Importance and correlation of sudden onset, presence and recovery of olfactory and gustatory dysfunctions in COVID-19 patients: A cross-sectional study

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Abstract

Background: Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), may be associated with acute onset of smell and taste dysfunction along with other common presenting symptoms such as cough, fever and myalgia. Our study aims to analyze the presence of olfactory and gustatory dysfunctions Olfactory and gustatory dysfunctions (OGDs) in patients with COVID-19 and to assess their onset and recovery.

Materials and Methods: The cross-sectional study was conducted in March 2021 retrospectively at Care Multispecialty Hospital, Vadodara. A total 301 patients were admitted, among those 280 qualify according to inclusion criteria and 3 patients denied to participate in the study. All patients presenting with laboratory-confirmed real-time reverse transcriptase polymerase chain reaction test for SARS-CoV-2 were included in the study. All 277 patients were undergone a diagnostic questionnaire through telephonic conversation which include patient main symptoms and self-assessment of loss of smell and taste and their onset and recovery.

Results: Two hundred and seventy-seven patients were included in this study. One hundred and fifty-three patients (55%) reported olfactory and gustatory disorders. Loss of taste and smell were more frequently reported in female patients (72.8%) than male patients (48%). Onset of these symptoms concomitant with other typical symptoms of COVID-19 is in 58.2% of cases. Recovery of symptoms in most patients was in 5–10 days and faster in younger patients.

Conclusion: Olfactory and gustatory disorders (OGDs) related to COVID-19 are frequently reported and more common in female patients. Rapid recovery was observed in most cases. Altogether OGDs can possibly act pivot screening or diagnostic tool for COVID-19 pandemic.

Keywords: Anosmia, COVID-19, gustatory, loss, olfactory, SARS-CoV-2, smell, taste

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INTRODUCTION

Coronavirus disease-2019 (COVID-19) is an ongoing viral pandemic, caused by severe acute respiratory syndrome corona virus-2 (SARS-CoV-2), was first discovered in Wuhan, China, in late 2019 and then rapidly spread globally to the rest of the world.[1] It was declared as global pandemic by the World Health Organization on March 11, 2020.[2] More than 120,383,919 people have infected with SARS-CoV-2 along with 2,664,386 over fatalities as of March 17, 2021.[3] It is transmitted by the infected droplets through the upper respiratory tract while sneezing, coughing, talking without covering the mouth and nose, hand to mouth to eye contact and through contaminated hard surface and close proximity enhances SARS-CoV-2 spread.[4] Fever, cough, shortness of breath, myalgia, sore throat, nausea, vomiting and diarrhea are the common clinical manifestation of COVID-19 patients.[5] Recently, several surveys, case reports, case series and reviews proposed that OGDs in COVID-19 patients are a noteworthy finding, and in some patients, these were the first symptoms.[6-26] Little knowledge is available on the presence, onset and recovery time of these disorders.

The aim of this study was to investigate the presence, onset and recovery of OGDs in laboratory-confirmed SARS-CoV-2 patients.

MATERIALS AND METHODS

This study was conducted in mid of March, from March 7, 2021, to March 16, 2021, retrospectively at Care Multispecialty Hospital, Vadodara, on the total 301 admitted patients. Two hundred and eighty patients qualified to enroll in study according to inclusion criteria and among those 3 patients denied to participate in the study. All 277 patients were undergone a diagnostic questionnaire through telephonic conversation which include patient main symptoms and self-assessment of loss of smell and taste and their onset and recovery [Appendix 1]. All patients were informed about the study, and informed verbal consent was obtained. Study was approved by the Institutional Ethics Committee, Anand Multispecialty Hospital (number-SOP#AIEC-01-04), Vadodara. The study included all reverse transcriptase-polymerase chain reaction (RT-PCR)-confirmed patients with COVID-19. All administrative data were extracted from hospital databases, and questionnaire was dictated to the patients through telephonic interview.

