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Original article

Olfactory and gustatory dysfunctions in COVID-19 outpatients: A prospective cohort study

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ABSTRACT

Objectives: To describe the characteristics, evolution and risk factors for long-term persistence of olfactory and gustatory dysfunctions (OGD) in COVID-19 outpatients.
Patients and methods: We conducted a prospective study in SARS-CoV-2 infected outpatients with OGD. Weekly phone interviews were set up starting from COVID-19 onset symptoms and over the course of 60 days, using standardized questionnaires that included a detailed description of general symptoms and OGD. The primary outcome was the proportion of patients with complete recovery of OGD at D30. Rate and time to recovery of OGD, as well as risk factors for late recovery (> 30 days), were evaluated using Cox regression models.
Results: Ninety-eight outpatients were included. The median time to onset of OGD after first COVID-19 symptoms was 2 days (IQR 0–4). The 30-day recovery rate from OGD was 67.5% (95% CI 57.1–75.4) and the estimated median time of OGD recovery was 20 days (95% CI 13–26). Risk factors for late recovery of OGD were a complete loss of smell or taste at diagnosis (HR = 0.26, 95% CI 0.12–0.56, $P = 0.0005$) and age over 40 years (HR = 0.56, 95% CI 0.36–0.89, $P = 0.01$).
Conclusions: COVID-19 patients with complete loss of smell or taste and over age 40 are more likely to develop persistent OGD and should rapidly receive sensorial rehabilitation.

1. Introduction

Olfactory impairment following an upper respiratory tract infection is common and up to 40% of cases of anosmia in adults have been related to post-viral olfactory dysfunction [1]. Acute olfactory and gustatory dysfunctions (OGD) appear to be even more prevalent in mild-to-moderate COVID-19 patients (40 to 80%) [2–5], whereas these symptoms have rarely been reported in hospitalized patients (about 5%) [6].

As some patients experience long-term manifestations of COVID-19 [7] including OGD [8,9], a better knowledge of the temporal dynamics and risk factors potentially associated with persistent symptoms would be useful for more appropriate patient management. Although prospective studies have been conducted, such factors have not yet been reported. However, the monitoring of patients was not sufficiently close and OGDs were at times subject to self-assessùent, which may have been less sensitive than a clinician's evaluation [8,9].

Herein, we conducted the COVID-19 Infection and Related ANOsmia and ageusia (CIRANO) prospective study – with a systematic weekly teleconsultation – in order to describe the characteristics and evolution of OGD over time and to investigate the factors associated with persistent OGD.

2. Material and methods

2.1. Study population

The COVID-PSL study at Pitié-Salpêtrière University Hospital (Paris, France) involved a prospective cohort of 429 adult outpatients with confirmed SARS-CoV-2 infection and mild-to-moderate

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COVID-19. The CIRANO study followed a subsample of the COVID-PSL cohort: all patients experiencing OGD were included from March 20, 2020 until April 20, 2020. SARS-CoV-2 diagnosis was based on specific RT-PCR (cobas 6800, Roche Molecular Systems, Branchburg, NJ) testing of nasopharyngeal swab samples, or on the presence of anti-SARS-CoV2 antibodies (Abbott ARCHITECT SARS-CoV-2 immunoassay, Abbott Diagnostic, Chicago, USA). All patients gave their informed consent to study participation.

2.2. Data collection

Weekly phone interviews were performed from the clinical onset of COVID-19 and during 30 days. In case of persistent OGD beyond day 30, follow-up continued every 2 weeks until day 60. Data were collected through a standardized questionnaire including demographics, onset of COVID-19 symptoms, general symptoms (i.e. general infectious, respiratory and gastrointestinal symptoms), onset of OGD (defined as D0), and characteristics of OGD: anosmia or hyposmia (complete or partial loss of smell), parosmia (distortion of smell), phantosmia (presence of smell in absence of stimulus), ageusia or hypogeusia (complete or partial loss of taste), parageusia (distortion of taste). To prevent any confusion with retronasal olfactory dysfunction, gustatory dysfunction referred strictly to trouble detecting at least one of the four basic tastes (sweet, salty, bitter, and sour). At each teleconsultation, patients were asked whether symptoms were stable, improving, or resolved, and about potential impact on appetite and psychological state.

