SPECIAL ARTICLE COVID-19

Analysis of Ear, Nose and Throat Manifestations in COVID-19 Patients

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Abstract

Introduction Coronavirus disease 2019 (COVID-19) has dramatically spread all over the world, crossing the borders of all countries. It is presented mainly by lower respiratory tract symptoms such as fever, cough, dyspnea, and chest tightness. However, COVID-19 causes different upper respiratory tract-related symptoms including nasal congestion, sore throat, and olfactory dysfunction.

Objective To discuss different ear, nose and throat (ENT) manifestations in COVID-19-positive patients and their relation to other manifestations and to the severity of COVID-19.

Methods We detected ENT manifestations in polymerase chain reaction (PCR)-confirmed positive COVID-19 patients at Zagazig Isolation Hospitals (Zagazig University hospitals, Zagazig Chest hospital, Al-Ahrar hospital, and Zagazig Fever hospital) with proportional allocation in the period from April 15 to June 15, 2020. All patients were subjected to full history taking and COVID-19 was categorized into 4 classes of severity after all patients underwent computed tomography (CT) of the chest. Afterwards, the collected data was analyzed and compared.

Results Among the included 120 COVID-19 patients, the most frequent reported ENT manifestations were; sore throat (30%), nasal congestion (28.3%), nasal obstruction (26.7%), sneezing (26.6%), headache (25%), smell and taste dysfunction (25%), rhinorrhea (20%), upper respiratory tract infection (URTI) (15%), and tonsil enlargement (10%). The most common non-ENT manifestations were fever (88.3%), cough (63.3%), and dyspnea (45%).

Conclusion Fever and cough are the dominant symptoms of COVID-19, but ENT manifestations for COVID-19 are common and should be a part of the suspected clinical criteria for COVID-19, particularly if the nasal examination was nonsignificant. The most common symptoms are sore throat, followed by nasal congestion and obstruction, headache, and lastly, olfactory dysfunction.

Keywords
► COVID-19
► coronavirus
► nose
► hyposmia
► ENT
► otorhinolaryngology

Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), first known as the 2019 novel Coronavirus (2019-nCoV), started in Wuhan, in China, in December 2019.[1] Since that moment, the new virus, also known as Coronavirus Disease 2019 (COVID-19), has dramatically spread all over the world, crossing the borders of all countries until the World Health Organization (WHO) confirmed it as a pandemic disease on March 11, 2020.[2]

The SARS-CoV-2 is part of the species of the SARS-related coronaviruses that have led to previous epidemics over the last 2 decades, such as the SARS-CoV in 2002–2003 in China,[3] and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012–2013 in Saudi Arabia.[4]

COVID-19 is presented mainly by lower respiratory tract-related symptoms such as fever, cough, dyspnea, and chest tightness that could progress rapidly to acute respiratory distress syndrome (ARDS).[5] However, COVID-19 also causes different upper respiratory tract-related symptoms including nasal congestion, sore throat, and olfactory dysfunction.[6]

The available data on ENT manifestations of COVID-19 is sparsely published and, to the best of our knowledge, review studies on olfactory dysfunction in COVID-19-positive patients are few and lacking. Olfactory and taste dysfunctions in COVID-19 patients were sparsely mentioned in the literature and there is still a paucity of peer-reviewed literature to support a causal association between anosmia and COVID-19.[7]

Thus, the aim of the present study was to detect, analyze, and discuss the different ENT manifestations in COVID19-positive patients and their relation to other manifestations and to COVID-19 severity.

