective tests 1-month after the onset of the infection. Irrespective to the method used to evaluate the prevalence of SLS (patient-reported outcome questionnaire*versus* objective tests), these data indicate that SLS could be more prevalent in mild-to-moderate forms of the infection.

According to a previous study conducted in the same population and with the same methods, self-reported SLS concerned more than 70% of mild COVID-19 patients and, among them, 62% had abnormal objective evaluations.*3* The higher incidence of SLS in mild forms of COVID-19 suggests a relative compartmentalization of the disease. Such compartmentalization may involve differences in immune responses to SARS-CoV-2 at the level of nasal and olfactory mucosa. In patients with potent mucosal immune responses, viral replication and dissemination to the lower respiratory tract may be better controlled and this could be at the expense of local inflammation and symptoms involving nasal and bulb regions. In patients with less potent mucosal immune responses, viral replication could spread to the lower respiratory tract and lead to systemic immune response and inflammation. This hypothesis is supported by our observation that nasal burning was inversely correlated with SARS-CoV-2 serum IgG whereas severe forms of the disease have been positively correlated with SARS-CoV-2 IgG responses.*7* Further studies are needed to test this hypothesis. Both age and diabetes could be favoring factors in the development of SLS, which is well known in other olfactory diseases.*8,9*

The main limitations of the present study are the low number of patients and the performance of olfactory tests one month after the onset of symptoms. Performing the tests during hospitalization was difficult due to the sanitary situation, the patient clinical state, and the difficulties to correctly sense the pens with transnasal oxygenation. Although this possibility is not supported by patient-reported symptoms, the delay between the onset of symptoms and the objective olfactory testing may underestimate the incidence of olfactory dysfunction.

Author contribution:

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Acquisition, analysis, or interpretation of data : Lechien, Saussez, Khalife, Place, Ducarme, Machayekhi, de Terwangne.

Drafting of the manuscript: Lechien, Saussez, Journe, Marchant.

Critical revision of the manuscript for important intellectual content: Saussez, Chiesa, Journe, De Riu, Vaira, Marchant.

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Table 1: Epidemiological & Clinical Characteristics of Patients .

Characteristics	Patients (N-%)
Age (Mean - SD) - yo	58.8 ± 12.9
Gender (Female/Male)	25/22
Ethnicity (N - %)	
Caucasian	44 (93.6)
North African	2 (4.3)
Black African	1 (2.1)
Smoker	0 (0)
Patients with seasonal allergy	12 (25.5)
Comorbidities	
Hypertension	10 (21.3)
GERD	9 (19.1)
Hypothyroidism	9 (19.1)

Characteristics	Patients (N-%)
Diabetes	7 (14.9)
Asthma	5 (10.6)
Heart problems	4 (8.5)
Neurological diseases	3 (6.4)
Renal failure	2 (4.2)
Hepatic insufficiency	1 (2.1)
Untreated cancer	1 (2.1)
Depression	1 (2.1)
Autoimmune disease	0 (0)
Respiratory insufficiency	0 (0)
General Symptoms (N - %)	
Asthenia	44 (93.6)
Fever (>38C)	44 (93.6)
Anorexia	44 (93.6)
Dyspnea	41 (87.2)
Cough	38 (80.9)
Myalgia	36 (76.6)
Headache	35 (74.5)
Diarrhea	32 (68.1)
Arthralgia	27 (57.4)
Chest pain	26 (55.3)
Nausea/vomiting	24 (51.1)
Abdominal pain	22 (46.8)
Conjonctivitis	14 (29.8)
Ear, nose and throat Sympotms (N - %)	
Rhinorrhea	33 (70.2)
Nasal obstruction	30 (63.8)
Dysphonia	27 (57.4)
Throat sputum	26 (55.3)
Postnasal drip	25 (53.2)
Sore throat	23 (48.9)
Dysphagia	21 (44.7)
Face pain/heaviness	18 (38.3)
Nose burning	15 (31.9)
Ear pain	14 (29.8)
Presumed hyposmia	10 (21.3)
Presumed anosmia	8 (17.2)
Cacosmia	8 (17.2)
Taste dysfunction	6 (12.8)
Phantosmia	1 (2.1)
Hospitalization Findings	
ICU patients	8 (17.0)
Duration of symptoms before hospitalization (Mean, SD)	10.7±5.0
Hospitalization Duration (Mean, SD - Range, days)	8.7 ± 4.8 (2-21)
Chest CT-scan findings (Lung Involvement)	
10-25%	9 (19.1)
25-50%	23 (48.9)
>50%	6 (12.8)
>75%	1 (2.1)
Missing data	8 (17.0)

Characteristics	Patients (N-%)
Biology Features	
Hemoglobin (g/dL)	14.0 ± 1.6
Neutrophils (10^3/µl)	6.8 ± 3.4
Lymphocytes (10^3/µl)	1.1 ± 0.5
Lymphopenia	34 (72.3)
Normopenia	13 (27.7)
Patelets (10^3/µl)	242.9 ± 113.2
CRP (mg/L)	119.5 ± 110.1
Creatinin (mg/dL)	1.1 ± 0.8
Bilirubin (mg/dL)	0.5 ± 0.3
D-Dimer (µg/L)	1258.0 ± 531.1
LDH (UI/L)	362.4 ± 138.3
Na+ (mmol/L)	136.9 ± 3.6
K+ (mmol/L)	4.1 ± 0.7
Cl- (mmol/L)	97.2 ± 4.1
1-month Mean (SD) IgG level	173.3 ± 80.6

Table 1 footnotes : Abbreviations: CRP= C-reactive Protein; CT=computed tomography; GERD=gastroesophageal reflux disease; SD=standard deviation.

Table 2: Olfactory Outcomes .

Olfactory Outcomes	
Aroma Perception Disorder	*N=12*
Total vs Partial loss of aroma perception sense	1 (2.1)/6 (12.8)
Distortion	5 (10.6)
Olfactory Outcomes	
Variable olfactory dysfunction	8 (44.4)
Nasal Obstruction related Dysfunction	5 (27.8)
Non-variable	3 (16.7)
Did not remember	2 (11.1)
Onset of Smell Dysfunction	*N=18*
Before the other symptoms	1 (5.6)
Concomittant with other symptoms	9 (50.0)
After the other symptoms	8 (44.4)
Did not remember	0 (0)
Sniffin'sticks tests (Mean, SD)	*N=47*
Mean value	12.7 ± 2.8
Anosmic	4 (8.5)
Hyposmic	9 (19.1)
Normosmic	34 (72.3)
SNOT-22 (Mean, SD)	41.1±18.6

Table 2 footnotes : Abbreviations: SD= standard deviation; SNOT-22= sino-nasal outcome-22 questionnaire.