The main study outcome was the proportion of individuals with OGD recovery at D30. The secondary outcomes were median time to OGD recovery, the proportion of individuals with OGD recovery at D60, and risk factors for persistent OGD after D30.

The evaluated risk factors included age, gender, cycle threshold (Ct) value of SARS-CoV-2 RT-PCR (as a proxy for nasopharyngeal viral load), intensity of OGD (partial or complete loss), and number of olfactory and gustatory symptoms at diagnosis.

2.3. Statistical analysis

Data were summarized using the following descriptive statistics: non-missing sample size, median, and interquartile range (IQR) for continuous variables. The frequency and percentages (based on the non-missing sample size) of observed levels were reported for categorical variables. The rate and time to OGD recovery and analyses of factors associated with OGD recovery were evaluated using Cox regression models, accounting for staggered entries in the study. Models included age ($\leq$ or > 40 years), gender, RT-PCR Ct values, intensity of OGD, and number of olfactory or gustatory symptoms at diagnosis. We also plotted the Kaplan–Meier curves for OGD recovery.

2.4. Ethics

The research was conducted according to the recommendations outlined in the Helsinki declaration. This study was approved by an institutional review board (CPP Ile-de-France X, Paris, France, No. 47-2020).

3. Results

In the COVID-PSL cohort, 300 patients (69.9%) experienced OGD, of whom 98 were enrolled in the CIRANO study. Two patients were lost to follow-up after day 21 and day 30; no participant was hospitalized, required oxygen therapy or died. SARS-CoV-2 diagnosis was based on positive RT-PCR tests ($n = 96$) or positive SARS-CoV-2 antibody tests ($n = 2$).

Table 1
Main characteristics of patients included in the CIRANO study ($n = 98$).

Demographic characteristics	
Age, median, (IQR), years	34.5 (27.9–47.9)
Gender	
Female, No. (%)	74 (75.5)
Male, No. (%)	24 (24.5)
Place of work	
Care facility, No. (%)	94 (95.9)
Other, No. (%)	4 (4.1)
Profession	
Healthcare worker, No. (%)	84 (85.7)
Technical officer, No. (%)	3 (3.1)
Medico-technical assistant, No. (%)	4 (4.1)
Administrative agent, No. (%)	3 (3.1)
Other, No. (%)	4 (4.1)
Olfactory disorders	
Time interval between onset of the first COVID-19 symptoms and olfactory disorders, median, (IQR), days	2 (0–4)
Hyposmia, No. (%)	9/95 (96.9)
Anosmia, No. (%)	86/95 (90.5)
Parosmia, No. (%)	6/95 (6.3)
Phantosmia, No. (%)	15/95 (15.8)
Gustatory disorders	
Delay between onset of the first COVID-19 symptoms and gustatory disorders, median, (IQR), days	3 (0–4)
Hypogeusia, No. (%)	27/67 (40.3)
Ageusia, No. (%)	40/67 (59.7)
Dysgeusia, No. (%)	11/67 (16.4)
Consequences of olfactory and gustatory disorders	
Anorexia, No. (%)	62 (63.3)
Psychological impact, No. (%)	45 (45.9)
Associated symptoms	
No associated symptoms, No. (%)	9 (9.2)
Headache, No. (%)	70 (71.4)
Asthenia, No. (%)	98 (69.4)
Cough, No. (%)	67 (68.4)
Myalgia, No. (%)	55 (56.1)
Fever, No. (%)	52 (53.1)
Rhinorrhea, No. (%)	48 (49.0)
Diarrhea, No. (%)	26 (26.5)
Dyspnea, No. (%)	20 (20.4)
Nausea and/or vomiting, No. (%)	15 (15.3)
Odynophagia, No. (%)	12 (12.2)
Chills, No. (%)	12 (12.2)
Abdominal pain, No. (%)	12 (12.2)

IQR: interquartile range.

All of the descriptive characteristics are reported in Table 1. In short, patients were mainly healthcare workers (86%), particularly nurses. They were primarily females (76%), with a median age of 34.5 years (IQR 27.9–47.9).

