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ORIGINAL ARTICLE:

Prevalence of Olfactory and Gustatory Dysfunctions among COVID-19 Patients

Mohamed Adel Mobasher[*1] , Ehsan hindawy[1], Mohammad Waheed El-Anwar [1],Abobakr Abdelmoghny [1]
[1]Otorhinolaryngology-Head and Neck Surgery, Faculty of Medicine, Zagazig University, Egypt.

Corresponding author:
Mohamed Adel Mobasher

Email :
mohamedmobasher@hotmail.com

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ABSTRACT

Background: COVID-19 was identified at the beginning in Wuhan, Hubei province, China, on December 31, 2019. The established symptoms of Corona virus Disease are fever, sore throat, dry cough, dyspnea, fatigue, myalgia, and headache. Olfactory and gustatory dysfunctions are prominent as a new symptom. They may occur in many conditions related to nerve damage, autoimmune disease, cancer, radiotherapy, inflammation, hormone imbalance, psychologic problems, ageing. We aimed to evaluate prevalence of the olfactory and gustatory dysfunctions (OGDs) between patients infected with the new Corona virus Disease 2019 (COVID-19). **Methods:** This study is a cross-sectional and it enrolled patients diagnosed as having COVID-19 disease confirmed by PCR for whom history taking, clinical examination and smell identification test were performed. **Results:** Within included 200 patients with age ranged from 21 to 60 years (mean=f 32.41), 59% of the studied patients aged 28 years and more, 42.5% of our patients were males and 57.5% of them were females. Lymphopenia was present in 70.5% of them. Olfactory and gustatory impairment were prevailed in 79% of the patients. The association between presence of olfactory and gustatory impairment and all of gender, age group, lymphopenia or presence of local or systemic diseases is statistically non-significant. Females, aged <28 years, lymphopenia and systemic diseases non-significantly increased risk.

Conclusion: Olfactory and gustatory dysfunctions are common in COVID-19 patients and may be considered as early symptoms in the clinical course of the disease.

Keywords: Corona Virus Disease, Covid-19, Olfactory and Gustatory dysfunctions, Smell, PCR.

INTRODUCTION

Corona viruses are important human and animal pathogens. By the end of 2019, the novel corona virus in Wuhan had been identified as the cause of a cluster of pneumonia cases with a rapid spread, leading to an epidemic across China, followed by a global pandemic. In February 2020, the World Health Organization (WHO) identified COVID-19, which represents the 2019 corona virus disease. The virus that causes COVID-19 has been classified as severe acute respiratory syndrome virus 2 (SARS-CoV-2); previously, it was referred to as 2019-nCoV [1].

COVID-19 has spread in Europe with a new atypical presentation with olfactory dysfunction (OD) and gustatory dysfunction (GD) even in many patients without nasal obstruction or rhinorrhea. Initially, the presence of COVID-19 was not

considered in some of these patients as they did not have fever, cough, and or other systemic symptoms [2].

The advent of the global COVID-19 pandemic has prompted a debate regarding consideration of the olfactory dysfunction as COVID-19 symptom. Media reports of dozens of alleged cases of anosmia, in the absence of other nasal or respiratory symptoms in patients who have tested positive for COVID-19, are unacceptable level of evidence in the scientific literatures [3].

While previous literature recommenced to suggest COVID-19 infection in patients had anosmia without finding in nasal cavity [4]. By analyzing patients confirmed to have COVID-19 in France, it was confirmed that OD was seen in 47% of cases with a change in taste in 85%. OD was the third symptom in 38% of cases. It was noted that OD appeared 4.4 days after the beginning of infection [5].

Gustatory dysfunctions are taste disturbances that range from hypogeusia, dysgeusia, phantogeusia and ageusia. It may occur in many situations related to inflammation, autoimmune disease, nerve damage, malignancy, radiotherapy, hormone imbalance, psychologic problems, ageing, etc. Loss of taste has also been reported more often in viral upper respiratory infections and after influenza-like illness. It is noted that disturbances in the sense of smell and taste are associated with COVID-19 [6].

