Prevalence of Olfactory and Gustatory Dysfunctions Among Patients Infected with Novel Coronavirus Disease 2019 (COVID-19) Olfactory and Gustatory Dysfunctions in Coronavirus Disease 2019

Original Article

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ABSTRACT

Objectives: We performed a cross-sectional study to estimate the prevalence of Olfactory and Gustatory Dysfunctions (OGDs) among patients infected with novel Coronavirus Disease 2019 (COVID-19).

Background: COVID-19 was first identified in Wuhan, Hubei province, China, on December 31, 2019. The identified symptoms of COVID-19 are fever, dry cough, sore throat, dyspnea, fatigue, myalgia, and headache. Olfactory and gustatory dysfunctions are emerging as a new symptom. They may occur in many situations related to nerve damage, autoimmune disease, malignancy, radiotherapy, inflammation, hormone imbalance, psychologic problems, ageing, etc…

Patients and Methods: The study enrolled 200 patients diagnosed as having COVID-19 infection confirmed by PCR.

Results: Age ranged from 21 to 60 years with mean 32.41 years. Fifty nine percent of the studied patients aged 28 years and more, 42.5% of our patients were males and 57.5% of them were females. Our patients had positive PCR for COVID-19. Lymphopenia was present in 70.5% of them. Olfactory and gustatory impairment were prevailed in 79% of the patients. There is statistically non-significant association between presence of olfactory and gustatory impairment and all of gender, age group, lymphopenia or presence of local or systemic diseases. Females, aged from <28 years, lymphopenia, and systemic diseases non-significantly increased risk.

Relation between patient's results and types of graft used showed no statistically significant differences between them.

Conclusion: Olfactory and gustatory dysfunction are common in patients with COVID-19 and may represent early symptoms in the clinical course of infection.

Key Words: Coronavirus Disease, Gustatory dysfunctions, Olfactory.

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INTRODUCTION

Coronaviruses are important human and animal pathogens. At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. It rapidly spread, resulting in an epidemic throughout China, followed by a global pandemic. In February 2020, the World Health Organization designated the disease COVID-19, which stands for coronavirus disease 2019. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); previously, it was referred to as 2019-nCoV.[1]

The spread of the COVID-19 infection in Europe has highlighted a new atypical presentation of the disease: patients with olfactory and gustatory dysfunctions. Many patients infected by SARS-CoV-2 presented with severe olfactory and gustatory dysfunctions without rhinorrhea or nasal obstruction. At baseline, no COVID-19 was suspected in some of these patients, because they had no fever, cough, or other systemic complaints.[2]

The advent of the global SARS-CoV-2 coronavirus pandemic has prompted debate about whether olfactory dysfunction should be considered a symptom of infection. Media reporting of alleged dozens of cases of anosmia, in the absence of other nasal or respiratory symptoms in patients who are positive for COVID-19, is not an acceptable level of evidence in the scientific literature.[3]

By analysis of 114 patients confirmed with COVID-19 in France, it was confirmed that OD was seen in 47% of cases, with taste alteration in 85%. OD was the third symptom in 38% of cases. OD developed 4.4 days after the onset of infection.[4]

Gustatory dysfunctions are taste disturbances varying between hypogeusia, dysgeusia, phantogeusia, and ageusia. They may occur in many situations related to nerve

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damage, autoimmune disease, malignancy, radiotherapy, inflammation, hormone imbalance, psychologic problems, ageing, etc. Taste loss was also reported often to occur in viral upper respiratory infections and following an influenza-like illness. It is noted the association of disturbances in smell and taste with COVID-19.[5]

In a survey done on positive and mild symptomatic SARSCoV-2 outpatients in Italy it was found that 64.4% had some degree of taste or smell alterations. The timing of the onset of this symptom was analyzed and it was found that 11.9% had it before other symptoms, 22.8% had along with other symptoms, 26.7% had afterwards, and 3% had it as their only symptom. Women (72.4%) presented more frequently with an altered sense of smell or taste than men (55.7%).[6]

Olfactory and Gustatory dysfunction was seen in Indian Population with COVID-19 disease in 28 (18.41%) and 20 (13.15%). Dysgeusia was noticed in 20/152 patients (13.15%). Recovery in olfactory dysfunction and Dysgeusia was complete in all patients. Olfactory and gustatory dysfunctions are significant part of clinical spectrum of COVID-19 disease In Indian Population.[7]

The aim of this present study is to estimate the prevalence of olfactory and gustatory dysfunctions (OGDs) among patients infected with novel coronavirus disease 2019 (COVID-19).

