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Letter to the Editor

# Anosmia in COVID-19 patients

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*To the Editor:*

Coronaviruses (CoVs)—including SARS-CoV-2, the cause of the current pandemic of coronavirus disease 2019 (COVID-19)—have a propensity for neuroinvasion [1,2]; olfactorial neurons are currently being discussed as a portal of entry for neuroinvasion and the spread of CoVs after infection of neural cells from the CNS to the periphery via a transneural route [1]. A quarter of admitted COVID-19 patients report a disturbance to their sense of smell [3], which may be related to this capability. We hypothesized that loss of smell is often not noted subjectively and that the proportion of affected patients is higher than 25%. Burghart Sniffin' Sticks®, a widely used screening test for smelling disorders, was used according to the manufacturer's specifications in a prospective cross-sectional study to objectify the magnitude of the smelling disorder caused by SARS-CoV-2 [4,5]. The proportion of anosmia in patients with a positive PCR result for SARS-CoV-2 in nasopharyngeal swaps or sputum was compared in those reporting a loss of smell, in those who did not, and in uninfected controls. The study was approved by the university hospital ethical committee (No. 184/20), and written informed consent was obtained from all study participants.

We tested 45 consecutive hospitalized COVID-19 patients and 45 uninfected controls (age (median years ± STD) 56 ± 16.9 and 54 ± 18.3, respectively). Controls consenting to the study were inpatients from non-COVID wards ($n = 17$, 38%), healthcare workers ($n = 21$; 47%) and healthy subjects working in administration ($n = 7$; 16%). All controls were untested for SARS-CoV-2, but none of them or their household members had been diagnosed with COVID-19 and none developed clinical COVID-19 symptoms within the subsequent 3 weeks. They correctly identified a median of 11 out of 12 odours of Sniffin' Sticks, none was anosmic, 12/45 (27%, 95%CI 14–41%, age 63 ± 19.6) were hyposmic, and 33 (73%, 95%CI 58–85%, age 49 ± 10.2) were normosmic. A higher percentage of COVID-19 patients (18/45, 40%) were diagnosed with anosmia ($p < 0.001$); COVID-19 patients smell on average four fewer sticks than uninfected controls (Supplementary Material Fig. S1). The Sniffin' Stick test was more sensitive in detecting anosmia in comparison to self-reporting or taking a medical history: 44% of anosmic and 50% of hyposmic patients did not report having smelling problems (Table 1). The clinical picture, laboratory test results, and outcome at day 15, or by counting the worst outcome during the hospital stay defined by a rating on a 6-point ordinal scale was similar in patients with and without anosmia or hyposmia.

Hyposmia and anosmia are symptoms often noticed by COVID-19 patients [3]. Using a quantitative and objective test, almost half of the patients were found to be anosmic, and another 40% were hyposmic. Still, in our cohort only 49% of patients reported a smelling dysfunction, which is more than in a recently published survey [3], but significantly less than diagnosed by the Sniffin' test. Thus, the magnitude of the olfactory dysfunction in COVID patients is underreported, with more than 80% of COVID-19 patients having hyposmia or anosmia, in comparison to the uninfected controls where no participant was anosmic and 27% were hyposmic. In a large German community sample ($n = 7267$) a similarly low percentage of anosmia (5%) has been reported using the same test; however, the 12-stick test cannot distinguish properly between hyposmia and normosmia [5], and thus the high percentage of 44% of our COVID-19 patients with hyposmia needs to be interpreted carefully. Patients were not tested after having been discharged, but telephone interviews even with patients with mild to moderate COVID-19 showed that not all patients had returned to normal ability to smell 15 days after the start of the first symptoms, although no other symptoms persisted.

Olfactorial neurons are discussed as a portal of entry for neuroinvasion by CoVs, which may be transferred to the central nervous

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**Table 1**
Characteristics and results of COVID-19 patients

