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Letter to the Editor

Long-term persistence of olfactory and gustatory disorders in COVID-19 patients

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To the Editor

High rates of taste and smell disorders were observed in patients with confirmed COVID-19 at the acute stage. In one meta-analysis of 15 studies involving 3739 patients, gustatory and olfactory disorder rates were estimated to be 49.1% and 61.3%, respectively [1]. In another meta-analysis of 24 studies with data from 8438 patients, the pooled proportions of those presenting with olfactory and gustatory dysfunction were 41.0% and 38.2%, respectively [2]. In our experience with 3737 COVID-19 patients, 39.2% reported anosmia and 37.8% ageusia [3]. Most studies addressing recovery rates were conducted during the first month after onset of symptoms. In one monocentre study with a 2-month follow-up conducted in 89 French patients with anosmia and or ageusia, 29 (32.6%) still reported these symptoms at day 60, based on questionnaire [4]. In another multicentre study conducted in 117 Italian patients with olfactory and/or gustatory disorders, 14 (12.0%) were still symptomatic at day 60, based on psychophysical tests [5]. In the present study we aimed to assess recovery rates at more than 6 months after onset of symptoms.

Patients who reported anosmia and/or ageusia at the acute phase of a COVID-19 PCR-confirmed episode were retrospectively identified from a cohort of 3737 patients seen at our institute between 3 March and 27 April 2020 [3]. Information about demographics, comorbidities and initial symptoms were retrieved from medical files. All patients were called by telephone between 1 and 3 November 2020 with the aim to evaluate recovery rates of olfactory and gustatory dysfunction using a questionnaire (please [Supplementary material](#)). Patients were asked whether or not they fully recovered their sense of smell or taste and to state the approximate duration of symptoms. Assuming a 50% loss in follow-up, a total of 200 patients were randomly selected to reach a convenience sample of 100 patients for this preliminary study. Data was pseudonymized and statistical analysis was conducted using R (R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2020. URL: <https://www.Rproject.org/>). The chi-squared or the Fisher exact test was used to compare differences between proportions when appropriate. Quantitative data means were compared using Student t-test.

Of 200 patients, 75 (37.5%) were lost in follow-up and 125 (62.5%) answered the questionnaire. Responding patients were relatively young with a low prevalence of comorbidities and presented with non-severe COVID-19 infection ([Table S1](#)). Their characteristics did not significantly differ from those of patients lost in follow-up (data not shown). Most patients presented with both taste and smell disorders. Mean time between symptom onset and follow-up questionnaire was about 7 months. Of the patients, 68.1% recovered their sense of smell and 73.0% their sense of taste during the first 6 weeks following the onset of symptoms ([Fig. 1](#)). Anosmia tended to take more time to resolve than ageusia. Of 125 patients with taste and smell disorders at the acute phase of COVID-19, 30 (24.0%) reported persistent taste and smell disorders 7 months

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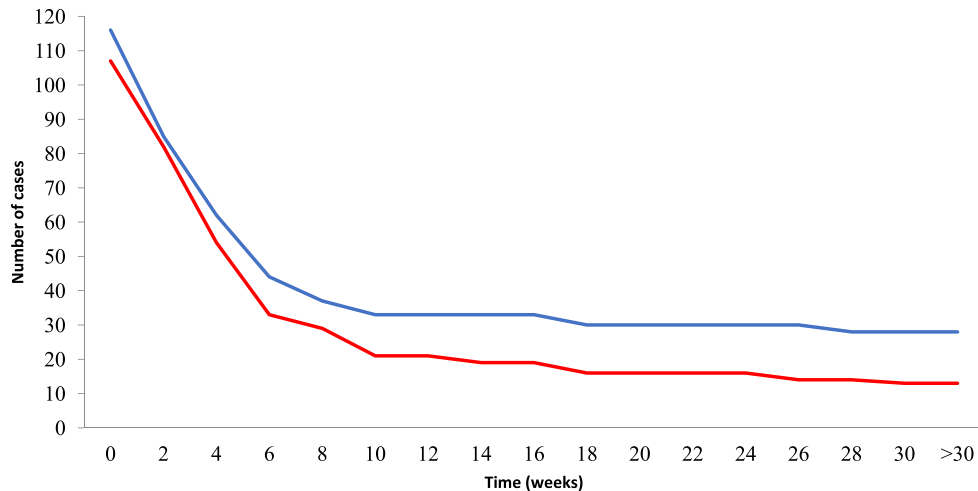