In a survey of SARSCoV-2 outpatients with positive and mild symptoms in Italy, 64.4% were found to have some degree of taste or smell changes. The timing of the onset of these symptoms was analyzed and it was found that 11.9% experienced them before the other symptoms, 22.8% experienced other symptoms, 26.7% experienced them after and 3% were their only symptoms. Women (72.4%) frequently showed a change in their sense of smell or taste compared to men (55.7%) [7].

Olfactory and Gustatory dysfunction was seen in Indian population with COVID-19 disease in 28 (18.41%) and 20 (13.15%). Dysgeusia was observed in 20/152 patients (13.15%). Recovery of olfactory dysfunction and Dysgeusia was absolute in all patients. Olfactory and gustatory dysfunctions are important part of clinical spectrum of COVID-19 disease in Indian population [8]. Literature on smell and taste affection in COVID-19 patients are growing [9]. Therefore, the aim of this study was to evaluate the prevalence of olfactory and gustatory dysfunctions (OGDs) between patients infected with the new corona virus disease 2019 (COVID-19).

METHODS

A cross-sectional study was carried out on patients confirmed positive by PCR test for COVID-19 during a 2 years period. Cases with severe symptoms (who require mechanical ventilation), patients <18 years, pregnant women, dementia cases (who unable to report functional symptoms), cases with pre COVID-19 history of allergic rhinitis, nasal polypi, chronic rhinosinusitis and or smell disorders, head trauma and other potential reasons include neurodegenerative diseases, radiotherapy, structural brain disease, toxic chemical exposure, metabolic diseases and side effects of medication or drugs were excluded.

Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Each patient included in the study was subjected history taking, clinical examination and smell identification test.

For smell identification test, the patient was informed about the test. The patient placed the index finger over one nostril to close it (e.g., left index finger over left nostril) and then the eyes closed then the patient was instructed to sniff repeatedly and to tell the examiner when an odor was detected. The test scent was placed 30 cm or less from the nose. The used test odors were non irritating substances like vanilla, lemon, freshly ground coffee and tobacco.

Statistical analysis: The information was gathered; tabulated and analyzed. Data analysis was carried out using the SPSS (Statistical Package for the Social Sciences) version 20. Quantitative variables were described by their means and standard deviations. Categorical variables were described by their absolute frequencies and compared using Chi square test. Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were used to verify assumptions for use in

parametric tests. The statistical significance level was set at 5% (P< 0.05).

RESULTS

The study included 200 COVID-19 confirmed patients with an age range from 21 to 60 years (mean+ 32.41). Fifty nine percent of the studied patients aged 28 years and more and 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 sinonasal diseases and 15.5% had systemic disease 7 (3.5%) were diabetic, 6 (3%) had co-morbid diabetes and cardiac disease, 13 (6.5%) had co-morbid 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 non-significant statistical association between presence of olfactory and gustatory impairment and all of gender, age, lymphopenia and presence of local or systemic diseases. Females, age <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 Range **<28 years** **≥28 years**	 32.41 ± 10.371 21 – 60 82 118	 41 59
Gender: Male Female	 85 115	 42.5 57.5

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

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

Systemic disease: Absent Present	 133 (84.2) 25 (15.8)	 36 (85.7) 6 (14.3)	0.06	0.807	1.13 (0.43 – 2.96)

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

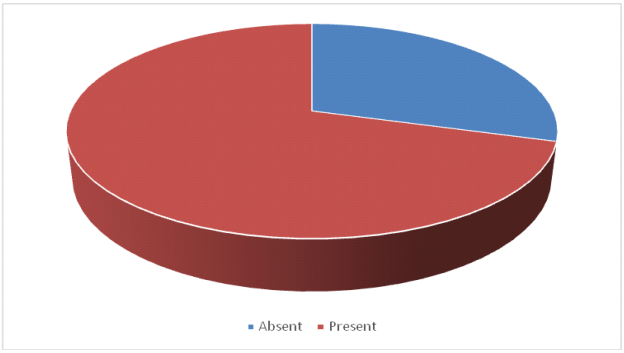

Figure (1): Pie chart showing distribution of the studied patients according to lymphopenia