Olfactory disorders were reported in 95 patients (97%), whereas gustatory disorders occurred in 67 (68%). The median time to onset of OGD after initial COVID-19 symptoms was 2 (IQR 0–4) and 3 days (IQR 0–4), respectively. OGDs were present at onset of COVID-19 in 30% of patients. Complete loss of smell occurred in 91% of patients with OD, whereas gustatory symptoms appeared less pronounced (complete loss in only 60% of patients with GD). Only 9% of patients had isolated OGD. Apart from OGD and headaches, no other neurological manifestation was reported. Regarding OGD consequences, 63% of patients reported anorexia, and 46% described psychological impact, mostly anxiety.

The median time to complete recovery of OGD was 20 days (95% CI 13–26): 20 days (95% CI 12–25) for OD and 16 days (95% CI 10–24) for GD. At D30, 67.5% of patients (95% CI 56.7–75.6) reported complete resolution of OD and 72.8% (95% CI 60.3–81.3) for GD. At D60, persistent OGDs were present in 17% and 10% of patients, respectively (Fig. 1).

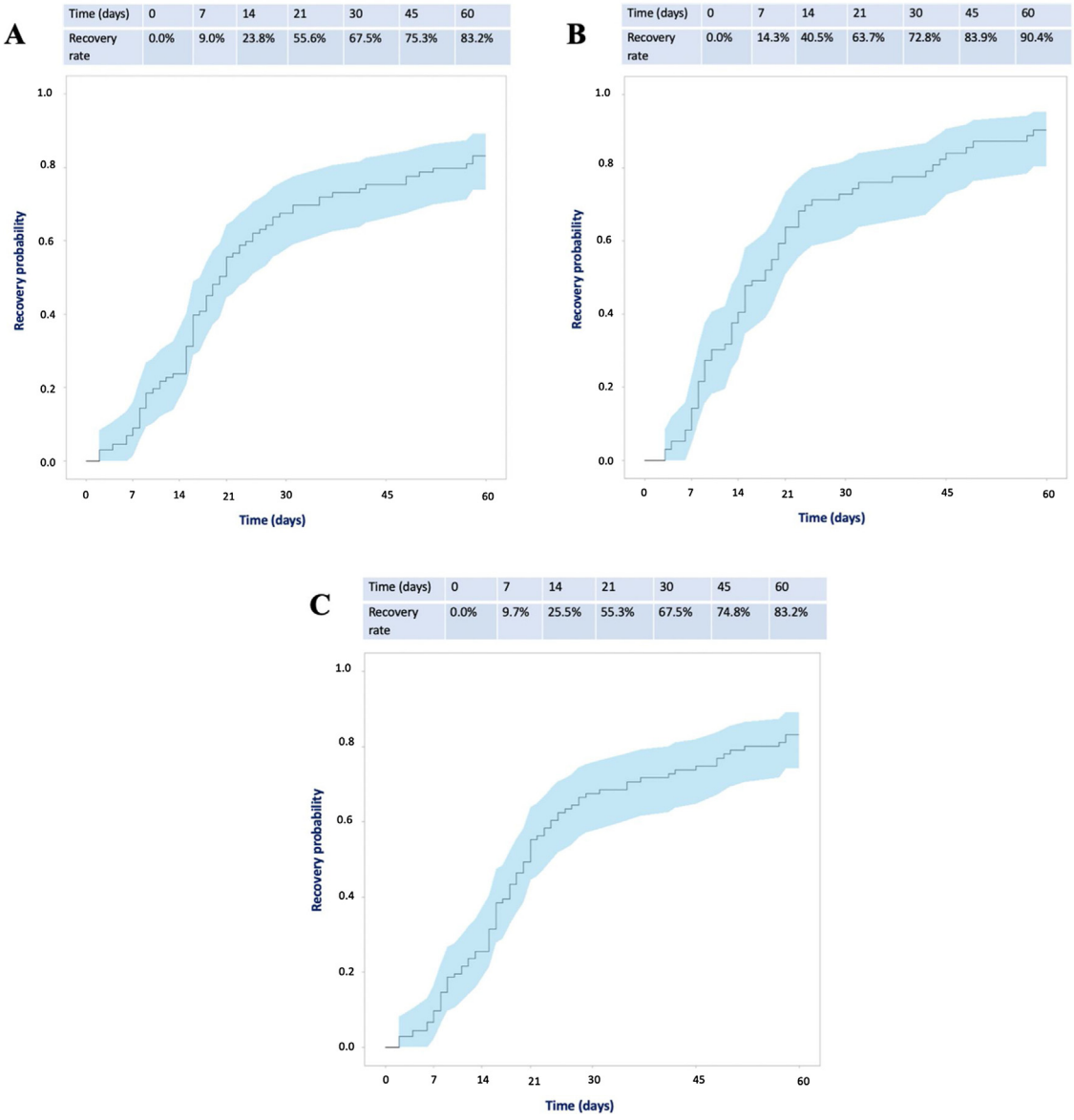

Fig. 1. Evolution and recovery of OGD over time. A. Olfactory dysfunction. B. Gustatory dysfunction. C. Cumulated olfactory and gustatory dysfunctions.

The multivariable analysis highlighted two factors independently associated with the persistence of OGD (Table 2). Patients aged over 40 years (Hazard Ratio [HR] = 0.56, 95% CI 0.36–0.89, $P = 0.01$) and those with a complete loss of smell or taste at diagnosis (HR = 0.26, 95% CI 0.12–0.56, $P = 0.0005$) were more likely to have long-term persistence of symptoms (> 30 days). Gender, Ct value of SARS-CoV-2 PCR and number of OGD symptoms at diagnosis were not associated with the persistence of symptoms.

4. Discussion

Our study highlights the evolution of smell and taste disorders over the course of COVID-19. Olfactory and gustatory symptoms usually appear early – during the first 2–3 days – and last less than 30 days in two-thirds of cases. In addition, GD disappears more rapidly than OD. We also identified predictors of late recovery: complete loss of smell and taste at diagnosis and age over 40 years were associated with longer duration of OGD. To our knowledge, this is the first longitudinal cohort to highlight risk factors for persistent OGD symptoms [8,9].