Materials and Methods

The present cross-sectional study was conducted on 127 patients at Zagazig Isolation Hospitals (Zagazig university hospitals, Zagazig Chest hospital, Al-Ahrar hospital, and Zagazig Fever hospital) with proportional allocation in the period from April 15 to June 15, 2020. All enrolled subjects or their relatives signed the informed consent form after explanation of the purpose of the research. All included patients were diagnosed as having confirmed COVID-19 by polymerase chain reaction (PCR) test. Suspected and non-confirmed COVID-19 cases were excluded. The present study was conducted according to the declaration of Helsinki on Biomedical Research Involving Human Subjects, and Zagazig University' International Review Board (IRB) approval was obtained. All patients were subjected to full history taking, and COVID-19 was categorized into 4 classes of severity after all patients underwent computed tomography (CT) of the chest: (1) mild: mild respiratory symptoms without imaging features of pneumonia; (2) moderate: fever, respiratory symptoms with imaging findings of pneumonia; (3) severe: shortness of breath, systemic oxygen (O2) saturation < 93% at rest on room air, respiratory rate > 30 breaths per minute, ratio of the systemic arterial partial O2 pressure to the fraction of inspired air $O2 \leq 300$ mmHg, or > 50% progress of radiologic pulmonary lesions over 24 to 48 hours; and (4) critical: demanding mechanical ventilation, extracorporeal membrane oxygenation, or other organ support therapy in the intensive care unit (ICU).[8] The following data was collected from all patients: epidemiological data, age, gender, special habit (smoking), comorbidities, history of chronic ENT disease and/or surgery, COVID-19 severity, ENT manifestations, and other COVID-19 manifestations.

Statistical Methods

All analyses were performed using IBM SPSS Statistics for Windows, Version 20 (IBM Corp., Armonk, NY, USA). Quantitative data were presented with means and standard deviations (SDs). Qualitative data were presented as number and percentage. The *t*-test was used to compare quantitative data, while qualitative data was compared using the chi-squared test (X2). Yates correction was performed when at least 20% of the expected frequencies were < 5. Values were considered statistically significant if $p < 0.05$.

Results

Among the 127 studied laboratory-confirmed positive COVID-19 patients, 120 were included in the present study (7 patients were severe cases and we could not take history from them or from their relatives), 62 were females (51.7%), and 58 were males (48.3%), with a mean age of 44.35 ± 15.16 years old (range = 16–79 years old). Only 1 patient was 16 years old, and all other patients were > 20 years old, comprising 18 single and 102 married patients. A total of 94 patients were smokers, 4 were former smokers, and 22 nonsmokers. A total of 36 medical staff patients (30%) (26 physicians, 8 pharmacists, and 2 dentists) were included. In 64 patients, there were other comorbidities, including 16 with hypertension, 20 with diabetes mellitus, 10 with bronchial asthma, 10 with thyroid dysfunction (8 with hypothyroidism, 2 with hyperthyroidism), 2 patients with past history of cerebrovascular stroke, 6 with hepatic disease (all were compensated), 6 cardiac patients, 4 renal failure patients, and 2 pregnant patients with anemia.

A total of 42 patients (35%) had a history of chronic ENT diseases; 8 had obstructive sleep apnea (OSA), 10 had allergic rhinitis, 14 had sinonasal polypi, and 6 had chronic sinusitis.

The severity of COVID-19 was mild in 74 patients (61.7%), with a mean age of 37.6 ± 11.6 years old (range: 16–64 years old); moderate in 26 patients (21.7%), with a mean age of 50.8 ± 13.88 years old (range: 33–79 years old); and severe in 20 patients (16.7%), with a mean age of 61.5 ± 9.18 years old (range: 49–73 years old) (►Table 1).

It was found that the mean age was significantly higher with increasing severity of the disease ($F = 37.227$; $p < 0.0001$).