PATIENTS AND METHODS:

A cross-sectional study was carried out on 200 patients of age group between 20 and 60 years with test confirmed COVID-19 status during a 2 years period.

Inclusion criteria:

Patients with test confirmed COVID-19 status based on typical history and clinical features in patients attending Military Quarantine Hospital of Alexandria.

Exclusion criteria:

• Patients with Severe symptoms (SARI/Patient who need mechanical ventilation).

• Pregnant women.

• Patients with dementia (who cannot report functional symptoms).

• Patients with previous long standing history of nasal obstruction, nasal discharge and nasal surgeries which might confound the results of olfactory assessment.

• Head trauma.

• Other potential causes include neurodegenerative diseases, structural brain disease, toxic chemical exposure, metabolic diseases and side effects of medication or drugs.

• Patients who refused to give consent.

Methods:

Each patient included in the study was subjected to:

I. Epidemiological history.

II. Clinical manifestations; fever and/or respiratory symptoms, with special reference to Olfactory and Gustatory symptoms.

III. Laboratory investigations; real-time fluorescence (RT-PCR), SARS-CoV-2 specific IgM and IgG and olfactory test. Coronavirus disease 2019 was diagnosed by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) of pooled nasopharyngeal and throat swab specimens targeting the E-gene of SARS-CoV-2.

IV. Smell identification test. The patient is informed that we are going to test the sense of smell. The patient places an index finger over one nostril to block it (e.g., right index finger over right nostril).He or she then closes the eyes. Then the patient is instructed to sniff repetitively and to tell the examiner when an odor is detected. The test odor is placed within 30 cm or less of the nose. Test odors are non irritating substances like vanilla, lemon, freshly ground coffee and tobacco.

Statistical analysis:

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 20. Quantitative variables were described using their means and standard deviations. Categorical variables were described using their absolute frequencies and were compared using Chi square test. Kolmogor¬ov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were used to verify assumptions for use in parametric tests. The levelstatistical significance was set at 5% ($P<0.05$).

RESULTS:

Age ranged from 21 to 60 years with mean 32.41 years. Fifty nine percent of the studied patients aged 28 years and more. About 43% of them were males (Table 1).

All the patients had positive PCR for COVID-19. Lymphopenia present in 70.5% of them (Figure 1).

Regarding present history, all patients had no local diseases and 15.5% had systemic disease (7 (3.5%) were diabetic, 6 (3%) had comorbid diabetes and cardiac disease,

13 (6.5%) had comorbid diabetes and hypertension while 5 (2.5%) patients had rheumatoid arthritis) (Figure 2).

Olfactory and gustatory impairment prevailed in 79% of the studied patients (Figure 3).

There is statistically non-significant association between presence of olfactory and gustatory impairment and all of gender, age group, lymphopenia, presence of local or systemic diseases. Females, aged from <28 years, lymphopenia, and systemic diseases non-significantly increased risk by 1.02, 1.99, 1.09 and 1.13 folds respectively (Table 2).

Table (1): Distribution of the studied patients according to demographic data

	N=200	%
Age (year):		
Mean ± SD	32.41 ± 10.371	
Range	21 – 60	
<28 years	82	41
≥28 years	118	59
Gender:		
Male	85	42.5
Female	115	57.5

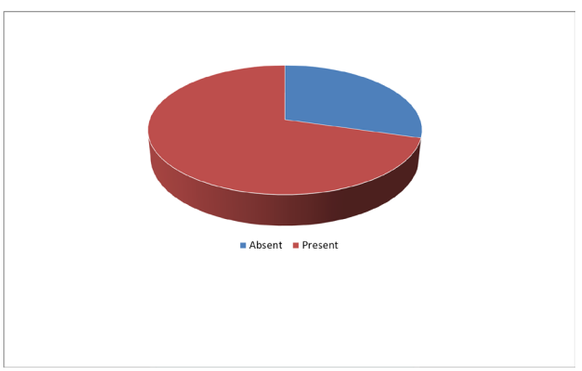

Fig. 1: Pie chart showing distribution of the studied patients according to lymphopenia.