The pathophysiological mechanisms leading to anosmia in the context of viral infections remain unclear but may be based on the neurotropic characteristics of SARS-CoV-2 [10]. Indeed, SARS-CoV-2 can bind to the angiotensin-converting enzyme 2 (ACE2) receptor and thereby enter human cells such as neurons [11]. In addition, the ability of SARS-CoV-1 (close to SARS-CoV-2) to invade the olfactory bulb, and consequently the central nervous system, have been highlighted in transgenic mice [12]. As a result, anosmia and ageusia in COVID-19 are very likely to be caused by the involvement of the olfactory and gustatory nervous systems [13,14]. Before the COVID-19 pandemic, post-viral anosmia had been investigated for other viruses [15]. In most cases, however, patients had associated congestion and obstruction, which were sufficient to explain the anosmia. In our study, only 49% of patients had symptoms of rhinitis, and direct infection of olfactory receptor neurons caused by SARS-CoV-2 could also be involved [16]. One reported argument against this hypothesis was that OGD recovery necessitated less than a week, whereas the replacement of neurons would take 8 to 10 days, with 5 additional days for cilia maturation [16,17]. However, our study and others highlighted a higher median recovery time than previously reported [8,9]. In our experience, the rapid

Table 2
Risk factors associated with persistent OGD.

	OGD recovery at d30		Univariate analysis		Multivariate analysis	
	No recovery (n = 31)	Recovery (n = 67)	HR (95% CI)	P-value	HR (95% CI)	P-value
Age						
Age, median, IQR, years	42.9 (29.3–48.7)	33.3 (27.1–45.1)	0.98 (0.96–1.00)	0.0916		
Age, classes, No. (%), years						
≤ 40	14 (24.6)	43 (75.4)	1	0.0277	1	0.0133
> 40	17 (41.5)	24 (58.5)	0.60 (0.38–0.95)		0.56 (0.36–0.89)	
Gender						
Male, No. (%)	8 (33.3)	16 (66.7)	1.10 (0.67–1.81)	0.7167		
Female, No. (%)	23 (31.1)	51 (68.9)	1			
Virology						
SARS-CoV-2 RT-PCR, median, Ct[a]	22.0 (20.5–25.1)	22.0 (20.0–27.6)	1.02 (0.97–1.07)	0.4278		
SARS-CoV-2 RT-PCR, Ct[a], classes, No. (%)						
< 22	12 (32.4)	25 (67.6)	1	0.7714		
[22–32]	10 (32.3)	21 (67.7)	0.96 (0.57–1.64)			
> 32	2 (33.3)	4 (66.7)	1.33 (0.55–3.21)			
Severity of OGD at diagnosis						
Partial loss, No. (%)	0 (0.0)	8 (100.0)	1	0.0015	1	0.0005
Total loss, No. (%)	31 (34.4)	59 (65.6)	0.30 (0.14–0.63)		0.26 (0.12–0.56)	
Number of olfactory and gustatory related symptoms[b], median, IQR	2 (1–2)	2 (1–2)	0.95 (0.72–1.26)	0.7157		