The severity of COVID-19 in females was mild in 40 patients, moderate in 18 patients, and severe in 4 patients, while the severity in males was mild in 34 patients, moderate in 8 patients, and severe in 16 patients, with a significant

Table 1 Relation between data of the patients and COVID-19 severity

|	Severity of COVID-19	Mild	Moderate	Severe	Test	p-value	Number
Age (years old)	Mean	37.6 ± 11.6	50.8 ± 13.88	61.5 ± 9.18	$F = 37.227$	< 0.0001	120
	Range	16–64	33–79	49–73			
Gender	Female	40	18	4	$X^2 = 11.412$	0.0033 Significant	62
	males	34	8	16			58
Comorbidity	Present	34	16	14	$X^2 = 4.558$	0.102 NS	64
	Absent	40	10	6			56
Comorbidity	Single	34	6	6	$X^2 = 28.489$	< 0.0001	18
	Multiple	0	10	8			46
Smoking	Smoker	62	20	12	$X^2 = 23.336$ Yates $X = 16.23$	0.0001 S, Yates p-value = 0.0027),	94
	Nonsmoker	12	2	8			22
	Former smoker	0	0	4			4
ENT manifestations	present	24	10	6	$X^2 = 0.435$	0.8 NS	40
	No	50	16	14			80
Medical staff	Yes	26	8	2	$X^2 = 4.746$	0.09	36
	No	48	18	18			84

Abbreviations: F, ANOVA test; NS, non-significant; S, significant.

difference ($p = 0.0033$); more severe cases were observed in male patients ►**Fig. 1**.

The severity of COVID-19 in smokers was mild in 12 patients, moderate in 2 patients, and severe in 8 patients. In nonsmoker patients, the severity was mild in 62 patients, moderate in 20 patients, and severe in 12 patients. In former smokers, 4 cases were severe.

Severe COVID-19 cases were reported more significantly in former smokers and in smokers ($p = 0.0001$; $X2 = 23.336$), and after Yates correction (Yates p-value = 0.0027; Yates $X2 = 16.23$).

Most severe COVID-19 cases were reported in patients with comorbidities; COVID-19 was severe in 14 patients, moderate in 16 patients, and mild in 34 patients; while in patients without comorbidities, COVID-19 was severe in 6 patients, moderate in 10 patients, and mild in 40 patients. However, this difference was found to be statistically non-significant ($p = 0.102$).
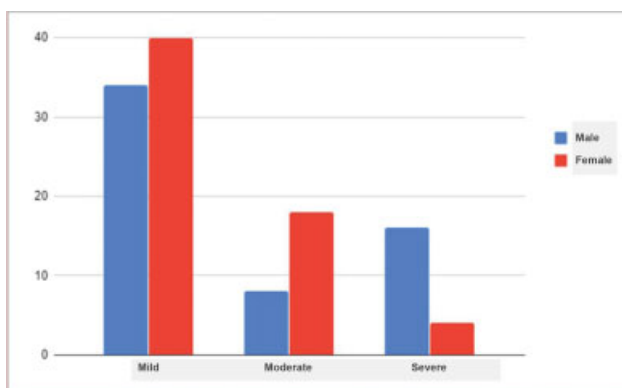
Fig. 1 Severity of COVID-19 between male and female patients.

However, when comparing COVID-19 severity in patients with multiple comorbidities with those with a single comorbidity, it was detected that multiple comorbidities were associated with a statically significantly higher incidence of severe disease than single comorbidities ($p < 0.0001$); the difference in the incidence of severe COVID-19 from patients without comorbidities was also statistically significantly ($X2 = 28.211$; $p < 0.0001$) (►**Table 1**).

The severity of COVID-19 in the medical staff was mild in 26 patients, moderate in 8 patients, and severe in 2 patients; while in nonmedical patients, 48 cases were mild, 18 cases were moderate, and 18 cases were severe, without significant difference between medical and nonmedical patients ($p = 0.09$).

The most frequently reported ENT manifestations were sore throat in 36 patients (30%), nasal congestion in 34 patients (28.3%), nasal obstruction in 32 patients (26.7%), sneezing in 32 patients (26.6%), headache in 30 patients (25%), olfactory and taste dysfunction in 30 patients (25%), runny nose or rhinorrhea in 24 patients (20%), upper respiratory tract infection (URTI) in 18 patients (15%), and tonsil enlargement in 12 patients (10%). When we revised the severity of COVID-19 disease in patients who had ENT symptoms, we found that 24 patients (20%) were mild cases, 10 patients (8.3%) were moderate cases, and 6 patients (5%) were severe cases, without a significant difference in COVID-19 severity between patients who had ENT manifestations and those who did not ($p = 0.8$) (►**Table 1**). ►**Fig. 2**.

