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

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Abstract

Coronavirus-disease-2019 (COVID-19) caused by the severe-acute-respiratory-syndrome-coronavirus-2 (SARS-CoV-2) shows a rapid spread over-the-world. Given scarce resources, non-laboratory diagnostics is crucial. In this cross-sectional study, two-thirds of European patients with polymerase chain reaction confirmed COVID-19 reported olfactory and gustatory dysfunction, indicating the significance of this history in the early diagnostics.

Keywords:

Coronavirus – COVID-19 – Olfaction – Sense of taste – Nasal symptoms

The rapid spread of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) urges clinicians and researchers to analyze the virus, characterize the disease, and find suitable treatment strategies. Currently, fever, (dry) cough and fatigue are regarded as the main and most common symptoms in the early disease stage of COVID-19.[1] Especially with the transfer of the pandemic to Europe, olfactory dysfunction has emerged as a new symptom of COVID-19.[2,3] Interestingly, this symptom was not reported by most of the early studies from China[4,5] and still seems rather uncommon in Chinese COVID-19 patients,[1] accounting for only up to 5% of the patients.[6]

Herein, we show for the first time the high prevalence of reduced olfaction and decreased sense of taste in European COVID-19 patients.

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 polymerase chain reaction (PCR) confirmed COVID-19 in a deep throat-swab between 22th and 28th March 2020 were retrospectively identified by the records of the University Hospital of Cologne, Cologne, Germany. Beside a COVID-19 confirmed by polymerase chain reaction (PCR) in a deep throat-swab (which is the institutional screening standard for diagnosis of SARS-CoV-2), inclusion criteria were age ≥ 18 years and adequate command of the German language. 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 asked using a standardized two-section questionnaire. Section 1 requested demographic data and general information, including the date of positive PCR confirmed test and date of contact to 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 yes, date of the beginning of each symptom was recorded. Furthermore, Total Nasal Symptom Score (TNSS) was evaluated as the sum of scores for each of nasal congestion, sneezing,

nasal itching, and rhinorrhea during COVID-19 using a four-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 which were bothersome but tolerable, and 3 matched severe symptoms that were hard to tolerate and interfered with daily activities or sleep. TNSS was then calculated by adding the score for each of the symptoms to 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 factors related to reduced olfaction as well as to a reduced sense of taste two general linear models were used with explanatory variables of age, gender, TNSS, fever, cough, sore throat, rhinitis, and headache, respectively. Furthermore, the associations between reduced olfaction and the sense of taste were investigated. The threshold for statistical significance was set at $p < 0.05$.

Results

72 patients with polymerase chain reaction confirmed COVID-19 agreed to participate and were enrolled in this study. None declined. Out of these 72 participants, 41 were males and 31 females with a mean age of 38 ± 13 years (range, 21 – 87 years; Table 1). 44 of the 72 included patients (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 asked 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 reduced a sense of taste was present in 50 COVID-19 patients (69%). 49 patients (68%) reported both symptoms, while one patient (1%) had only reduced sense of taste and four patients (6%) only reduced olfaction. Both symptoms occurred on average at the fourth day after the first symptoms had been noted. However, nine patients (13%) noticed that reduced olfaction and loss of sense occurred together on the first day they realized any symptoms. One patient had reduced sense of taste alone at the first day he realized any symptoms. Regarding nasal symptoms, 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 new medical treatment potentially influencing the sense of smell and taste.

The regression model for reduced olfaction was not significant (ANOVA: = 0.610) while the model for reduced sense of taste was highly significant (ANOVA: < 0.001). None of the investigated demographic factors including age and gender were associated with reduced olfaction or reduced sense of taste ($p \geq 0.05$, respectively). In addition, fever, cough, sore throat, rhinitis, headache, and TNSS were also not associated with reduced olfaction or reduced sense of taste ($p \geq 0.05$, respectively). However, there was significance between the presence of reduced olfaction and a reduced sense of taste ($p < 0.001$).

Discussion

Our study shows for the first time that both olfactory and gustatory dysfunction is very common in COVID-19 patients, with olfactory dysfunction even leveling the symptom 'cough' at > 70%. We also demonstrate that rhinitis and many of its associated symptoms (nasal congestions, sneezing, and rhinorrhea) regularly occur in these patients, a finding that has not been reported before. Others often see 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 two but just a co-existence. 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 dysfunction seem to develop in the early to mid-phase (average 4th day after the onset of symptoms) of the disease. There was only one participant of our study showing olfactory/gustatory dysfunction as the first symptom at all, but we would still regard it as a possible early-warning symptom, especially if it comes along 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 one of our patients experienced gustatory dysfunction alone with no smelling problems, indicates that more than one pathophysiological pathway might exist.

