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Olfactory and gustatory manifestations in hospitalized patients with COVID-19

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Abstract

Background: Pulmonary involvement is the main clinical and imaging feature of the novel corona virus disease (COVID-19). However, some patients present with upper airway symptoms.

Aim: In this study, we report upper respiratory manifestations, specifically focusing on smell and taste disorders in COVID-19.

Methods: We performed this cross-sectional prospective study in patients admitted to Masih Daneshvari Hospital, a tertiary referral center in Tehran, Iran, with severe COVID-19 as documented by the polymerase chain reaction assay.

Results: We included 268 hospitalized patients, 183 (68.3%) men and 85 (31.7%) women. The average age was 52.8±16.4. The sinonasal symptoms included nasal obstruction (44 [16.4%]), rhinorrhea (31 [11.5%]), sneeze (33 [12.3%]), headache (77 [28.6%]), facial pain (12 [4.5%]), associated with hypogeusia (65 [24.2%]) and olfactory dysfunction (90 [33.5%]). In 35 (38.9%) patients with olfactory symptoms, change in the smell was the sole initial manifestation of COVID-19. On logistic regression, the relationship between the olfactory symptoms and headache (p=0.002), nasal obstruction (p=0.0001) and sneeze (p=0.018) were statistically significant.

Conclusion: We report a considerable prevalence of olfactory and gustatory symptoms in hospitalized patients with COVID-19. Not infrequently, these symptoms were the sole initial presenting symptoms in the course COVID-19. During the current pandemic, we suggest that presence of these symptoms should mandate expedited screening for COVID-19, isolation and close monitoring of the patients for evolution of the clinical course.

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Introduction

In December 2019, several unexplained cases of pneumonia occurred in Wuhan, the capital of China's Hubei province, later proven to have been caused by a novel coronavirus (CoV-2) (1). Severe acute respiratory distress (SARS) caused by CoV-2 infection in humans is similar to SARS-CoV and Middle East Respiratory Syndrome (MERS). The World Health Organization (WHO) has named the disease coronavirus disease 2019 (COVID-19) and has declared it a pandemic (2).

SARS-CoV-2 is a betacoronavirus that is the seventh member of the Coronaviridae family of viruses (3). The whole-genome sequence of

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SARS-CoV-2 has 96·2% similarity to a bat SARS-CoV and less similarity to the genomes of SARS-CoV or MERS-CoV (4,5). Nevertheless, SARS-CoV-2 uses the same receptor as the SARS-CoV, the angiotensin-converting enzyme 2 (ACE2), for cell entry (4). COVID-19 is a recently reported disease that is increasingly recognised to involve different bodily organs. There is considerable data on the clinical and imaging findings of COVID-19 in the lower respiratory tract. However, information regarding manifestations in the upper respiratory tract is limited. While the most common symptoms at the onset of COVID-19 include fever, cough and fatigue, headache and upper respiratory symptoms are less common (6). Thus, more investigations on these manifestations and their potential causes in COVID-19 are warranted. In this study, we describe the upper respiratory tract and sinonasal manifestations, specifically the olfactory and gustatory symptoms, in patients hospitalized with confirmed SARS-CoV-2 infection at a single referral center in Tehran, Iran; and describe the association between the upper respiratory symptoms and the olfactory and gustatory manifestations in this cohort of patients.

Methods

Patient population and study end points

This cross-sectional study was performed at Masih Daneshvari Hospital in Tehran, Iran, which is a tertiary referral center for respiratory diseases. From March 1 to March 13, 2020, we prospectively collected data from consecutive adult (>18 years) hospitalized patients with confirmed SARS-CoV-2 infection by real-time polymerase chain reaction (PCR) performed on samples taken from pharyngeal swabs. The study population included patients who were hospitalized for COVID-19 and excluded the patients who were intubated and mechanically ventilated and the non-survivors. We asked the patients to fill in a questionnaire about the upper respiratory tract symptoms including nasal obstruction, rhinorrhea, sneeze, headache and facial pain. We divided the subjective olfactory complaints in three groups: anosmia for no sense of smell, hyposmia for reduced sense of smell, and parosmia for changed sense of smell, and defined the taste disorder as hypogeusia or reduced sense of taste. We recorded the time course of the olfactory and gustatory symptoms during the admission.

Data were analysed using SPSS statistics version 22·0 (IBM, New York, NY, USA).

Results

Demographics and clinical characteristics of the study population

The demographic and clinical characteristics of the study subjects are summarized in Table 1. A total of 268 hospitalized patients with confirmed SARS-CoV-2 infection were included in the study. The average age was 52.8 ± 16.4 years (range 20-93). 183 (68.3 %) were male and 85 (31.7 %) were female. The most common sinonasal symptoms were olfactory symptoms in 90 (33.5%), followed by headache in 77 (28.6 %) patients. Sinonasal symptoms were more prevalent in patients with olfactory or gustatory symptoms compared with patients who did not have these symptoms.