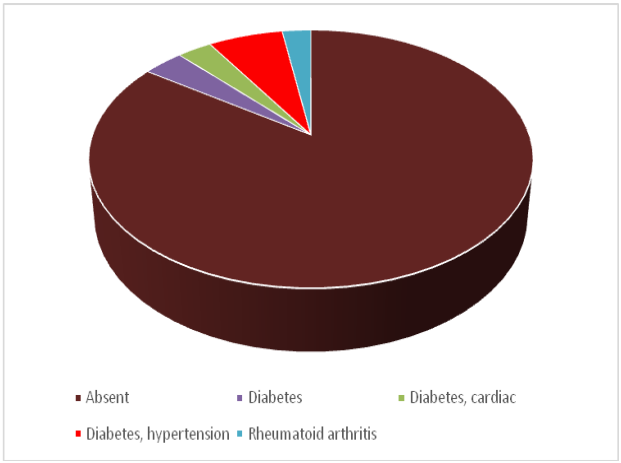

Figure (2): Pie chart showing distribution of the studied patients according to presence of systemic disease

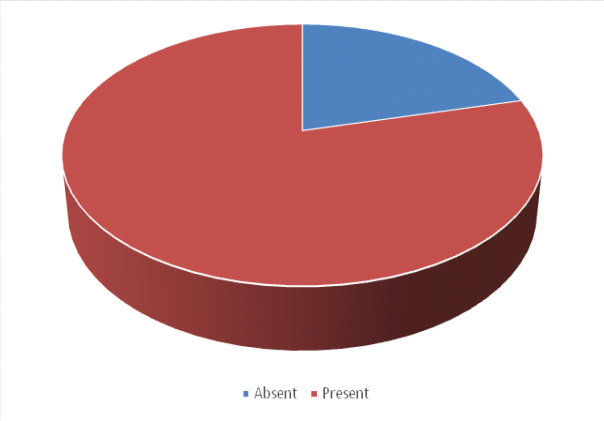

Figure (3): Pie chart showing distribution of the studied patients according to presence of olfactory and gustatory loss

DISCUSSION

The world has recently contracted severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) which causes COVID-19 that was first discovered in Wuhan, Hubei province, China, on December 31, 2019 [10]. Gengler et al [**11]** had supposed that the sinonasal tract may have an important role in the pathology of this viral infection. Human to human transmission is characterized by a disturbing exponential rate that has resulted in steep curves of attack in almost all countries. Presentation of COVID-19 alters from asymptomatic to influenza like symptoms i.e. runny nose, fever, nasal congestion to severe respiratory difficulty indicating mechanical ventilatory support [12].

Concurrent with the COVID-19 pandemic, Bagheri et al [13] have documented a new increment in patients come with anosmia, with Mao et al [14], initially reporting on this finding in February 2020. Eliezer et al [15], have described new-onset olfactory or gustatory dysfunctions in coincidence with other well-established COVID-19 symptoms and in patients with known positive COVID-19 PCR test. As a result of increasing recognition of olfactory or gustatory dysfunction as possible early manifestations of COVID-19, the Centers for Disease Control and Prevention (CDC) [16], has added ‘‘new loss of taste or smell’’ to its list of symptoms that may occur 2 to 14 days after exposure to COVID-19.

In an attempt to assist confidential reporting of olfactory dysfunctions related to COVID-19, the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) [17], has 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 manifestation in 26.6%. Hopkins et al [18] had similarly reported new-onset anosmia without any other COVID-19 related manifestations. Although Lovato and de Filippis (19) examined the upper airway COVID-19 associated symptoms, it was limited by they involved only hospitalized patients and did not involve any studies that dealt with olfactory or gustatory disturbances. In another study, sudden anosmia appeared in 97.4% with absence of nasal manifestations in Covid-19 patients making these patients ask medical advice from the otolaryngologists as the first-line physicians [4].

Within the current COVID-19 pandemic and its unsure pathogenesis, a comprehensive understanding of their enclosed manifestation is crucial to help early diagnosis, management, and proper attention for viral spread. In this context, we performed a cross-sectional study to evaluate the prevalence of Olfactory and Gustatory Dysfunctions (OGDs) between patients infected with novel Corona Virus Disease 2019 (COVID-19).