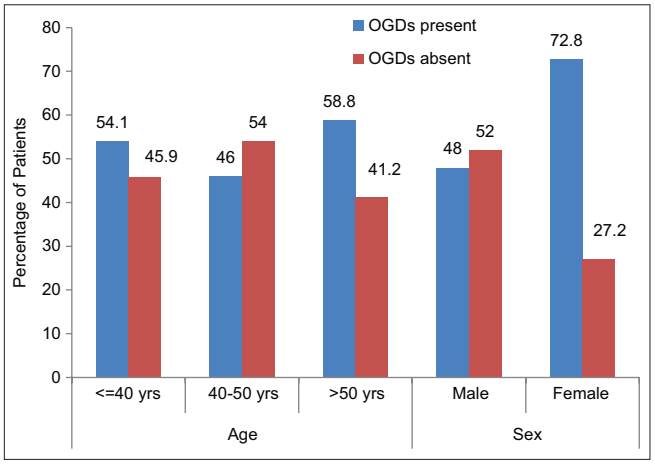
Inclusion criteria were age >18-year-old, RT-PCR laboratory-confirmed SARS-CoV-2-infected patients with symptoms of COVID-19 or patients without need of intensive care.

Exclusion criteria were declined informed consent, severe form of COVID-19 or patients on invasive ventilatory support care unit, patients with olfactory and gustatory dysfunction before SARS-CoV-2 infection.

Collected data were tabulated on excel worksheets and summarized using frequency and percentage association between categorical variables and results reported as medians and means and standard deviation as required and followed by statistical analysis using Pearson's Chi-square test using SPSS software Version 16 IBM Inc, Chicago, IL, USA.

RESULTS

A total of 277 hospitalized symptomatic patients were included in the study. Among 277 patients, 81 (29.2%) were female and 196 (70.8%) were male with a mean age of 51.47 ± 14.15 (range: 19–82 years). Most common symptoms were fever (82.3%), cough (61.4%), olfactory and gustatory dysfunctions (55%), sore throat (53.4%), myalgia (45.5%) and dyspnea (39.4%) [Table 1]. A total of 153 patients (55%) had reported olfactory and gustatory dysfunctions, among those about 47.7% had isolated olfactory dysfunction, 16.3% had isolated gustatory dysfunction and 35.9% had both olfactory and gustatory dysfunctions. Among 153 patients, 59 were female and 94 were male. OGDs were present in 72.8% among females and 48% among male patients [Table 2 and Graph 1]. Patients with OGDs divided into four groups, OGDs were (1) presenting complaint or 1–2 days before other typical symptoms, (2) concomitantly with other typical symptoms, (3) 1–3 days after typical symptoms and (4) patient did not remember. Nearly 26.8% developed



Graph 1: Presence of OGDs according to age and sex

before other typical symptoms or as first complaint, while 58.2% presented with symptoms or at the same time and 11.1% presented after typical symptoms. Around 3.9% of patients did not remember the specific time. Recovery in 64.1% of patients was in 5–10 days, in <5 days in 24.8% patients and in >10 days in 11.1% of patients [Table 3 and Graph 2]. Recovery was significantly faster in younger age group, about 70% of patients below 40 years of age recovered in <5 days of time. Comorbidities, diabetes and hypertension were present in 5.8% of patients, and there was no significant association of comorbidities and development of OGDs.

DISCUSSION

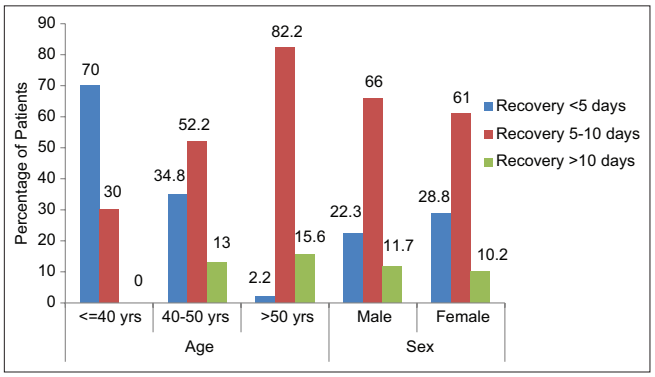
Olfactory and gustatory dysfunctions are highlighted as a new presentation of COVID-19 according to recent publications. Study supports that SARS-CoV-2 may cause OGDs and almost 95% have confirmed the olfactory disorders in SARS-CoV-2 infection.[6] Sudden onset of OGDs without any other respiratory disease should alert physician for possibility of COVID-19.[7]