When we revised the history of chronic ENT disease, we found that 40 patients had an ENT disease history (33.3%), and 80 patients did not have an ENT disease history (66.6%). No reported epistaxis, postnasal discharge, facial edema or
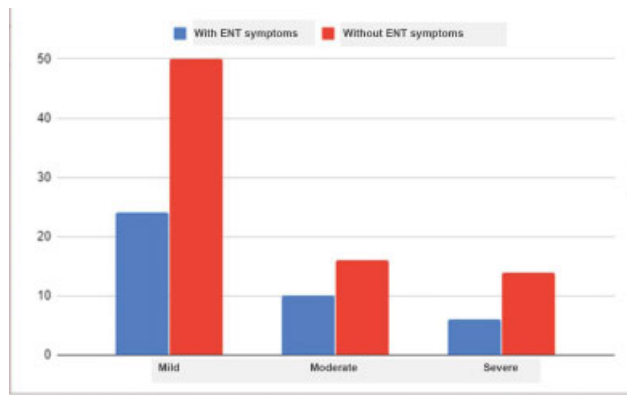
Fig. 2 Severity of COVID-19 between patients with ENT symptoms and patients without ENT symptoms.

tenderness, reduction of hearing, vertigo, hoarseness, or stridor.

The non-ENT manifestations in those patients were fever in 106 patients (88.3%), cough in 76 patients (63.3%), dyspnea in 54 patients (45%), asthenia/fatigue in 54 patients (45%), arthralgia/myalgia in 30 patients (25%), diarrhea in 28 patients (23.3%), expectoration in 18 patients (15%), chest pain in 10 patients (8.3%), nausea/vomiting in 12 patients (10%), hemoptysis in 6 patients (5%), acute respiratory failure (ARF) in 6 patients (5%), and constipation in 4 patients (3.3%).

All severe cases were admitted to the ICU (20 patients; 16.7%). Ten patients (2 females, 8 males) died (50% of the ICU patients and 8.3% of all the COVID-19 patients admitted to the hospital). A total of 60% of the patients who died had other comorbidities and were smokers. A total of 60% of the patients that died were within the age range between 50 and 55 years old, 20% were within the age range between 59 and 60 years old, and 20% were > 70 years old. None of the patients who died complained of anosmia, and only 10% of them suffered from sinusitis as an early manifestation.

Discussion

In December 2019, a novel coronavirus (CoV) epidemic produced by the severe acute respiratory syndrome coronavirus–2 (SARS-CoV-2) emerged from China.[9] On February 11, 2020, the WHO named the disease caused by this new virus as COVID-19. The widespread infectivity and distribution of COVID-19 make it an important pathogen with a limitless health threat.[10]

COVID-19 manifests with a wide-ranging clinical spectrum, ranging from no symptoms to septic shock and multiple organs dysfunctions.[11] Despite its rapid spread worldwide, the clinical characteristics of COVID-19 remain to a large extent imprecise.[9]

The nasal, nasopharyngeal and/or the oropharyngeal tissue are one of the main harbor sites of COVID-19 infection, being the main sites for collecting the sample for testing and a main source of transmission of infection. However, most published COVID-19 research focused on the manifestations and sequelae of the lower respiratory tract due to their life-threatening nature.

However, the literature on the ENT manifestations of COVID-19 is still scarce. Hence, it is worth studying the ENT manifestations of this novel virus and there is a demand to identify precisely the defining ENT epidemiological and clinical characteristics of COVID-19. Thus, in the present study, we studied, reported, and analyzed the different ENT manifestations in confirmed COVID19 patients and analyzed their relation to other manifestations and to the severity of COVID-19.