Olfactory manifestations in patients with COVID-19

The mean duration from the onset of illness to olfactory symptoms was 3.1±1.7 days. The mean age of patients was not different in patients with versus without olfactory symptoms (p> 0.05). We did not find a significant association between the olfactory symptoms and sex (p> 0.05). Moreover, 39 (43.3%) patients had anosmia, 40 (44.5%) hyposmia, and 11(12.2%) parosmia. In 35 (38.9%) of patients with olfactory symptoms, change in smell was the sole initial manifestation of COVID-19, whereas in 26 (28.9%) of patients, olfactory symptoms and other symptoms of COVID-19 were simultaneously present. The onset of the olfactory symptoms was sudden in 37 (41.1%)

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and gradual in 36 (40%) of patients, and 17 (18.9%) patients did not recall the details of the symptom onset.

There was associated headache in 20 (57.1%) patients in whom the first symptom of COVID-19 was olfactory. Moreover, 17 (45.9%) patients with sudden onset of olfactory symptoms had headache. On logistic regression model, the relationship between the olfactory symptoms and headache (p=0.002), sneeze (p=0.018) and nasal obstruction (p=0.0001) were statistically significant (Table 2).

Table 1. Demographic and clinical characteristics

Characteristics	Total (n=268)	Olfactory symptoms (n=90)	No olfactory symptoms (n=178)	Gustatory symptoms (n=65)	No gustatory symptoms (n=203)	p value	
						Olfactory vs no olfactory symptoms	Gustatory vs no gustatory symptoms
Age	52·8 ± 16·4	50·6±15	53·86±17·05	47·8±14·6	54·35±16·67	0·147	0·007
Sex							
Male	183 (68·3 %)	56 (62·2%)	126 (70·8%)	42 (64·6%)	141 (69·5%)	0·183	0·600
Female	85 (31·7%)	34 (37·8%)	52 (29·2%)	23 (35·4%)	62 (30·5%)		
Age decades							
20-30	22 (8·2%)	11 (12·2%)	13 (7·3%)	9 (13·8%)	14 (6·9%)	0·050	0·057
31-40	56 (20·9%)	15 (16·7%)	40 (22·5%)	15 (23·1%)	40 (19·7%)		
41-50	50 (18·7%)	20 (22·2%)	30 (16·8%)	13 (20%)	37 (18·2%)		
51-60	51 (19%)	19 (21·1%)	31 (17·4%)	15 (23·1%)	36 (17·8%)		
61-70	48 (17·9%)	18 (20%)	30 (16·8%)	9 (13·8%)	39 (19·2%)		
>70	41 (15·3%)	7 (7·8%)	34 (19·2%)	4 (6·2%)	37 (18·2%)		
Sinonasal symptoms							
Nasal obstruction	44 (16·4%)	33 (36·6%)	11 (6·2%)	22 (33·8%)	22 (10·8%)	<0·0001	<0·0001
Rhinorrhea	31 (11·5%)	18 (20%)	13 (7·3%)	13 (20%)	18 (8·9%)	0·002	0·014
Sneeze	33 (12·3%)	24 (26·6%)	9 (3·4%)	14 (21·5%)	19 (9·3%)	<0·0001	0·009
Headache	77 (28·6%)	48 (53·3%)	29 (16·2%)	28 (43%)	49 (24·1%)	<0·0001	0·003
Facial pain	12 (4·5%)	11 (12·2%)	1 (0·56%)	6 (9·2%)	6 (2·9%)	<0·0001	0032

Gustatory manifestations in patients with COVID-19

Of the participants in the study, 65 patients (24.2%) had a change in taste, all with hypogeusia. The mean age of patients with gustatory symptoms was lower than patients without gustatory symptoms (p=0.007) (Table 1). We did not find a significant association between the gustatory symptoms and sex (p> 0.05). Moreover, 49 (75.3%) patients with hypogeusia had a concomitant olfactory symptom. Among the 49 patients with concomitant gustatory and olfactory symptoms, olfactory change was the initial symptom in 27

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(55.1%), whereas gustatory symptom was the first symptom in 9 (18.4%) and both olfactory and gustatory symptoms occurred simultaneously in 13 (26.5%) patients.

Headache was the most common symptom in patients with both olfactory and gustatory symptoms (54%). We found a significant association between the gustatory symptoms and nasal obstruction (p=0.003) (Table-2).