The mean age of the patients in the current study was 32.41 years, 42.5% of our patients were males

and 57.5% of them were females. But, Yadav et al [8] evaluated prevalence of Olfactory and Gustatory dysfunction in 152 COVID-19 patients with 43 years mean age (51.3% males and 48.7% females). Our patients had positive PCR for COVID-19. Lymphopenia was present in 70.5% of them. Saniasiaya et al [21], estimated the combined total prevalence of olfactory dysfunction in COVID-19 patients. They confirmed COVID-19 in 97.5% of patients by using the RT-PCR method.

In the current study, all patients had no local diseases and 15.5% had systemic disease; 3.5% diabetic, 3% diabetes and cardiac disease, 6.5% diabetes and hypertension and 2.5% rheumatoid arthritis. Lechien et al [2] found that the most common co morbidities with COVID-19 were allergic rhinitis, hypertension, asthma and hypothyroidism.

In the present study, olfactory and gustatory impairment were prevailed in 79% of the studied patients while it was 45% in the study of Benezit et al. 20 patients (67%) in the study of Chung et al [22]. While, Kaye et al study [23] reported OD as the first symptom in 11.8% and 26.6% respectively. Vaira et al [24] observed OD in 61.1% (44/72) of cases. Yan et al [25] reported OD in 68% in the study group. Luers et al [26] observed OD in 74% (53/72) of patients. Giacomelli et al [27] reported 33.9% reported at least one taste or olfactory disorder and 18.6% had both. In our study, there is non-significant statistical association between presence of olfactory and gustatory impairment and all of gender, age, lymphopenia or presence of local or systemic diseases. Females, age <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 [22] 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 OD was not significantly associated with nasal discharge or nasal obstruction.

In this present study, there was no significant association between comorbidities and the presence of olfactory or gustatory dysfunctions. OD was not significantly associated with rhinorrhea or nasal obstruction. There was a significant positive association between olfactory and gustatory dysfunctions**.** same results were found for gustatory dysfunction. Klopfenstein et al [5], reported diarrhea in > 50% of patients.

Some studies demonstrated a high prevalence of gustatory dysfunction among patients with COVID-19. Kaye et al [23], did not differentiate between olfactory and gustatory dysfunction in the COVID-19 Anosmia Reporting Tool, instead considered the gustatory dysfunction to be a consequence of olfactory dysfunction. Vaira et al [24], tried to detected gustatory dysfunctions in a reported measure of combined ‘‘chemosensory dysfunction’’. While Lechien et al [2] used a validated measure to evaluate for gustatory dysfunctions with the taste component of the NHANES.

It remains unclear whether gustatory dysfunctions represent a clear clinical manifestation of the virus or whether they occur secondary to olfactory dysfunctions. Although olfactory loss commonly seen in upper respiratory infections, the pathogenesis responsible for COVID-19-mediated olfactory or gustatory disturbances has not yet been definitively determined. One possible mechanism is that COVID-19 may specifically target cells in the sinonasal tract, including the olfactory epithelium [28]. The virus appears to target the angiotensin-converting enzyme 2 (ACE2) receptor, its highest levels are probably expressed in goblet and ciliated cells in the nasal epithelium, also in the lung and respiratory tract epithelial cells [29].

A study dedicated to olfactory epithelial cell types showed that while ACE2 is not directly expressed by olfactory sensory or olfactory bulb neurons, ACE2 can be found in sustentacular and basal cells [30]. Furthermore, while they are often recognized as respiratory pathogens, it is known that corona viruses are potentially neuro invasive in humans. These viruses can invade the central nervous system through the olfactory bulb after infection in the nose. This fact may explain why a relatively high proportion of COVID-19 patients appear to have neurological manifestations [31].

In a cohort of patients with COVID-19 from 3 large hospitals in China, Mao et al [14] showed that 36.4% had neurological symptoms including ‘‘peripheral nervous system complications’’ such as impaired sense of taste and smell. Alternative hypotheses have also been proposed to explain olfactory and gustatory impairment in COVID-19 including the role of increased exposure to chemicals and disinfectants. There has also been a

growing focus on the temporal relationship between olfactory dysfunction caused by COVID-19 and other sinonasal symptoms including rhinorrhea and nasal congestion. Xydakis et al [32] reported that these other symptoms in general may be relatively less common.