Many viruses affecting the upper aerodigestive tract (e.g. rhinovirus, parainfluenza Epstein-Barr virus, and some coronavirus) 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-Converting-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 (i.e., 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 directly. Detailed clinical evaluation and functional tests regarding olfactory and gustatory dysfunctions including exact grading and duration of the complaints are now a high priority.

Notes:

Acknowledgment:

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.

Conflict of Interest:

None of the authors has a conflict of interest. All authors have no financial or proprietary interest in any material or method mentioned in the manuscript. All authors have control of all primary data and they agree to allow to review the data upon request.

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Table 1: Demographics and Symptoms of 72 Patients with Confirmed COVID-19

Gender	
Male, *n (%)*	41 (56.9 %)
Female, *n (%)*	31 (43.1 %)
Age (years)	
Male, *mean ± SD (range)*	40.74 ± 14.21 (range, 24 - 72)
Female, *mean ± SD (range)*	35.87 ± 12.60 (range, 21 - 87)
Potential incubation period (days), *mean ± SD (range)*	3.11 ± 2.03 (range, 0 - 8)
Duration since first symptom occurred (days), *mean ± SD (range)*	13.38 ± 3.20 (range, 6 - 22)
Duration since positive PCR confirmed test (days), *mean ± SD (range)*	6.92 ± 1.44 (range, 3 - 9)
Fever	
n (%)	36 (50.0%)
Duration of occurrence since first symptom (days), *mean ± SD (range)*	0.94 ± 1.79 (range, 0 - 7)
Cough	
n (%)	54 (75.0%)
Duration of occurrence since first symptom (days), *mean ± SD (range)*	1.74 ± 2.81 (range, 0 - 13)
Sore Throat	
n (%)	45 (62.5%)
Duration of occurrence since first symptom (days), *mean ± SD (range)*	1.51 ± 2.46 (range, 0 - 11)
Rhinitis	
n (%)	40 (55.6%)
Duration of occurrence since first symptom (days), *mean ± SD (range)*	2.10 ± 2.31 (range, 0 - 8)
Muscle aches	
n (%)	51 (70.8%)
Duration of occurrence since first symptom (days), *mean ± SD (range)*	1.29 ± 1.97 (range, 0 - 8)
Headache	
n (%)	56 (77.8%)
Duration of occurrence since first symptom (days), *mean ± SD (range)*	1.48 ± 2.69 (range, 0 - 14)
Diarrhea	
n (%)	22 (30.6%)
Duration of occurrence since first symptom (days), *mean ± SD (range)*	6.09 ± 6.73 (range, 0 - 32)
Reduced olfaction	
n (%)	53 (73.6%)
Duration of occurrence since first symptom (days), *mean ± SD (range)*	3.56 ± 3.07 (range, 0 - 12)
Reduced sense of taste	
n (%)	50 (69.4%)
Duration of occurrence since first symptom (days), *mean ± SD (range)*	3.38 ± 3.06 (range, 0 - 12)

Table 2: Graded Nasal Symptoms of 72 Patients with confirmed COVID-19

Graded Nasal Symptoms	
Nasal congestion, *mean ± SD (range)*	1.15 ± 1.18 (range, 0 - 3)
None, *n (%)*	33 (45.8%)
Mild, *n (%)*	7 (9.7%)
Moderate, *n (%)*	20 (27.8%)
Severe, *n (%)*	12 (16.7%)
Nasal Sneezing, *mean ± SD (range)*	0.67 ± 0.78 (range, 0 - 3)
None, *n (%)*	36 (50.0%)
Mild, *n (%)*	26 (36.1%)
Moderate, *n (%)*	8 (11.1(%)
Severe, *n (%)*	2 (2.8%)
Nasal Itching, *mean ± SD (range)*	0.13 ± 0.37 (range, 0 - 2)
None, *n (%)*	64 (88.9%)
Mild, *n (%)*	7 (9.7%)
Moderate, *n (%)*	1 (1.4%)
Severe, *n (%)*	0 (0.0%)
Rhinorrhea, *mean ± SD (range)*	0.76 ± 0.88 (range, 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, *mean ± SD (range)*	2.71 ± 2.50 (range, 0 - 9)