Olfactory and Gustatory Dysfunction in Coronavirus Disease 2019 (COVID-19)

Jan C. Luers,1 Alexander C. Rokohl,2 Niklas Loreck,2 Philomena A. Wawer Matos,2 Max Augustin,3,4,5 Felix Dewald,6 Florian Klein,6 Clara Lehmann,3,4,5 and Ludwig M. Heindl2

1Department of Otorhinolaryngology, University of Cologne, Faculty of Medicine and University Hospital of Cologne, Cologne, Germany, Department of Ophthalmology, University of Cologne, Faculty of Medicine and University Hospital of Cologne, Cologne, Germany, 2Department of Internal Medicine, Division of Infectious Diseases, University of Cologne, Cologne, Germany, 3Department of Otorhinolaryngology, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany, and 4Laboratory of Experimental Immunology, Institute of Virology, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly worldwide. Given scarce resources, nonlaboratory diagnostics are crucial. In this cross-sectional study, two-thirds of European patients with confirmed COVID-19 reported olfactory and gustatory dysfunction, indicating the significance of these symptoms in early diagnostics.

Keywords. Coronavirus; COVID-19; Olfaction; Sense of taste; Nasal symptoms.

METHODS

This study was conducted by the University Hospital of Cologne, Cologne, Germany, in adherence to the tenets of the Declaration of Helsinki and its later amendments. Outpatients who had COVID-19 confirmed via polymerase chain reaction (PCR) in a deep throat-swab between 22 and 28 March 2020 were retrospectively identified by the records of the University Hospital of Cologne, Cologne, Germany. In addition to COVID-19 confirmed by PCR in a deep throat-swab (which is the institutional screening standard for a diagnosis of SARS-CoV-2), the inclusion criteria were age ≥18 years and adequate command of the German language. The exclusion criteria were hospitalization in the past or at the current time point caused by COVID-19 or at the current time point due to other reasons. All included patients were interviewed using a standardized 2-section questionnaire. Section 1 requested demographic data and general information, including the date of a positive PCR-confirmed test and dates of contact with confirmed COVID-19 patients. Section 2 assessed the detailed history of symptoms potentially associated with COVID-19. First of all, patients were asked for the onset of fever, cough, sore throat, rhinitis, muscle aches, headache, diarrhea, reduced olfaction, and a reduced sense of taste during COVID-19. If present, the date of the beginning of each symptom was recorded. Furthermore, a total nasal symptom score (TNSS) was evaluated as the sum of scores for nasal congestion, sneezing, nasal itching, and rhinorrhea during COVID-19 using a 4-point scale (0–3) [7]. A score of 0 indicated no symptoms, 1 documented mild symptoms that were easily tolerated, 2 described the awareness of symptoms that were bothersome but tolerable, and 3 matched severe symptoms that were hard to tolerate and interfered with daily activities or sleep. The TNSS was then calculated by adding the score for each of the symptoms for a total score between 0–12.

All statistical analyses were performed using commercial software (SPSS Version 26.0 for Windows, SPSS, Inc., Chicago, IL). To investigate the factors related to reduced olfaction and a reduced sense of taste, 2 general linear models were used with explanatory variables of age, gender, TNSS, fever, cough, sore throat, rhinitis, and headache. Furthermore, the associations between reduced olfaction and the sense of taste were investigated. The threshold for statistical significance was set at P < .05.

RESULTS

There were 72 patients with PCR-confirmed COVID-19 who agreed to participate and were enrolled in this study. No patients declined. Out of these 72 participants, 41 were males and 31 females, with a mean age of 38 ± 13 years (range, 21–87 years;
Of the 72 included patients, 44 (61%) had known contact with individuals with confirmed COVID-19. The mean potential incubation time of these 44 patients was 3 ± 2 days. Patients were interviewed 13 ± 3 days (range, 6–22 days) after the first symptom occurred and 7 ± 1 days (range, 3–9 days) after a positive COVID-19 test. The most common general symptoms included headache (78%), cough (75%), and muscle aches (71%), while diarrhea was relatively rare (31%; Table 1).