The results of the present study agree with previous reports[12,13] that fever (reported in 88.3% of the patients) and cough (reported in 63.3% of the patients) are the dominant symptoms of COVID-19. We reported gastrointestinal (GIT) symptoms; mainly diarrhea (23%), nausea and vomiting (10%,) and constipation (3%), which is in line with other studies.[13]

All the reported ENT manifestations in COVID-19 patients are nonspecific and, therefore, could be easily missed, and no emergency ENT symptoms, such as nosebleed, throat bleeding, or stridor were reported in COVID-19 cases.

In our study, 98 patients (81.6%) had at least 1 ENT manifestation. The most frequent reported ENT symptoms were: sore throat (30%), nasal congestion and nasal obstruction (28.3 and 26.7%, respectively), sneezing in 32 patients (26.6%), while headache, anosmia and taste affection had the same percentage (25%). Rhinorrhea was reported in 24 patients (20%), and tonsil enlargement in 12 patients (10%). Speth et al.[14] reported nasal obstruction in 49.5% of the patients, runny nose in 35%, and olfactory dysfunction in 61%.

In the present study, 40 patients (33.3%) had a history of chronic ENT diseases; 8 cases of OSA, 10 of allergic rhinitis, 14 of sinonasal polyps, and 8 of chronic sinusitis.

It is remarkable that 6.6% of the COVID-19 patients had OSA; although the direct association between OSA and COVID-19 has not been reported yet, untreated OSA patients suffer from chronic intermittent hypoxia that leads to hypertension, heart failure, cerebrovascular disease and obesity; those are risk factors for higher severity of COVID-19. Angiotensin converting enzyme 2 (ACE2) is the entry receptor of COVID-19;[15] in OSA patients, dysregulation of the renin angiotensin system occurs.[16] Therefore, we agree with a previous study[17] that we need to keep in mind the effect of disturbed sleep on the immune system and that we may protect OSA patients from COVID-19 if we treat them. In addition, we need to keep in mind that patients who recovered from severe COVID-19 cases may be under risk of OSA due to lung fibrosis.[18]

A total of 26.6% of our patients (32 cases) were suffering from allergic rhinitis and sinusitis with or without nasal polyps, which is similar to what has been reported by in the study by Speth et al.,[14] in which 36% of the patients were allergic. In a study from China,[19] asthma and respiratory allergy were not included as risk factors for severe COVID-19; many studies[20,21] tried to investigate this point and found that ACE2 expression is markedly decreased in the nasal and respiratory mucosa in allergic patients. COVID-19 uses ACE2 enzyme to enter the cell; so, to some extent, allergic patients

are protected from the severity of COVID-19. Actually, we did not report any severe cases among our allergic patients; all of them were mild and moderate cases.

The clinical presentation of COVID-19 might be confused with allergic rhinitis (AR); sudden and complete anosmia may be an early sign of COVID-19 infection, differentiating it from AR;[22] in our study, 80% of AR patients (8 out of 10) complained of sudden complete anosmia.

The mortality rate in ICU patients was of $\sim$ 50%, which is similar to that of Wang, in Wuhan, China (62.5%), and to that in Washington, USA (50%),[23] considering that the included patients were only patients who were admitted to hospitals. The fatality rate of all COVID-19 patients in our study was of 8.3%; this is quite similar to a Chinese metanalysis, which reported a fatality rate of 7%.[13] Another study in the USA reported a fatality rate of 21%;[24] this discrepancy can be attributed to difference in demographic characteristics, race and comorbidities between Egypt and other countries.