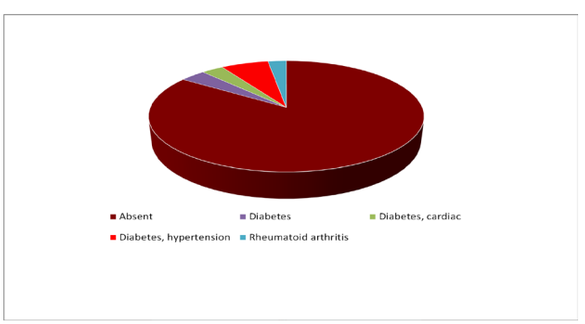

Fig. 2: Pie chart showing distribution of the studied patients according to presence of systemic disease.

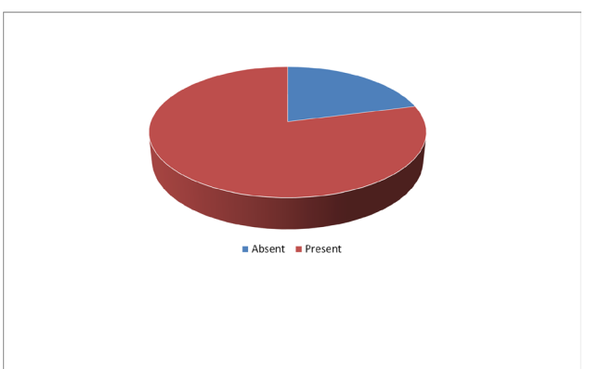

Fig. 3: Pie chart showing distribution of the studied patients according to presence of olfactory and gustatory loss.

Table (2): Relation between presence of olfactory and gustatory impairment and the studied risk factors

Parameter	Olfactory impairment		Test		COR (95% CI)
	Present N=158 (%)	Absent N=42 (%)	χ^2	P	
Gender:					
Male	67 (42.4)	18 (42.9)	0.003	0.958	1.02 (0.51 – 2.03)
Female	91 (57.6)	24 (57.1)			
Age:					
<28 years	70 (44.3)	12 (28.6)	3.395	0.065	1.99 (0.95 – 4.17)
≥ 28 years	88 (55.7)	30 (71.4)			
Lymphopenia:					
Absent	46 (29.1)	13 (31.0)	0.054	0.816	1.09 (0.52 – 2.28)
Present	112 (70.9)	29 (69.0)			
Local disease:					
Absent	158 (100)	42 (100)	NA		
Systemic disease:					
Absent	133 (84.2)	36 (85.7)	0.06	0.807	1.13 (0.43 – 2.96)
Present	25 (15.8)	6 (14.3)			

χ^2 Chi square test COR crude odds ratio CI Confidence interval

DISCUSSION

The world has recently been afflicted by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19). The 2019 novel coronavirus (COVID-19) was first identified in Wuhan, Hubei province, China, on December 31, 2019, in association with a severe human respiratory disease.[8] Gengler *et al*.[9] have postulated that the sinonasal tract may play a significant role in the pathogenesis of this viral infection. Human-to-human transmission is characterized by a troubling exponential rate, which has led to steep curves of onset in many areas.

Clinical presentation of COVID-19 patients vary from asymptomatic to common cold like symptoms i.e. nasal discharge, fever, nasal congestion to severe respiratory difficulty requiring assisted mechanical ventilation support.[10]

Concurrent with the COVID-19 pandemic, Bagheri *et al*.[11] have reported a recent increase in patients presenting with anosmia, with Mao *et al*.[12] initially reporting on this finding in February 2020. Eliezer *et al*.[13] have described new-onset olfactory or gustatory dysfunction in conjunction with other well-established symptoms of COVID-19 infection, as well as in patients with known positive diagnosis of COVID-19 by laboratory testing.