Reduced olfaction occurred in 53 COVID-19 patients (74%), while a reduced sense of taste was present in 50 COVID-19 patients (69%). There were 49 patients (68%) who reported both symptoms, while 1 patient (1%) had only a reduced sense of taste and 4 patients (6%) only reported reduced olfaction. Both symptoms occurred, on average, at the fourth day after the first symptoms had been noted. However, 9 patients (13%) noticed that reduced olfaction and a reduced sense of taste occurred together on the first day they realized any symptoms. A single patient had a reduced sense of taste alone on the first day he realized any symptoms. Nasal symptoms, the mean TNSS was 2.71 ± 2.50 (range, 0–9; Table 2). While a lot of patients had nasal congestion (54%), nasal sneezing (50%), and rhinorrhea (53%), nasal itching was rare (11%). None of the included participants reported any new medical treatment potentially influencing the sense of smell and taste.

Table 1. Demographics and Symptoms of 72 Patients With Confirmed Coronavirus Disease 2019

| Demographics and Symptoms | Gender       | Male, n (%) 41 (56.9 %) | Female, n (%) 31 (43.1 %) |
|---------------------------|--------------|--------------------------|---------------------------|
| Age, years                | Male, mean ± SD (range) 40.74 ± 14.21 (24–72) | Female, mean ± SD (range) 35.87 ± 12.60 (21–87) |
| Duration since first symptom occurred, days, mean ± SD (range) | 3.11 ± 2.03 (0–8) |
| Duration since positive PCR-confirmed test, days, mean ± SD (range) | 6.92 ± 1.44 (3–9) |
| Fever                     | n (%) 36 (50.0%) |
| Duration of occurrence since first symptom, days, mean ± SD (range) | .94 ± 1.79 (0–7) |
| Cough                      | n (%) 54 (75.0%) |
| Duration of occurrence since first symptom, days, mean ± SD (range) | 1.74 ± 2.81 (0–13) |
| Sore throat                | n (%) 45 (62.5%) |
| Duration of occurrence since first symptom, days, mean ± SD (range) | 1.51 ± 2.46 (0–11) |
| Rhinitis                   | n (%) 40 (55.6%) |
| Duration of occurrence since first symptom, days, mean ± SD (range) | 2.10 ± 2.31 (0–8) |
| Muscle aches               | n (%) 51 (70.8%) |
| Duration of occurrence since first symptom, days, mean ± SD (range) | 1.29 ± 1.97 (0–8) |
| Headache                   | n (%) 56 (77.8%) |
| Duration of occurrence since first symptom, days, mean ± SD (range) | 1.48 ± 2.69 (0–14) |
| Diarrhea                   | n (%) 22 (30.6%) |
| Duration of occurrence since first symptom, days, mean ± SD (range) | 6.09 ± 6.73 (0–32) |
| Reduced olfaction          | n (%) 53 (73.6%) |
| Duration of occurrence since first symptom, days, mean ± SD (range) | 3.66 ± 3.07 (0–12) |
| Reduced sense of taste     | n (%) 50 (69.4%) |
| Duration of occurrence since first symptom, days, mean ± SD (range) | 3.38 ± 3.06 (0–12) |

Abbreviations: PCR, polymerase chain reaction; SD, standard deviation.

Table 2. Graded Nasal Symptoms of 72 Patients With Confirmed Coronavirus Disease 2019

| Graded Nasal Symptoms                  | Mean ± SD (Range) |
|---------------------------------------|-------------------|
| Nasal congestion                      | 1.15 ± 1.18 (0–3) |
| None, n (%)                           | 33 (45.8)         |
| Mild, n (%)                           | 7 (9.7)           |
| Moderate, n (%)                       | 20 (27.8)         |
| Severe, n (%)                         | 12 (16.7)         |
| Nasal sneezing                        | .67 ± .78 (0–3)   |
| None, n (%)                           | 36 (50.0)         |
| Mild, n (%)                           | 26 (36.1)         |
| Moderate, n (%)                       | 8 (11.1)          |
| Severe, n (%)                         | 2 (2.8%)          |
| Nasal itching                         | .13 ± .37 (0–2)   |
| None, n (%)                           | 64 (88.9)         |
| Mild, n (%)                           | 7 (9.7)           |
| Moderate, n (%)                       | 1 (1.4)           |
| Severe, n (%)                         | 0 (0)             |
| Rhinorrhea                             | .76 ± .88 (0–3)   |
| None, n (%)                           | 34 (47.2)         |
| Mild, n (%)                           | 25 (34.7)         |
| Moderate, n (%)                       | 9 (12.5)          |
| Severe, n (%)                         | 4 (5.6)           |
| Total nasal symptom score             | 2.71 ± 2.50 (0–9) |