A total of 60% of the patients who died had other comorbidities (diabetes, hypertension, renal failure, cardiac), which is in line with Lui K. et al.,[25,26] who found that the fatality rate of patients with viral pneumonia increased when they had another comorbidity, a result similar to that of our study. The mortality of males in our study was higher than that of females (60% male), which is in line with a recent meta-analysis that showed that male sex is a risk factor for death from COVID-19;[27] we noticed that all males who died were heavy smokers (100% smokers) and had comorbidities. It is known that smoking is a risk factor for developing acute respiratory distress syndrome (ARDS),[28] but a recent meta-analysis showed that smoking doubles the mortality risk of COVID-19.[29]

The age of the patients who died ranged from 50 to 72 years old. The mortality of COVID-19 increases with age, since older patients have other comorbidities and may develop more severe complications than younger patients.[30]

None of the dead patients suffered from anosmia; olfactory dysfunction was detected in 25% of the included patients, with no significant difference between males and females (16 female and 14 male patients). In < 5% of the patients with olfactory dysfunction, COVID-19 was severe or critical. This may reflect no association between disease severity and olfactory dysfunction, but it may be due to more orientation to respiratory and critical manifestations in severe COVID-19 patient with missed asking about olfactory dysfunction. This may also be due to the fact that, in critical condition, mostly oxygen therapy and/or intubation are used. Our results were similar to those of other studies that stated that the prevalence of olfactory dysfunction in association with COVID-19 ranges from 19.4 to 85.6%.[31,32] Mao et al.[33] detected anosmia in 5.1% of their studied cases, and El-Anwar et al.[34] detected an incidence of 6%. Most COVID-19 studies did not mention olfactory dysfunction, particularly the early and primary reports, and most COVID-19 patients (66%) reported a complete recovery of their chemosensitive functions during the course of the disease.[35]

Olfactory dysfunctions in COVID-19 patients were sporadically mentioned in the literature, with a lack of the peer-reviewed literature to support a causal association between anosmia and COVID-19.[7] In addition, most studies on smell in COVID-19 patients did not entirely define the clinical manifestations of the patients. This reflects the importance of the present study.

Menni et al.[36] suggested that a combination of loss of smell and taste, fever, persistent cough, fatigue, and GIT symptoms is a predictive of COVID-19 positive testing. However, they did not study anosmia as a part of other manifestations. Vroegop et al.[37] recommend COVID-19 suspicion and initiating testing or self-isolation for patients with anosmia without nasal obstruction or runny nose.

Acute smell loss is 13.2 times more likely in COVID-19 patients than in normal individuals, and acute smell loss is 4.5 times more likely in COVID -19 patients than in than influenza patients.[38]

Therefore, if we select ENT manifestations to be added to the definition of suspected cases or to the covid-19 triage checklist, we will select sore throat and nasal congestion and/or obstruction, followed by olfactory dysfunction. Therefore, COVID-19 triage checklists need to be revised.

In the present study, we tried to overcome the limitations that are usually met during studies[34] on the novel COVID-19 by using a precise definition of the clinical manifestations during data collection, with complete documentation, using a universal questionnaire for all the patients, and by studying only confirmed COVID-19 cases based on RT-PCR testing and chest CT. To the best of our knowledge, this is the first study that reported all the ENT manifestations with a clear description and definition of the COVID-19 manifestation and that analyzed the relations between these manifestations and the severity of the disease. The limitation of the present study is missed asymptomatic or mild cases managed at home that were not included.

We hope that the present article will contribute to the understanding of the epidemiology of COVID-19, establishing a standard universal questionnaire for well-defined COVID-19 manifestations to make the COVID-19 data well defined, complete and homogenous, and guide infection control measures, while also delivering insights on the diagnostic topographies of the ENT manifestations. Otolaryngologists, physicians, patients, and the community should be mindful of the ENT manifestations of COVID-19 patients so as not to delay the diagnosis of COVID-19.

Conclusion

Fever and cough are the dominant symptoms of COVID-19, but ENT manifestations of COVID-19 are common and should be a part of the suspected clinical criteria for COVID-19, particularly if the nasal examination was nonsignificant. The most common symptoms are sore throat, nasal congestion and obstruction, headache, and, lastly, olfactory dysfunction. A universal questionnaire via well-defined COVID-19 manifestations is required to make the COVID-19 data accurately defined, homogenous and complete.

Conflict of Interests
The authors have no conflict of interests to declare.

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