Table 2. Sinonasal symptoms associated with olfactory or gustatory manifestations

Sinonasal symptoms	Olfactory symptoms		Gustatory symptoms	
	OR (95% CI)	p value	OR (95% CI)	p value
Nasal obstruction	5·20 (2·24-12·01)	0·000	3·22 (1·48-6·98)	0·003
Rhinorrhea	1·13 (0·39-3·25)	0·825	1·52 (0·60-3·85)	0·374
Sneeze	3·33 (1·23-9·01)	0·018	1·57 (0·65-3·78)	0·313
Headache	2·91(1·46-5·8)	0·002	2·91(0·65-2·70)	0·443
Facial pain	9·20 (0·98-85·87)	0·051	9·20 (0·47-6·4)	0·408

CI=confidence interval; OR=odds ratio

Discussion

In this study, we investigated the upper airway symptoms and their association with smell and taste disorders in patients hospitalized with COVID-19 in Iran. We report the following clinical findings: i) ~one-third of patients hospitalised with COVID-19 had olfactory symptoms, with both anosmia and hyposmia equally distributed in prevalence, ii) the olfactory symptoms were sudden onset in ~45% of patients, iii) in ~39% of patients with olfactory symptoms, change in smell was the sole initial manifestation of COVID-19, iv) headache and nasal obstruction were independently associated with the olfactory symptoms, v) hypogeusia was present in ~one-fourth of patients, often associated with and preceded by the olfactory symptoms.

Compared to prevalence of 85.6% and 88.0% for olfactory and gustatory dysfunctions in a previous report from mild-to-moderate COVID-19 European patients (7), ~one fourth and one-third of patients in this study had gustatory or olfactory symptoms. We questioned directly and specifically about the smell and taste problems in our admission charts, otherwise there was a high likelihood that these symptoms may have gone unnoticed in many patients due to the severity of the disease. Other likely explanations for the discrepancy may be different virulence of SARS-CoV-2 in the Iranian versus other population.

Viral infections are the most common cause of smell disorders (e.g. anosmia or hyposmia) (8). Smell disorders are seen in two forms: conductive or sensorineural olfactory loss (9). The most common form, conductive olfactory loss, is secondary to congestion, secretions and inflammatory changes in the nasal mucosa in the early days of viral infection with symptoms of nasal obstruction and rhinorrhea (9). Conversely, in post-viral olfactory disorder, the smell disorders including anosmia, hyposmia or parosmia occur after the resolution of upper airway viral infection, independently of nasal obstruction (10,11).

Coronaviruses are a known cause of post-viral olfactory disorder (12). Damage caused by coronaviruses may be seen in different locations from olfactory epithelium and receptor cells to olfactory bulb and central processing pathways (8, 9). Commonly, taste disorders occur secondary to olfactory dysfunction like other viral infections of the upper airways (13). In this study, only ~36% of patients with olfactory symptoms had nasal obstruction, while majority (~75%) of patients

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with taste disorder also had a smell disorder. Taken together, these findings implicate sensorineural olfactory loss as the main cause of the smell disorder in COVID-19 and suggest that gustatory symptoms occur secondary to the olfactory dysfunction or due to other unknown effects of the virus.

In ~39% of patients with olfactory symptoms, the change in smell was the first symptom of COVID-19. Therefore, during the COVID-19 pandemic, olfactory symptoms like hyposmia, anosmia or parosmia may be considered as alarm signs for infection with SARS-CoV-2, mandating diagnostic testing, early isolation and close monitoring of the patients for other symptoms of COVID-19.

Headache was present in ~29% of our study population, however it is not a commonly reported symptom in most reports of COVID-19, with its prevalence ranging from 4% to 13.1% (14-19). Interestingly, in our study, headache significantly associated with the olfactory symptoms. This association may indicate involvement of the central nervous system by SARS-CoV-2(19,20). Human neuronal cells express the ACE2 receptor, which is the cellular binding site for the spike protein of SARS-CoV-2 and a potential for neurotropism has been documented for almost all betacoronaviruses (21). For instance, SARS-CoV particles were found in the brains of patients infected with the virus (20) and olfactory neuropathy has been reported during SARS outbreak without any improvement after 2 years (22). Moreover, in experimental models, corona-related viruses could involve the olfactory bulb with minimal injury of the nasal mucosa (23), while intranasal introduction of SARS-CoV or MERS-CoV is shown to induce brain damage, probably via the olfactory nerve(21,24). Lastly, trans-synaptic transfer of other coronaviruses has been demonstrated (20). Histopathologic examination of nasal mucosa, especially olfactory cleft area, olfactory bulb, and central nervous system on autopsy would shed light on the involvement of these organs during the course of COVID-19.

This study has some limitations. The present study was performed in a single center. We did not perform direct smell and taste identification tests and the data were collected by a questionnaire.

Conclusion

In conclusion, we report a relatively high prevalence of olfactory and gustatory symptoms in hospitalised patients with COVID-19 that were infrequently associated with upper respiratory symptoms and not uncommonly were the sole initial presenting symptoms in the course of the disease. During the current pandemic, we strongly suggest that specific attention is given to these symptoms in assessing the patients with suspected COVID-19, the presence of which may indicate the need for expedited testing for SARS-CoV-2, and isolation and close monitoring of the patients for evolution of the clinical course.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Ethics

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