In a primary revision of the data obtained through the COVID-19 Anosmia Reporting Tool for Clinicians from the AAO-HNS, Kaye et al [23] showed that only 25% of patients reported nasal congestion prior to complaining anosmia while only 18% reported rhinorrhea prior to anosmia.

Beltran-Corbellini et al [33], reported that only 12.9% of COVID-19 patients have olfactory or gustatory dysfunction also complaining nasal obstruction. Similarly, Lechien et al [2], found that 79.7% of COVID-19 patients still reported anosmia without nasal obstruction or rhinorrhea.

Chung et al [22] confirmed that olfactory dysfunction is common and may be the only symptom in COVID-19. OD related to Corona virus disease 2019 can be severe and prolonged. Tong et al [34], determined the combined global prevalence of olfactory and gustatory dysfunction in patients infected with COVID-19. They concluded that olfactory and gustatory dysfunction are common symptoms in COVID-19 patients and may represent early symptoms in the clinical course of infection. Hajikhani et al [35], established prevalence rates for anosmia and gustation in COVID-19 positive patients. The estimated rate of taste disorder was 49% in patients with COVID-19 while it was 61% for olfactory disorder. They showed high rates of taste (49%) and smell (61%) disorders in patients with COVID-19 positive. Therefore, loss of olfactory and loss of gustation should be routinely considered when infected with COVID-19. Luers et al [26], reported that two-thirds of patients with confirmed COVID-19 on Europe have olfactory and gustatory dysfunction that indicate the importance of these symptoms in early diagnostics. Also, Yadav et al [8], concluded that in the clinical spectrum of COVID-19 disease olfactory and gustatory dysfunctions considered a significant part. For many patients with COVID-19, it appears that olfactory dysfunction may be the initial presenting symptom. This was the case in 26.6% of patients in the AAO-HNS analysis, the presence of olfactory dysfunction led to the recommendation for laboratory COVID-19 testing [23]. Similarly, Beltran-Corbellini et al [33], described that in 35.5% of COVID-19 patients olfactory or gustatory dysfunction was the initial symptom with acute onset in 70.9% of COVID-19 patients have olfactory or gustatory dysfunction involved in their study. This incident is supported by Gane et al [36], reporting onset of anosmia in the absence of other symptoms or early in the clinical course, usually within days of disease onset.

Overall, this evidence has significant insinuation. First, it provides credence to the expanding belief that olfactory dysfunction in the absence of other sinonasal symptoms may be indicative of COVID-19 infection. It also highlights the potential benefit of screening patients based on the presence of olfactory dysfunction, as several authors have concluded [32].

Hopkins and Kumar [18], suggested that olfactory dysfunction should lead to a high level of clinical suspicion for COVID-19, along with advices for self-isolation, confirmatory testing, or other public health measures related to COVID-19.

Finally, the fact that other sinonasal symptoms appear to be less common argues against the possibility that olfactory loss caused by COVID-19 is related to nasal inflammation, mucosal edema, and airflow limitation, as it happened with other upper respiratory infections [28].

Zhou et al [37], discovered the role of Angiotensin converting enzyme 2 (ACE2) in the pathological process of SARS-CoV-2. Brann et al [30], studied and explained the role of 2 genes: ACE2 and TMPRSS in supporting cells of olfactory epithelium, stem cells and nasal respiratory epithelium describing the potential mechanism of anosmia in COVID-19 patients. These 2 genes play a possible role in transport of SARS-CoV-2 inside the cell. Cao et al [38], described the expression of quantitative trait loci (eQTLs) variants of the ACE2 gene which can be a reason for ACE2 polymorphisms and ACE2 expression levels among Asian and European populations. It can be one of possible pathogen in variety of expression in olfactory dysfunction in different countries or races. However, its exact aetiology is a matter of further detailed research to verify the role of the ACE 2 receptor.

CONCLUSION

Olfactory and gustatory dysfunctions are common in COVID-19 patients and perhaps represent the early patients complains in the clinical course of COVID-

19 infection. Otolaryngologists and others specialty medical colleagues need to be more vigilant about the symptoms of olfactory/gustatory dysfunction to diagnose COVID-19 patients at an early stage.

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