HR: hazard ratio; IQR: interquartile range.
[a] Ct were available for 74 patients.
[b] There are five olfactory and gustatory related symptoms: anosmia or hyposmia, parosmia, phantosmia, ageusia or hypogeusia, parageusia.

onset of OGD within two days, as well as the long recovery time would suggest a direct viral mechanism.

Our cohort was primarily composed of young female healthcare workers. During the first wave of COVID-19 in France, healthcare workers – who are known to be predominantly female – had greater access to SARS-CoV-2 PCR. That said, other studies have also reported a predominance of women (from 63 to 77%) experiencing OGD in a COVID-19 context [2,8,18]. Whether genetic differences could be responsible for differing OGD prevalence between women and men remains to be determined. Similarly, as OGD appears to be less frequent in Asian than in European populations, it has been hypothesized that genetic differences in SARS-CoV-2 entry receptors could explain the discrepancy [19].

Our study has several limits. First, because of the lockdown and recommended isolation for COVID-19 patients, we were not able to physically examine patients. However, its bears mentioning that OGDs are subjective symptoms that could to some extent rely on the patient's perception. Since the end of the lockdown, objective measurements using psychophysical olfactory tests have indeed been performed [20]. Second, our data focused only on outpatients with mild-to-moderate disease. Although prevalence of OGD seems lower in hospitalized patients with a more severe disease, our results cannot be extrapolated to them. Therefore, new investigations would be interesting, in particular to analyze the correlation between severity of the disease and duration of symptoms. Third, our patients were monitored for only two months. Extended aftercare could determine whether patients may have permanent aftereffects. Finally, Ct values for SARS-CoV-2 PCR, a proxy for viral quantification, were available for only 74 patients (76%). The statistical power in our study may consequently have been too low to detect any association between Ct values and OGD recovery, as previously described in the literature [21]. Besides, as PCR tests may have been performed a few days after the onset of symptoms, the peak of viral load may have been missed.

Several therapies such as zinc, intranasal corticoid injections and systemic steroids have been used in post-viral OD, but have never proven to be effective [22]. To date, the only approved treatment is daily and long-term olfactory rehabilitation, which could improve the olfactory capacities of patients up to 30% [23]. However, whether olfactory rehabilitation could be effective in COVID-19 patients with anosmia still remains to be demonstrated.

5. Conclusions

In summary, OGD in COVID-19 usually appear in the first days of illness and last less than 30 days. Patients with complete loss of smell or taste and over age 40 are more likely to develop long-term persistent sensory symptoms and should rapidly receive sensorial rehabilitation. Further studies are required to investigate new therapeutic approaches concerning COVID-19-related OGD.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments.

Disclosure of interest

C. Delorme received a research grant from the *Fédération Internationale de l'Automobile* and travel grant from Merz-pharma, Boston Scientific and Medtronic.

The other authors declare that they have no competing interest.

Contribution of authors

L. Cousyn and B. Sellem: conceptualization, methodology, validation, investigation, data curation, writing–original draft, visualization, supervision.

R. Palich, D. Bendetowicz, C. Delorme, R. Tubiana, M-A. Valantin, S. Seang, L. Schneider, A. Fayçal and Y. Dudoit: conceptualization, investigation, writing–review & editing.

R. Agher, A. Ndoadoumgue and L. Assoumou: software, formal analysis, resources, data curation, writing–review & editing.

B. Abdi: resources, writing–review & editing.

C. Katlama: conceptualization, methodology, validation, investigation, writing–original draft, visualization, supervision.

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