

Prevalence of Taste and Smell Dysfunction in Coronavirus Disease 2019

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IMPORTANCE Early diagnosis of coronavirus disease 2019 (COVID-19) may help control the diffusion of the disease into the population.

OBJECTIVE To investigate the presence of sinonasal manifestations at the onset of COVID-19 to achieve an earlier diagnosis.

DESIGN, SETTING, AND PARTICIPANTS This retrospective telephone survey study investigated patients diagnosed with COVID-19 from March 5 to March 23, 2020, who were hospitalized or discharged from a single referral center. Patients who were unable to answer (intubated, receiving noninvasive ventilation, or deceased) or unreachable by telephone were excluded. Of 359 consecutive patients, 204 fulfilled the inclusion criteria; 76 were unable to answer, 76 were unreachable by telephone, and 3 refused.

EXPOSURES Sinonasal manifestations reported before COVID-19 diagnosis were studied with a validated questionnaire: Italian Sino-Nasal Outcome Test 22 (I-SNOT-22). If reduction of taste and/or smell was documented by item 5 of the I-SNOT-22, further inquiries were made to score them separately on a scale from 0 to 5, with 0 indicating no problem and 5 indicating problem as bad as it can be.

MAIN OUTCOMES AND MEASURES The prevalence of sinonasal manifestations preceding COVID-19 diagnosis.

RESULTS Among the 204 patients enrolled (110 [53.9%] male; mean [SD] age, 52.6 [14.4] years), the median I-SNOT-22 total score was 21 (range, 0-73). I-SNOT-22 identified 116 patients (56.9%) with reduction of taste and/or smell, 113 (55.4%) with taste reduction (median score, 5; range, 2-5), and 85 (41.7%) with smell reduction (median score, 5; range, 1-5). Eighty-two patients (40.2%) reported both. Severe reduction of taste was present in 81 patients (39.7%), and severe reduction of smell was present in 72 patients (35.3%). Only 12 patients (14.8%) with severe taste reduction and 12 patients (16.7%) with severe smell reduction reported severe nasal obstruction. Severe reduction of taste and smell was more prevalent in female vs male patients (odds ratios, 3.16 [95% CI, 1.76-5.67] vs 2.58 [95% CI, 1.43-4.65]) and middle-aged vs younger patients (effect sizes, 0.50 [95% CI, 0.21-0.78] vs 0.85 [95% CI, 0.55-1.15]). No significant association was observed between smoking habits and severe reduction of taste (odds ratio, 0.95; 95% CI, 0.53-1.71) and/or smell (odds ratio, 0.65; 95% CI, 0.35-1.21).

CONCLUSIONS AND RELEVANCE The findings of this telephone survey study suggest that reduction of taste and/or smell may be a frequent and early symptom of COVID-19. Nasal obstruction was not commonly present at the onset of the disease in this study. The general practitioner may play a pivotal role in identifying potential COVID-19 in patients at an early stage if taste and/or smell alterations manifest and in suggesting quarantine before confirmation or exclusion of the diagnosis.

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In December 2019, an outbreak of pneumonia of unknown origin was observed in the city of Wuhan, Hubei Province, China. A novel coronavirus, the 2019 new coronavirus, then named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the etiologic agent responsible for the outbreak.^{1,2} Coronavirus disease 2019 (COVID-19) then spread outside Hubei to many countries outside China. It was defined as a pandemic by the World Health Organization on March 11, 2020.³

As of April 4, 2020, a total of 1 203 459 cases of COVID-19 were diagnosed in the world.⁴ Italy was the third most affected country, with 124 632 total cases, 15 362 deaths, and 3994 patients currently classified as presenting with serious or critical conditions and hospitalized in intensive care units.⁴ Most cases in Italy were found in the Lombardy region, and the increasing number of hospitalized patients requiring invasive ventilatory assistance posed the risk of exceeding total intensive care unit capacity.^{5,6}