Due to increasing awareness of olfactory or gustatory dysfunction as potential early symptoms of COVID-19 infection, the Centers for Disease Control and Prevention (CDC)[14] added ‘‘new loss of taste or smell’’ to its list of symptoms that may appear 2 to 14 days after exposure to COVID-19.

In an effort to facilitate confidential reporting of olfactory dysfunction associated with COVID-19, the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS)[15] released the COVID-19 Anosmia Reporting Tool for Clinicians. Anosmia was present in 73% of cases prior to laboratory diagnosis of COVID-19 and was the presenting symptom in 26.6%. Hopkins *et al*.[16] have similarly reported new-onset anosmia in the absence of any other symptoms associated with COVID-19.

Although Lovato and de Filippis[17] examined the upper airway symptoms associated with COVID-19, it was limited by the fact that it considered only hospitalized patients and did not include any studies that addressed olfactory or gustatory disturbances.

Given the scale of the current pandemic and the uncertain pathogenesis of COVID-19, a thorough understanding of the related symptomatology is critical to facilitate early diagnosis, treatment, and appropriate vigilance for viral spread. In this context, we performed a cross-sectional study to estimate the prevalence of Olfactory and Gustatory Dysfunctions (OGDs) among patients infected with novel Coronavirus Disease 2019 (COVID-19).

The study enrolled 200 patients diagnosed as having COVID-19 infection confirmed by PCR. Age ranged from 21 to 60 years with mean 32.41 years. Fifty nine percent of the studied patients aged 28 years and more, 42.5% of our patients were males and 57.5% of them were females. Benezit *et al*.[18] studied 68 patients with COVID-19 and concluded that 45% had OD. But, Yadav *et al*.[7] evaluated prevalence of Olfactory and Gustatory dysfunction in 152 COVID-19 patients with 78 (51.3%) male patients and 74 (48.7%) female patients. Age of the study group was in the range of 14–77 years, with mean 43.03 ± 16.10 years.

Our patients had positive PCR for COVID-19. Lymphopenia was present in 70.5% of them. Saniasiaya *et al*.[19] estimated the overall pooled prevalence of olfactory dysfunction in COVID-19 patients. They confirmed COVID-19 in 97.5% of patients by using the RT-PCR method.

Regarding present history, all patients had no local diseases and 15.5% had systemic disease; 7 (3.5%) were diabetic, 6 (3%) had comorbid diabetes and cardiac disease, 13 (6.5%) had comorbid diabetes and hypertension while 5 (2.5%) patients had rheumatoid arthritis. Lechien *et al*.[2] found that the most prevalent comorbidities of patients were allergic rhinitis, asthma, high blood pressure, and hypothyroidism.

Olfactory and gustatory impairment were prevailed in 79% of the studied patients. Chung *et al*.[20] quantitated olfactory function in COVID-19 patients and reported olfactory symptoms in 12 of 18 (67%) COVID-19 patients. Kaye *et al*.[21] observed olfactory dysfunction as the first symptom in 11.8% and 26.6% respectively.

Vaira *et al*.[22] study on 72 subjects reported olfactory dysfunction in 61.1% (44/72) of cases. Yan *et al*.[23] reported olfactory dysfunction in 68% in the study group (59 subjects). Luers *et al*.[24] reported olfactory dysfunction in 74% (53/72) of patients. Giacomelli *et al*.[25] reported a study on 59 patients, 20 (33.9%) reported at least 1 taste or olfactory disorder and 11 (18.6%) both.

In our study, there is statistically non-significant association between presence of olfactory and gustatory impairment and all of gender, age group, lymphopenia or presence of local or systemic diseases. Females, aged from <28 years, lymphopenia, and systemic diseases non-significantly increased risk by 1.02, 1.99, 1.09 and 1.13 folds respectively.

