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LETTER TO THE EDITOR

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In response to: Olfactory dysfunction in COVID-19, new insights from a cohort of 353 patients: The ANOSVID study

Dear Editor,

We have read with interest the recent article by Mercier et al.[1] which has the merit of investigating whether there are correlations between the presence of olfactory dysfunction (OD) and epidemiological, clinical, and prognostic parameters in patients affected by coronavirus disease 2019 (COVID-19).

However, in our opinion, the conclusions reached by Mercier et al. should be considered with caution.

First, the authors' correlation analysis is based on self-reported olfactory loss alone. It has been previously demonstrated that this evaluation methodology, compared with psychophysical tests, is a source of important bias as it significantly underestimates the real prevalence and severity of OD.[2,3] Moreover, the retrospective study design, with subjects being questioned on both the severity and duration of OD more than 9 months earlier, is at high risk of recall bias, especially in those subjects who suffered with severe COVID-19 and were more likely tend to neglect or minimize symptoms such as OD. These possible sources of bias become even more important if we want to distinguish subjects with anosmia, hyposmia, and normosmia as patients are unable to provide an objective and standardized categorization of their olfactory function.[2,3]

The authors explore a topic that has been the subject of heated debate in the past such as the prognostic value of OD and, based on the results obtained, seek to draw conclusions about the olfactory loss pathogenesis following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

As the authors summarize, the literature is controversial, but studies that suggest an inverse association between severity of COVID-19 and associated OD are limited by their retrospective nature. Prospective studies have failed to demonstrate such associations.[4,5] The prospective human challenge study highlights that in many cases anosmia resolved within days, and lagged behind other symptoms, likely resolving before recovery from severe COVID-19 in those who were hospitalized.

Interestingly, while acknowledging that the pathogenesis of OD is still controversial, the authors' starting hypothesis is that anosmia and hyposmia may have different pathogenesis. The first could be linked to phenomena of neuroinvasion while the second could have an ENT origin due to nasal inflammation. This hypothesis, although not supported by any previous study, would be then justified by the results noted by the authors. However, the authors' pathogenetic hypothesis does not emerge from the results but represents a fundamental determinant of the methodological setting of the second part of the analysis since, somewhat unusually, subjects with hyposmia are included in the normosmic group and not in that of subjects with OD. The fact that there were no differences depending on which group the hyposmics are assigned to should suggest that there are no pathogenesis differences between anosmia and hyposmia rather than the other way around.

The fascinating pathogenic hypothesis of neuroinvasion has never received stronger confirmations than sporadic radiological reports that detected changes in the size of the olfactory bulb on MRI[6,7] and the evidence that SARS-CoV-2 itself had the ability to pass the blood–brain barrier. Also in the article cited by the authors, which analyzes the biopsy samples of 33 subjects who died from COVID-19, viral RNA was detected in only five subjects (in the olfactory bulb in three cases and in the cerebellum in two cases).[8] Although the role of neuroinvasion should not be completely ruled out,[9] the damage caused by the virus on the inflammatory epithelium is instead well documented by several anatomopathological reports[10,11] and this is currently the most solid pathogenetic hypothesis at the basis of both initial anosmia and hyposmia in COVID-19. This is also supported by the complete regression of anosmia in most cases within a few weeks[12] and the relative infrequency of other neurological symptoms in COVID-19 patients.[13]

Emerging evidence supports downregulation of olfactory receptors and their signaling components as a likely mechanism for persistent OD,[14] and again could cause both hyposmia and anosmia.

In our opinion, the evidence in the literature and the results presented by the authors suggest that anosmia and hyposmia are two sides of the same coin and that the initial severity of OD is due to the extent of damage on the olfactory epithelium rather than to different pathogenetic mechanisms.

AUTHOR CONTRIBUTIONS

Luigi Angelo Vaira: Conception, review of the literature, writing and reviewing the manuscript, and final approval. **Giacomo De Riu**: Writing and reviewing the manuscript, and final approval. **Paolo Boscolo-Rizzo**: Writing and reviewing the manuscript, and final approval. **Claire Hopkins**: Writing and reviewing the manuscript, and final approval. **Jerome R. Lechien**: Conception, review of the literature, writing and reviewing the manuscript, and final approval.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

1. Mercier J, Osman M, Bouiller K, et al. Olfactory dysfunction in COVID-19, new insights from a cohort of 353 patients: the ANOSVID study. J Med Virol. 2022;:. doi:10.1002/jmv.27918
2. Boscolo-Rizzo P, Hummel T, Hopkins C, et al. High prevalence of long-term olfactory, gustatory, and chemesthesis dysfunction in post-COVID-19 patients: a matched case-control study with one-year follow-up using a comprehensive psychophysical evaluation. *Rhinology*. 2021;59:517-527.
3. Hannum ME, Ramirez VA, Lipson SJ, et al. Objective sensory testing methods reveal a higher prevalence of olfactory loss in COVID-19-positive patients compared to subjective methods: a systematic review and meta-analysis. *Chem Senses*. 2020;45:865-74.
4. Vaira LA, Hopkins C, Petrocelli M, et al. Do olfactory and gustatory pshychophysical scores have prognostic value in COVID-19 patients? A prospective study of 106 patients. *J Otolaryngol Head Neck Sur*. 2020;49:56.
5. Killingley B, Mann AJ, Kalinova M, et al. Safety, tolerability and viral kinetics during SARS-CoV-2 human challenge in young adults. *Nat Med*. 2022;28:1031-1041.
6. Kandemirli SG, Altundag A, Yildirim D, Tekcan Sanli DE, Saatci O. Olfactory bulb MRI and paranasal sinus CT findings in persistent COVID-19 anosmia. *Acad Radiol*. 2021;28:28-35.
7. Politi LS, Salsano E, Grimaldi M. Magnetic resonance imaging alteration of the brain in a patient with coronavirus disease 2019 (COVID-19) and anosmia. *JAMA Neurol*. 2020;77:1028-1029.
8. Meinhardt J, Radke J, Dittmayer C, et al. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nat Neurosci*. 2021;24:168-175.
9. de Melo GD, Lazarini F, Levallois S, et al. COVID-19-related anosmia is associated with viral persistence and inflammation in human olfactory epithelium and brain infection in hamsters. *Sci Trasl Med*. 2021;13:eabf8396.
10. Khan M, Yoo SJ, Clijsters M, et al. Visualizing in deceased COVID-19 patients how SARS-CoV-2 attacks the respiratory and olfactory mucosae but spares the olfactory bulb. *Cell*. 2021;184:5932-5949.
11. Vaira LA, Hopkins C, Sandison A, et al. Olfactory epithelium histopathological findings in long-term coronavirus disease 2019 related anosmia. *J Laryngol Otol*. 2020;134:1123-1127.
12. Petrocelli M, Cutrupi S, Salzano G, et al. Six-month smell and taste recovery rates in coronavirus disease 2019 patients: a prospective psychophysical study. *J Laryngol Otol*. 2021;135:436-441.
13. Vaira LA, Lechien JR, Khalife M, et al. Psychophysical evaluation of the olfactory function: European multicenter study on 774 COVID-19 patients. *Pathogens*. 2021;10:62.
14. Zazhytska M, Kodra A, Hoagland DA, et al. Non-cell-autonomous disruption of nuclear architecture as a potential cause of COVID-19-induced anosmia. *Cell*. 2022;185:1052-1064.