COVID-19 most commonly manifests as fever, dry cough, shortness of breath, sputum production, fatigue, and musculoskeletal pain. Less common symptoms include headache, sore throat, hemoptysis, nausea, vomiting, and diarrhea.⁷⁻¹⁰ Respiratory tract infections, such as influenza, should be included in the differential diagnosis given the similarity of symptoms.¹¹ Sinonasal and ocular manifestations can be considered because of the mechanism of transmission of the virus. The presence of specific olfactory and taste disorders has been recently reported in a small group of patients.¹² Ocular manifestations are still under investigation.^{13,14}

The disease has been characterized as a mild form without pneumonia or only mild pneumonia that spontaneously resolves without complications in approximately 80% of cases. Severe disease has occurred in 14% of cases, which developed into moderate to severe pneumonia with mild or acute respiratory distress syndrome. Critical cases account for 5% of the total cases and manifest as moderate to severe acute respiratory distress syndrome with septic shock and multiorgan failure in the final stages.¹⁵

Diagnosis is based on clinical characteristics and confirmed by a real-time polymerase chain reaction (PCR) test of a respiratory tract swab specimen.⁷ Chest computed tomography (CT) has been proposed as an alternative diagnostic method, especially in individuals with negative real-time PCR results.^{7,16} However, chest CT findings may be normal at initial presentation; therefore, normal chest CT findings cannot exclude the presence of COVID-19.¹⁷

Clinical suspicion remains crucial for the diagnosis of COVID-19. Sinonasal manifestations may be present in the early stage of the disease, and their recognition could help formulate a more accurate and timely diagnosis, prompting the use of additional diagnostic methods when suspicion is raised. The objective of the study was to identify the characteristics and prevalence of early sinonasal manifestations that precede the diagnosis of COVID-19.

Key Points

Question Are there relevant sinonasal manifestations associated with the onset of coronavirus disease 2019?

Findings This survey study of 204 patients with coronavirus disease 2019 found that taste reduction was present in 55.4% of patients, whereas smell reduction was present in 41.7% of patients. Severe nasal obstruction was uncommon at the onset of the disease (7.8%).

Meaning The findings suggest that coronavirus disease 2019 should be suspected when severe reduction of taste and smell are present in the absence of nasal obstruction.

Methods

Study Population

This retrospective survey study included all patients diagnosed with COVID-19 from March 5 to March 23, 2020, who were admitted to the Humanitas Clinical and Research Hospital. The inclusion criterion was a laboratory-confirmed SARS-CoV-2 infection in patients who presented with cough and/or fever. The Allplex 2019 n-CoV Assay (Seegene Inc), based on real-time PCR, was used to detect SARS-CoV-2. All patients, whether hospitalized or discharged, were interviewed via telephone. The survey was administered in 2 days in March 2020. The survey inquired about symptoms from the onset to laboratory confirmation. Patients who were unable to answer (intubated, receiving noninvasive ventilatory assistance, or deceased) or unreachable by telephone were excluded from the study. Written informed consent was obtained before enrollment, and all data were deidentified. The study was approved by the Ethics Committee of Humanitas Clinical and Research Center.

Data Sources

Medical history and general symptoms related to COVID-19 were collected for each patient by telephone interview. Sinonasal and ocular manifestations were studied. The Italian version of the Sino-Nasal Outcome Test 22 (I-SNOT-22)¹⁸ was administered to all patients, and the total score was calculated, with a minimum score of 0 indicating no problem and a maximum score of 110 indicating problem as bad as it can be. A second analysis of items 1 to 12 (physical symptoms) excluding items 13 to 22 (health and quality of life) was performed to avoid bias resulting from psychological implications related to a COVID-19 diagnosis. Ocular symptoms were investigated with an anamnesis obtained by telephone. Information regarding the day of onset of each symptom was collected. In cases in which a reduction or a loss of taste and/or smell was documented by item 5 of the I-SNOT-22, further inquiries were made to investigate them separately. A score of 0 to 5 was recorded, as in the I-SNOT-22, with 0 indicating no problem and 5 indicating problem as bad as it can be.

Statistical Analysis

Because the primary end point was to estimate patients' adherence to the study and the prevalence of sinonasal

manifestations in COVID-19, a sample size of 200 patients was considered to be sufficient. This sample size could ensure a precision of less than 3.5% in estimating the prevalence of sinonasal manifestations. The prevalence of sinonasal manifestations is given as numbers (percentages). Continuous data with approximately symmetrical distribution are given as means (SDs); if distribution was asymmetrical, data are given as mean and median (range). Age was categorized in decades. I-SNOT-22 items 1 to 12 were scored on a Likert-like scale and were categorized as not present (score of 0), mild (score of 1-3), or severe (score of 4-5). No missing data were reported.