Fig. 1. Number of patients with persistence of anosmia (red curve) and ageusia (blue curve) overtime.

after onset of symptoms. Of them, all reported anosmia at the acute phase and 26 an associated ageusia. Twenty-one of 30 (70.0%) reported partial recovery of olfaction sense and 7/30 (23.3%) no recovery at all, while 10/26 (38.5%) reported partial recovery of gustatory sense and 3/26 (11.5%) no recovery at all. Female patients were more likely to report persistent symptoms than male patients (73.3% versus 26.7%, respectively, p 0.02) (Table S2). Age, comorbidities, time between onset of symptoms and admission, severity of disease at admission and viral load did not significantly associated with persistence of symptoms.

Our study has several limitations including its small sample size and its interview-based design. In one study, about 10% patients self-reporting normal olfactory and gustative function were showed to have chemosensitive disorder on objective testing [5]. In addition, 37.5% of patients were lost in follow-up, and one possible reason is that they have recovered very well without any residual taste and smell problems. Nevertheless in this preliminary study, we identified a high 24% rate of persistence of olfactory or gustatory symptoms in COVID-19 patients more than 7 months after onset of symptoms with 23.3% and 11.5% of patients with persistent symptoms reporting complete anosmia or ageusia. Given the high prevalence of infection in the general population, COVID-19 will result in a large number of patients with long-term morbidity. Further studies based on validated discrimination tests including psychophysical tests or electrophysiological methods should be conducted to better characterize long-term olfactory and gustative disorder in COVID-19 patients. In addition, because hypometabolism of the olfactory/rectal gyrus was associated with persistence of anosmia and ageusia in a preliminary report, exploration of these patients with ^{18}F -FDG brain positron emission tomography should be of great interest [5]. We did not find any predictive factors other than female sex for the persistence of symptoms, in line with results of another study [6].

Transparency declaration

Conflict of Interest Disclosures: None reported. Funding/Support: We had no dedicated support for the research.

Ethics approval

This study was approved by our institutional review board committee (Méditerranée Infection no. 2020-021) and conducted in the context of standard care.

Author contributions

Conceptualization: Philippe Gautret, Didier Raoult; Formal analysis: Van Thuan Hoang; Investigation: Nhu Ngoc Nguyen, Jean Christophe Lagier; Writing: original draft: Philippe Gautret; Writing: review and editing: Nhu Ngoc Nguyen, Van Thuan Hoang, Jean Christophe Lagier, Didier Raoult; Supervision: Philippe Gautret.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2020.12.021>.

References

- [1] Hajikhani B, Calcagno T, Nasiri MJ, Jamshidi P, Dadashi M, Goudarzi M, et al. Olfactory and gustatory dysfunction in COVID-19 patients: a meta-analysis study. *Physiol Rep* 2020;8:e14578.
- [2] Agyeman AA, Chin KL, Landersdorfer CB, Liew D, Ofori-Asenso R. Smell and taste dysfunction in patients with COVID-19: a systematic review and meta-analysis. *Mayo Clin Proc* 2020;95:1621–31.
- [3] Lagier J-C, Million M, Gautret P, Colson P, Cortaredona S, Giraud-Gatineau A, et al. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: a retrospective analysis. *Travel Med Infect Dis* 2020;36:101791.
- [4] Carvalho-Schneider C, Laurent E, Lemaignan A, Beaufils E, Bourbao-Tournois C, Laribi S, et al. Follow-up of adults with non-critical COVID-19 two months after symptom onset. *Clin Microbiol Infect* 2021;27:258–63.
- [5] Guedj E, Million M, Dudouet P, Tissot-Dupont H, Bregeon F, Cammilleri S, et al. ^{18}F -FDG brain PET hypometabolism in post-SARS-CoV-2 infection: Substrate for persistent/delayed disorders? *Eur J Nucl Med Mol Imaging* 2020;30:1–4.
- [6] Vaira LA, Hopkins C, Petrocelli M, Lechien JR, Chiesa-Estomba CM, Salzano G, et al. Smell and taste recovery in coronavirus disease 2019 patients: a 60-day objective and prospective study. *J Laryngol Otol* 2020;134:703–9.