Chung *et al*.[20] found that age, gender distribution, and initial presenting symptoms of COVID-19 patients with (n = 12) and without (n = 6) olfactory symptoms were not significantly different. Lechien *et al*.[2] observed that olfactory dysfunction was not significantly associated with Nasal discharge or nasal obstruction. There was no significant association between comorbidities and the development of olfactory or gustatory dysfunctions. Olfactory dysfunction was not significantly associated with rhinorrhea or nasal obstruction. There was a significant positive association between olfactory and gustatory dysfunctions. Similar results were found for gustatory dysfunction. Klopfenstein *et al*.[4] observed diarrhoea in > 50% of patients.

Some studies demonstrated a significant prevalence of gustatory dysfunction among patients with COVID-19. Kaye *et al*.[21] did not differentiate between olfactory and gustatory dysfunction in the COVID-19 Anosmia Reporting Tool, instead considering gustatory dysfunction a sequela of olfactory dysfunction.

Vaira *et al*.[22] attempted to capture gustatory dysfunction in a reported measure of combined ‘‘chemosensory dysfunction’’. Lechien *et al*.[2] used a validated measure to assess for gustatory dysfunction with the taste component of the NHANES.

It remains unclear as to whether gustatory dysfunction represents a distinct clinical manifestation of the virus or if this occurs secondary to olfactory dysfunction. Although olfactory loss commonly presents in the setting of upper respiratory infections, the pathogenesis responsible for COVID-19-mediated olfactory or gustatory disturbances has not yet been definitively identified. One potential mechanism is that COVID-19 may specifically target cells in the sinonasal tract, including the olfactory epithelium.[26]

The virus appears to target the angiotensin-converting enzyme 2 (ACE2) receptor, perhaps the highest levels of which are expressed in goblet and ciliated cells in the nasal epithelium, as well as in the lung and by respiratory tract epithelial cells.[27]

Dedicated study of olfactory epithelium cell types has demonstrated that while ACE2 is not expressed directly by olfactory sensory or olfactory bulb neurons,

ACE2 can be found on sustentacular and basal cells.[28] Furthermore, while frequently recognized as respiratory pathogens, coronaviruses are known to be potentially neuroinvasive in humans. These viruses can invade the central nervous system through the olfactory bulb following intranasal infection. This fact may explain why a relatively high proportion of COVID-19 patients appear to have neurological manifestations.[29]

In a cohort of patients with COVID-19 from 3 large hospitals in China, for example, Mao *et al*.[12] demonstrated that 36.4% had neurological symptoms, including ''peripheral nervous system complications'' such as taste and smell impairment. Alternative hypotheses to explain olfactory and gustatory impairment in COVID-19, including the role of increased exposure to chemicals and disinfectants, have also been proposed.

There has also been increased focus on the temporal relationship between COVID-19-mediated olfactory dysfunction and other sinonasal symptoms, including rhinorrhea and nasal congestion. Xydakis *et al*.[30] suggested that these other symptoms may be relatively less common overall.

In a preliminary review of the data obtained through the COVID-19 Anosmia Reporting Tool for Clinicians from the AAO-HNS, Kaye *et al*.[21] demonstrated that only 25% of patients reported nasal congestion prior to experiencing anosmia, while only 18% reported rhinorrhea prior to anosmia.

Beltran-Corbellini *et al*.[31] demonstrated that only 12.9% of COVID-19 patients experiencing olfactory or gustatory dysfunction also reported nasal obstruction. Similarly, Lechien *et al*.[2] found that in COVID-19 patients without nasal obstruction or rhinorrhea, 79.7% still reported anosmia.

Chung *et al*.[20] proved that olfactory dysfunction is common in COVID-19 and may be the only symptom. Coronavirus disease 2019-related OD can be severe and prolonged. Tong *et al*.[32] determined the pooled global prevalence of olfactory and gustatory dysfunction in patients with the 2019 novel coronavirus (COVID-19). They concluded that olfactory and gustatory dysfunction are common symptoms in patients with COVID-19 and may represent early symptoms in the clinical course of infection.