Associations are expressed as effect size for continuous variables and odds ratio (OR) or relative risk for categorical ones. Associations between severe reduction of taste and/or smell (score of 4-5) and sex adjusted by age were explored with logistic regression analysis. Statistical analyses were performed with Stata, version 15 (StataCorp LLC).

Results

Demographic Characteristics

Of 359 patients who received a diagnosis of COVID-19 in the Humanitas Clinical and Research Center, 204 fulfilled the inclusion criteria (110 [53.9%] male; mean [SD] age, 52.6 [14.4] years). A total of 155 patients were excluded from the study: 76 were unable to answer (25 intubated, 10 receiving noninvasive ventilatory assistance, and 41 deceased), 76 were unreachable by telephone, and 3 refused to participate. All clinical characteristics, general symptoms at the onset, and comorbidities are reported in Table 1.

Epidemiologic and Clinical Characteristics

The median I-SNOT-22 total score was 21 (range, 0-73). The median score of items 1 to 12 (physical symptoms) was 11 (range, 0-42). The prevalence of physical symptoms is reported in Table 2, together with the mean and median scores of symptomatic patients. The median time at onset of each physical symptom was between 4 and 7 days before the diagnosis (Table 2). Twenty-six patients (12.8%) reported ocular manifestations before the diagnosis. The median time from the onset of ocular manifestations to the diagnosis of COVID-19 was 6.5 days (range, 0-17 days).

Reduction of taste and/or smell was more frequent compared with the other symptoms investigated by I-SNOT-22 except for cough. A total of 116 patients (56.9%) reported reduction or loss of taste and/or smell in item 5 of I-SNOT-22. In the further inquiries performed to investigate taste and smell separately, 113 patients (55.4%) had taste reduction (median score, 5; range, 2-5) and 85 (41.7%) reported smell reduction (median score, 5; range, 1-5). Eighty-two patients (40.2%) reported both. Severe taste reduction was present in 81 patients (39.7%), whereas severe smell reduction was present in 72 patients (35.3%). A positive history of olfactory dysfunction was present in 3 cases (1.5%). Among items 1 to 4 (need to blow nose, sneezing, runny nose, and nasal obstruction) and 7 to 8 (postnasal drip and thick nasal discharge) of I-SNOT-22 (sinonasal manifestations), a significant association was found

Table 1. Clinical Characteristics, General Symptoms, and Comorbidities at the Onset of Coronavirus Disease 2019 in the Study Population

Variable	Patients, No. (%) (N = 204)
Age, y	
≤39	36 (17.6)
40-49	57 (27.9)
50-59	43 (21.1)
60-69	40 (19.7)
70-79	21 (10.3)
≥80	7 (3.4)
Sex	
Female	94 (46.1)
Male	110 (53.9)
Smoking history	
No	132 (64.7)
Yes	77 (35.3)
Exposure to source of transmission within past 14 d	
No	114 (55.9)
Yes	90 (44.1)
General symptoms at disease onset	
Fever	134 (65.7)
Dry cough	91 (44.6)
Fatigue	46 (22.6)
Headache	32 (15.7)
Myalgia or arthralgia	20 (9.9)
Diarrhea	17 (8.3)
Nausea or vomiting	12 (5.9)
Dyspnea	12 (5.9)
Comorbidities	
Hypertension	49 (24.0)
Allergy	30 (14.7)
Allergy to inhalants	21 (10.3)
Diabetes	23 (11.3)
Cardiovascular disease	15 (7.4)
Cancer	13 (6.4)
Chronic obstructive pulmonary disease	10 (4.9)

between nasal obstruction and severe reduction of taste (OR, 5.17; 95% CI, 1.61-16.67) and smell (OR, 6.40; 95% CI, 1.98-20.67). A total of 50 of 81 patients (61.7%) did not have nasal obstruction, and 42 of 72 (58.3%) had severe reduction of taste and smell.