| | | All | With anosmia[a] | With hyposmia | With normosmia |
|---|---|---|---|---|---|
| All (n, %, 95%CI) | | 45 | 18 (40%; 25–55%) | 20 (44%, 29–60%) | 7 (15%, 5–25%) |
| Sex (n) | Female | 20 | 8 | 8 | 4 |
| | Male | 25 | 10 | 12 | 3 |
| Age (median ± STD) | Years | 56 ± 16.9 | 56.5 ± 17.9 | 58 ± 17.5 | 49 ± 10.2 |
| Symptoms (n, %) | Temp ≥ 38.5°C | 35 (78%) | 12 (34%) | 16 (46%) | 7 (20%) |
| | Cough | 28 (62%) | 14 (50%) | 10 (36%) | 4 (14%) |
| | Headache | 10 (22%) | 6 (60%) | 4 (40%) | 0 |
| | Shortness of Breath | 20 (44%) | 13 (65%) | 5 (25%) | 2 (10%) |
| Laboratory values (mean ± STD)[b] | Leukocytes (Ths/μL] | 5.6 ± 2.8 | 6.3 ± 3.3 | 5.5 ± 1.9 | 4.3 ± 3.8 |
| | Lymphocytes (Ths/μL) | 1.1 ± 0.7 | 0.8 ± 0.6 | 1.1 ± 0.8 | 1.4 ± 0.8 |
| | CRP (mg/L) | 49 ± 50 | 60 ± 42 | 46 ± 49 | 19 ± 75 |
| | PCT (ng/mL) | 0.12 ± 1.3 | 0.13 ± 0.1 | 0.17 ± 2.0 | 0.1 ± 0.1 |
| | IL6 (pg/mL) | 26 ± 44 | 16 ± 34 | 27 ± 51 | 47 ± 44 |
| | LDH (U/L) | 284 ± 181 | 294 ± 258 | 271 ± 148 | 249 ± 75 |
| Sniffin test (median) | Correctly identified odours[c] | 8 | 3 | 9 | 11 |
| Report of impaired smelling (n, %, 95CI)[d] | yes | 22 (49%) | 10 (45%, 24–68%) | 10 (45%, 24–68%) | 2 (10%, 1–29%) |
| | no | 23 (51%) | 8 (34%, 16–57%) | 10 (43%, 23–65%) | 5 (21%, 7–43%) |
| Time course (days; median ± STD) | First symptom to first positive PCR result | 2 ± 4.2 | 2 ± 4.1 | 1.5 ± 3.7 | 2 ± 4 |
| | First symptom to reported impaired smelling | 5 ± 3.04 | 6.5 ± 3 | 2.5 ± 2.7 | 5.5 ± 2.5 |
| | First symptoms to Sniffin test | 10 ± 5.1 | 11 ± 4 | 8.5 ± 4.5 | 12 ± 7.5 |
| | First positive PCR result to Sniffin test | 4 ± 4.6 | 3.5 ± 3.9 | 4 ± 4.4 | 5 ± 6.3 |

COVID-19 patients diagnosed with Sniffin' sticks as normosmic, hyposmic or anosmic (correctly identifying 11–12, 7–10, and 0–6 odours of Sniffin' sticks, respectively) are shown. STD, standard deviation; 95%CI, 95% confidence interval; PCR, polymerase chain reaction.
[a] $p < 0.001$, $\chi^2$ test with null hypothesis that anosmia in COVID-19 is the same as in controls.
[b] ±2 days from the day of testing, $n = 33–41$.
[c] Linear regression analysis adjusted for age and sex shows that COVID-19 patients on average smell four fewer sticks than uninfected controls.
[d] At the day of testing.

system via a synapse-connected route [2]. Still it is unclear whether olfactory sensory neurons are directly involved in the pathogenesis of smelling loss in COVID-19. Given the large proportion of affected patients, the wide distribution of the angiotensin converting enzyme 2 (ACE2) receptors in the brain, the observation that HCoV are able to induce direct neuronal injury within brainstem cardiorespiratory centres in experimental animal models [2], and the increasing evidence that SARS-CoV 2 is also causing neurological complications, the clinical presentation of COVID-19 patients with deterioration at around 1 week and the acute respiratory failure may be related to the neuroinvasive potential of SARS-CoV-2.

In conclusion, all COVID-19 patients should be interviewed and if possible tested for olfactory disorders that often occur in COVID-19. Some patients have presented solely with this symptom, and primary physicians and otolaryngologist need to be aware of this putative presentation. Our study shows that anosmia and hyposmia often occur unnoticed in COVID-19 patients, and that for those patients an objective and quantifiable test is required. Anosmia is not a predictor of a severe COVID-19 manifestation.

## Authors contribution

Writing – original draft: DW and DH; writing – review and editing: DH, BL, NS, SR, WK, DW; conceptualization: DW; investigation: DH; methodology: BL; formal analysis: BL; resources: NS; funding acquisition: NS; project administration: DW and WK; supervision: WK and DW.

## Transparency declaration

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.05.017.

## References

[1] Bohmwald K, Gálvez NMS, Ríos M, Kalergis AM. Neurologic alterations due to respiratory virus infections. Front Cell Neurosci 2018;12:386. https://doi.org/10.3389/fncel.2018.00386.
[2] Li Y-C, Bai W-Z, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 2020. https://doi.org/10.1002/jmv.25728.
[3] Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa330.
[4] Hummel T, Rosenheim K, Konnerth C-G, Kobal G. Screening of olfactory function with a four-minute odor identification test: reliability, normative data, and investigations in patients with olfactory loss. Ann Otol Rhinol Laryngol 2001;110:976–81. https://doi.org/10.1177/000348940111001015.
[5] Hinz A, Luck T, Riedel-Heller SG, Herzberg PY, Rolffs C, Wirkner K, et al. Olfactory dysfunction: properties of the Sniffin' Sticks Screening 12 test and associations with quality of life. Eur Arch Oto-Rhino-Laryngol 2019;276:389–95. https://doi.org/10.1007/s00405-018-5210-2.