Hajikhani *et al*.[33] established prevalence rates for loss of olfaction and gustation in COVID-19 positive patients. The estimated rate of taste disorder in patients with COVID-19 was 49.0%. The estimated rate of olfactory disorder in patients with COVID-19 was 61.0%. They demonstrated high rates of taste (49.0%) and smell (61.0%) disorders in patients with confirmed COVID-19. Therefore, loss of olfactory and loss of gustation should routinely be considered in the setting of COVID-19 infection. Luers *et al*.[24] reported olfactory and gustatory dysfunction in two-thirds of European patients with confirmed COVID-19, indicating the significance of these symptoms in early diagnostics. Also, Yadav *et al*.[7] concluded that olfactory and gustatory dysfunctions are significant part of clinical spectrum of COVID-19 disease.

Perhaps more significantly, it appears that for many patients with COVID-19, olfactory dysfunction may be the initial presenting symptom. In the AAO-HNS analysis, this was the case in 26.6% of patients; in 40%, the presence of olfactory dysfunction contributed to the recommendation for laboratory COVID-19 testing.[21] Similarly, Beltran-Corbellini *et al*.[31] reported that olfactory or gustatory dysfunction was the initial symptom in 35.5% of COVID-19 patients, with acute onset in 70.9% of COVID-19 patients experiencing olfactory or gustatory dysfunction included in their study. This phenomenon is supported by Gane *et al*.[34] describing onset of anosmia in the absence of other symptoms or early in the clinical course, typically within days of illness onset.

Taken together, this evidence has significant implications. First, it lends credence to the growing belief that olfactory dysfunction in the absence of other sinonasal symptoms may be indicative of COVID-19 infection. It also highlights the potential utility of screening patients based on the presence of olfactory dysfunction, as inferred by several authors.[30]

Tong *et al*.[32] suggested that olfactory dysfunction should prompt a high level of clinical suspicion for COVID-19, along with recommendations for self-isolation, confirmatory testing, or other COVID-19-related public health measures.

Last, the fact that other sinonasal symptoms appear to be less common argues against the possibility that COVID-19-mediated olfactory loss is related to nasal inflammation, mucosal edema, and airflow limitation, as is the case with other upper respiratory infections.[26]

Zhou *et al*.[35] identified the role of Angiotensin converting enzyme 2 (ACE2) in the pathogenesis of SARS-CoV-2. Brann *et al*.[28] studied and explained the role of 2 genes: ACE2 and TMPRSS in olfactory epithelial support cells, stem cells, and nasal respiratory epithelium explaining the possible mechanism of anosmia in COVID-19 patients. These 2 genes play a potential role in transport of SARS-CoV-2 into the cell.

Cao *et al*.[36] reported expression quantitative trait loci (eQTLs) variants of the ACE2 gene which can be a cause for ACE2 polymorphisms and ACE2 expression levels between Asian and European populations. It can be one of possible aetiology in variety of expression in olfactory dysfunction in different countries or races. However, its exact aetiology is a matter of further detailed research to confirm ACE 2 receptors role.

CONCLUSION

Olfactory and gustatory dysfunction are common in patients with COVID-19 and may represent early symptoms in the clinical course of infection. Otolaryngologists and other medical specialty colleagues need to be extra vigilant about the symptoms of olfactory/gustatory dysfunction to diagnose COVID-19 patients at an early stage.

CONFLICT OF INTEREST

There are no conflicts of interest.

ABBREVIATIONS:

AAO-HNS: American Academy of Otolaryngology–Head and Neck Surgery

ACE2: Angiotensin-converting enzyme 2

CDC: Centers for Disease Control and Prevention

COVID-19: Causes coronavirus disease 2019

eQTLs: Expression quantitative trait loci

NHANES: National Health and Nutrition Examination Survey

OGDs: Olfactory and gustatory dysfunctions

RT-PCR: Real-time reverse-transcriptase polymerase chain reaction

SARI: Severe acute respiratory infections

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

TMPRSS: Transmembrane protease, serine 2

WHO: World Health Organization

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