A significant association was also found between runny nose and severe reduction of smell (OR, 7.00; 95% CI, 1.41-34.65). A total of 43 of 72 patients (59.7%) did not have runny nose but had severe reduction of smell (Table 3).

Severe reduction of taste was more prevalent in female patients (OR, 3.16; 95% CI, 1.76-5.67), and patients with severe reduction of taste were significantly younger than patients with no or mild symptoms (mean [SD] age, 48.3 [13.8] years vs 55.3 [14.2] years; effect size, 0.50; 95% CI, 0.21-0.78). Similarly, severe reduction of smell was more prevalent in female patients (OR, 2.58; 95% CI, 1.43-4.65), and patients with severe reduction of smell were significantly younger than patients with no or mild symptoms (mean [SD] age, 45.2 [12.7] years

Table 2. Sinonasal Manifestations Before Coronavirus Disease 2019 Diagnosis

Physical symptoms on I-SNOT-22	Patients, No. (%)	I-SNOT-22 score ^a		Time from onset to diagnosis, median (range), d
		Mean (SD)	Median (range)	
Cough	143 (70.1)	3.1 (1.2)	3 (1-5)	6 (0-20)
Loss of taste	113 (55.4)	4.3 (1.0)	5 (2-5)	4 (0-21)
Loss of smell	85 (41.7)	4.5 (0.8)	5 (1-5)	4 (0-21)
Need to blow nose	82 (40.2)	2.6 (1.1)	2 (1-5)	6 (0-20)
Runny nose	73 (35.8)	2.3 (1.1)	2 (1-5)	6 (0-20)
Nasal obstruction	70 (34.3)	2.7 (1.2)	3 (1-5)	6 (0-20)
Sneezing	66 (32.3)	2.2 (1.2)	2 (1-5)	6 (0-20)
Postnasal drip	47 (23.0)	2.3 (1.1)	2 (1-4)	7 (0-20)
Dizziness	43 (21.1)	3.1 (1.2)	3 (1-5)	5 (0-21)
Thick nasal discharge	29 (14.2)	2.1 (1.2)	2 (1-4)	6 (0-14)
Facial pain and/or pressure	26 (12.7)	3.2 (1.2)	3 (1-5)	5.5 (0-11)
Ear fullness	22 (10.8)	2.3 (1.1)	3 (1-5)	6 (0-11)
Ear pain	13 (6.4)	2.9 (1.1)	3 (1-5)	5 (2-11)

Abbreviation: I-SNOT-22, Italian version of the Sino-Nasal Outcome Test 22.

^a Mean and median scores of the I-SNOT-22 items related to physical symptoms were reported for symptomatic patients.

Table 3. Taste and Smell Reduction Associated With Sinonasal Manifestations of Coronavirus Disease 2019^a