Abbreviation: SD, standard deviation.
DISCUSSION

Our study shows for the first time that both olfactory and gustatory dysfunction are very common in COVID-19 patients, with olfactory dysfunction even leveling the symptom of “cough” at >70%. We also demonstrate that rhinitis and many of its associated symptoms (nasal congestions, sneezing, and rhinorrhea) regularly occur in these patients, which has not been reported before. Others have regarded olfactory dysfunction as a stand-alone nasal symptom in COVID-19 patients [7]. Surprisingly, in participants of our study rhinitis was not associated with reduced olfaction. Future studies must show whether there is really no pathophysiological link between the 2, but just coexistence. In addition, patients were not tested for other respiratory tract pathogens and, therefore, other infections were not excluded. This fact and the missing matched control group are significant limitations of this study and have to be evaluated in further studies. According to the results of the TNSS, the measured nasal symptoms (not the olfactory dysfunction) are mostly mild in nature and not particularly bothersome to these patients. Both olfactory and gustatory dysfunctions seem to develop in the early to mid-phase (average fourth day after the onset of symptoms) of the disease. There was only 1 participant of our study showing olfactory/gustatory dysfunctions as the first symptoms, but we would still regard them as possible early-warning symptoms, especially if they occur without rhinitis. Whether or not gustatory problems in COVID-19 patients really target the sense of taste is unclear. The gustatory system (transmitted via the glossopharyngeal, facial, and vagal nerve) only recognizes the basic tastes (sweet, sour, salty, bitter, and umami [glutamate]), but most of the culinary experiences are recognized by the olfactory nerve. The fact that 1 of our patients experienced gustatory dysfunction alone with no smelling problems indicates that more than 1 pathophysiological pathway might exist.

Many viruses affecting the upper aerodigestive tract (eg, rhinovirus, parainfluenza, Epstein-Barr virus, and some coronaviruses) can lead to olfactory dysfunction, mostly through an inflammatory reaction of the nasal mucosa. The pathophysiology through which SARS-CoV-2 affects the olfactory system is unclear. A key receptor for the entry of SARS-CoV-2 into the host cells is angiotensin-convertase enzyme 2 (ACE2) [8]. This receptor is expressed in multiple organs (heart, lungs, kidney, intestines, buccal cavity, brain, etc). A recent preprint study from India reported that inside the olfactory mucosa, the expression of ACE2 is restricted to a subset of sustentacular and horizontal basal cells and not the olfactory sensory neurons [8]. Thus, sustentacular and horizontal basal cells are thought to be highly susceptible to viral entry. Nonetheless, although these cells play a role in the maintenance of the olfactory organ (ie, metabolic and physical support to the olfactory mucosa, as well as regeneration), they are not sensory in function. Still, little is known about which cells of the olfactory mucosa are affected by SARS-CoV-2 and whether the virus can directly attack sensory cells or the olfactory bulb. Detailed clinical evaluations and functional tests regarding olfactory and gustatory dysfunctions, including exact grading and duration of the complaints, are now a high priority.

Notes

Author contributions. J. C. L. and A. C. R. contributed equally to this work and both should be considered as first authors. C. I. and L. M. H. contributed equally to this work and both should be considered as senior authors. All authors have control of all primary data and they agree to allow to review the data upon request.

Disclaimer. All procedures performed in this were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Formal approval to conduct this study was obtained from the Ethics Committee of the University of Cologne (No. 20–1161). Informed consent was obtained from all study participants.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Zhou M, Zhang X, Qu J. Coronavirus disease 2019 (COVID-19): a clinical update. Front Med 2020; 14:136–135. doi:10.1007/s11684-020-0767-8.
2. Luers JC, Klussmann JP, Guntinas-Lichius O. The COVID-19 pandemic and otolaryngology: what it comes down to? Laryngorhinootologie 2020; 99:287–291. doi:10.1055/a-1095-2344.
3. Giacomelli A, Pezzi L, Conti F, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis 2020; 71:889–890.
4. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382:1708–1720. doi:10.1056/NEJMo2002032.
5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395:497–506.
6. Mao L, Wang M, Chen S, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. medRxiv 2020; 77:1–9. doi:10.1101/2020.02.22.20026500.
7. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild to moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020; 277:2251–2261.
8. Gupta K, Mohanty SK, Kalra S, et al. The molecular basis of loss of smell in 2019-nCoV infected individuals. OSF Prepr 2020. doi:10.31219/osf.io/cm6sp.