I-SNOT-22 item	Taste			Smell		
	Scores 0-3 (n = 123)	Scores 4-5 (n = 81)	RR (95% CI)	Scores 0-3 (n = 132)	Scores 4-5 (n = 72)	RR (95% CI)
Need to blow nose						
Score 0	75 (61.0)	47 (58.0)	1 [Reference]	83 (62.9)	39 (54.2)	1 [Reference]
Scores 1-3	43 (35.0)	24 (29.6)	0.93 (0.63-1.37)	43 (32.6)	24 (33.3)	1.12 (0.74-1.69)
Scores 4-5	5 (4.0)	10 (12.4)	1.73 (1.13-2.64)	6 (4.5)	9 (12.5)	1.88 (1.15-3.06)
Sneezing						
Score 0	82 (66.7)	56 (69.1)	1 [Reference]	90 (68.2)	48 (66.7)	1 [Reference]
Scores 1-3	34 (27.6)	20 (24.7)	0.91 (0.61-1.36)	36 (27.3)	18 (25.0)	0.96 (0.62-1.49)
Scores 4-5	7 (5.7)	5 (6.2)	1.03 (0.51-2.07)	6 (4.5)	6 (8.3)	1.44 (0.78-2.65)
Runny nose						
Score 0	78 (63.4)	53 (65.4)	1 [Reference]	88 (66.7)	43 (59.7)	1 [Reference]
Scores 1-3	42 (34.2)	22 (27.2)	0.85 (0.57-1.26)	42 (31.8)	22 (30.6)	1.05 (0.69-1.59)
Scores 4-5	3 (2.4)	6 (7.4)	1.65 (0.99-2.73)	2 (1.5)	7 (9.7)	2.37 (1.55-3.63)
Nasal obstruction						
Score 0	84 (68.3)	50 (61.7)	1 [Reference]	92 (60.7)	42 (58.3)	1 [Reference]
Scores 1-3	35 (28.5)	19 (23.5)	0.94 (0.62-1.44)	36 (27.3)	18 (25.0)	1.06 (0.68-1.67)
Scores 4-5	4 (3.2)	12 (14.8)	2.01 (1.41-2.88)	4 (3.0)	12 (16.7)	2.39 (1.64-3.49)
Postnasal drip						
Score 0	97 (78.9)	60 (74.1)	1 [Reference]	104 (78.8)	53 (73.6)	1 [Reference]
Scores 1-3	23 (18.7)	16 (19.7)	1.07 (0.70-1.64)	23 (17.4)	16 (22.2)	1.22 (0.79-1.88)
Scores 4-5	3 (2.4)	5 (6.2)	1.64 (0.92-2.90)	5 (3.8)	3 (4.2)	1.11 (0.44-2.79)
Thick nasal discharge						
Score 0	107 (87.0)	68 (84.0)	1 [Reference]	116 (87.9)	59 (81.9)	1 [Reference]
Scores 1-3	14 (11.4)	10 (12.3)	1.07 (0.64-1.78)	13 (9.8)	11 (15.3)	1.36 (0.84-2.20)
Scores 4-5	2 (1.6)	3 (3.7)	1.54 (0.74-3.23)	3 (2.3)	2 (2.8)	1.19 (0.40-3.54)
Male sex	80 (65.0)	30 (37.04)	0.50 (0.35-0.72)	82 (62.1)	28 (38.9)	0.54 (0.37-0.80)
Smoking history						
No	80 (64.5)	52 (65)	1 [Reference]	82 (61.6)	50 (70.4)	1 [Reference]
Yes	44 (35.5)	28 (35)	0.97 (0.68-1.38)	51 (38.4)	21 (29.6)	0.75 (0.50-1.15)
Age, mean (SD), y	55.3 (14.2)	48.3 (13.8)	0.85 (0.55-1.15) ^b	56.6 (13.8)	45.2 (12.7)	0.50 (0.21-0.78) ^b

Abbreviations: I-SNOT-22, Italian version of the Sino-Nasal Outcome Test 22; RR, relative risk.

indicated.

^b These values are effect sizes.

^a Data are presented as number (percentage) of patients unless otherwise

vs 56.6 [13.7] years; effect size, 0.85; 95% CI, 0.55-1.15). No significant association was observed between smoking habits and severe reduction of taste (odds ratio, 0.95; 95% CI, 0.53-1.71) and/or smell (odds ratio, 0.65; 95% CI, 0.35-1.21). Reduction of taste, mild or severe, was associated with female sex, adjusted by age (OR, 1.78; 95% CI, 1.00-3.20). Reduction of smell, mild or severe, was associated with female sex, adjusted by age (OR, 2.20; 95% CI, 1.21-4.01). All the other physical symptoms investigated by I-SNOT-22 were not associated with sex.

Discussion

Patients with COVID-19 have a broad spectrum of clinical manifestations. Diagnosis can be challenging when fever or chest radiologic alterations are absent at the onset.⁸ Thus, investigating other early manifestations may be crucial. The transmission of SARS-CoV-2 occurs mostly by respiratory droplets.¹⁹ Consequently, it seems reasonable to hypothesize the direct involvement of the upper airways and eyes. The aim of our study was to investigate sinonasal manifestations at the onset of COVID-19. Recently, Italian authors¹² investigated olfactory and taste disorders in a small sample with a nonvalidated questionnaire. Our study investigated clinical sinonasal manifestations in patients with COVID-19 with the I-SNOT-22 because of the lack of other validated questionnaires. To our knowledge, no other studies have been reported using this validated test. Our study found that the median time of onset for each of the physical symptoms (items 1-12 of I-SNOT-22) associated with the diagnosis of COVID-19 was 4 to 7 days before the diagnosis. This clinical aspect may be crucial for the general practitioner in early identification of COVID-19.

In our study, few patients experienced ocular manifestations. We were unable to confirm whether these symptoms were attributable to virus-related ocular inflammation. Previous studies^{20,21} have found that, like SARS-CoV, SARS-CoV-2 binds to human angiotensin-converting enzyme 2, which is not expressed in the conjunctival and corneal epithelium. We thus presumed that lacrimal secretions were only a vehicle of transmission of the virus, which reached the nasal mucosa through the nasolacrimal ducts.^{13,22}

Total I-SNOT-22 scores were low and close to what would be seen in a healthy control population except for the reduction of taste and smell. The I-SNOT-22 documented taste and/or smell dysfunctions that differed from the common postinfectious olfactory disorder, which manifests in cases of rhinitis or other upper respiratory tract infections. A recent review²³ analyzed 5 Chinese studies and reported that the symptoms of COVID-19 were similar to other viral upper respiratory tract infections, including fever, cough, fatigue, and dyspnea. The authors found that sore throat was common (12.4%), whereas nasal congestion was not frequent (3.7%) and rhinorrhea was rare. Nevertheless, none of the articles included in this review reported data on smell and/or taste dysfunction. Other studies^{24,25} based on a large survey found that olfactory and gustatory disorders may be early symptoms associated with COVID-19. Our results showed a significant difference between reduction of taste

and/or smell compared with the other sinonasal manifestations. Olfactory and taste disorders are known to be associated with a wide range of viral infections.^{26,27} Rhinoviruses account for most pathogens responsible for upper respiratory tract infections, followed by adenoviruses. Such infections are characterized by several nasal manifestations, including congestion, rhinorrhea (anterior and posterior), sneezing, and headaches.²⁶ Patients with COVID-19 and olfactory dysfunction seem to experience milder nasal symptoms compared with patients with common upper respiratory tract infections. However, in our study, most patients with severe reduction of taste and smell did not report nasal obstruction. Experimental studies^{28,29} on transgenic mice demonstrated that SARS-CoV could reach the brain via the olfactory nerves, spreading to specific areas, including the thalamus and the brainstem. Because a recent study³⁰ reported that SARS-CoV is phylogenetically related to SARS-CoV-2, it is reasonable that SARS-CoV-2 may damage the olfactory pathways in a similar manner. The higher prevalence of taste dysfunction compared with smell dysfunction reported in our study may be explained by minor alterations in smell going unnoticed by patients who only report a reduction in taste. Furthermore, taste perception could be negatively affected by the impairment of retronasal olfaction, which is involved in taste intensity, appetite, and eating behavior.³¹ In addition, female and middle-aged patients presented more frequently with severe taste and smell reduction.

We investigated patients discharged shortly after accessing the emergency department of the Humanitas Clinical and Research Center, patients presenting with mild clinical manifestations, patients discharged after hospitalization, and hospitalized patients who were able to provide information at the time of the survey. A total of 43% of the patients did not fulfill the inclusion criteria because they were deceased, intubated, or receiving noninvasive ventilatory assistance at the time of the survey or they refused to participate for personal reasons. The high percentage of excluded patients was justified by the emergency situation.

Limitations

There are some limitations to the study related to disease diffusion in the current pandemic context. An objective smell assessment, such as the University of Pennsylvania Smell Identification Test,³² was not applied to confirm smell dysfunction to avoid the risk of transmission among health care professionals. This analysis was retrospective and involved patients with a positive real-time PCR result without a control group of patients with similar clinical symptoms but with a negative test result. This issue will be addressed in a prospective cohort study.

Conclusions

This study demonstrated that the onset of COVID-19 was associated with reduction of taste and/or smell. Nasal obstruction was rarely present at the onset of the disease. The

general practitioner may play a pivotal role in identifying potential COVID-19 at an early stage when taste and/or smell alterations manifest and in suggesting quarantine before confirmation or exclusion of the diagnosis.

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