Nearly 55.2% of patients reported OGDs in our study are comparable to other studies. Olfactory dysfunctions were in 26.4%, gustatory dysfunctions in 9.0% and both OGDs in 19.9% of cases. Many studies analyzed 70%–80% new onset OGDs usually present in COVID-19 patients.[8-10] According to a review, frequency of olfactory dysfunctions ranged between 22% and 68% and gustatory dysfunctions ranged between 20% and 33%.[11] Lechien *et al*., a multicenter European study, showed 85.6% and 88.0% of patients with olfactory and gustatory dysfunction, respectively.[12] According to a systematic review, the pooled proportion of patients having olfactory and gustatory dysfunctions were 41% and 38.2%, respectively, and high prevalence of olfactory dysfunction with the use of objective measurement as compared to self-reported cases.[13] Mao *et al*. studied the frequency of neurological manifestation in 214 COVID-19 patients in Wuhan, China, showed that 5.1% and 5.6% had olfactory and gustatory, respectively.[14] A cross-sectional study of 88 hospitalized patients in Milan, Italy, showed 33.9% affected by OGDs.[15] Hence, accordingly, we have noticed wide variation in results along different geographical location.

Table 1: Patients demographic and clinical data

Demographic and clinical data	Number and %
Total number of patients (*n*)	277
Sex	
Male	196
Female	81
Age (years)	
<40	74
40-50	50
>50	153
Age range	19-82
Sign and symptoms, *n* (%)	
Fever	228 (82.3)
Cough	170 (61.4)
OGDs	153 (55.2)
Sore throat	148 (53.4)
Myalgia	126 (45.5)
Dyspnea	109 (39.4)
OGDs, *n* (%)	
Absent	124 (44.8)
Present	153 (55.2)
Male	94
Female	59

OGDs: Olfactory and gustatory dysfunctions



Graph 2: Recovery of OGDs according to age and sex

Table 2: Onset of olfactory and gustatory dysfunctions

	Number of patients (*n*=153), *n* (%)	Isolated olfactory disorder, *n* (%)	Isolated gustatory disorder, *n* (%)	Both OGDs, *n* (%)
Onset symptoms				
Before the typical symptoms	41	16 (39)	7 (17.1)	18 (48.9)
With the typical symptoms	89	41 (46.1)	15 (16.9)	33 (37.1)
After typical symptoms	17	12 (70.6)	3 (17.6)	2 (11.8)
Not remember	6	4 (66.7)	0	2 (33.3)
Total	153	73 (47.7)	25 (16.3)	55 (35.9)
Chi-square test-*P* value		0.271		
Sex				
Male	94/196 (48)	37 (39.3)	17 (18.1)	40 (42.6)
Female	59/81 (72.8)	36 (61)	8 (13.6)	15 (25.4)
Chi-square test-*P* value		<0.001		

OGDs: Olfactory and gustatory dysfunctions

Table 3: Recovery in olfactory and gustatory dysfunctions according to age and sex

	Number of patients	Recovery (days)		
		<5, *n* (%)	5-10, *n* (%)	>10, *n* (%)
Age (years)				
≤40	40	28 (70)	12 (30)	0
40-50	23	8 (34.8)	12 (52.2)	3 (13)
>50	90	2 (2.2)	74 (82.2)	14 (15.6)
Chi-square test *P* value		<0.001		
Sex				
Male	94	21 (22.3)	62 (66)	11 (11.7)
Female	59	17 (28.8)	36 (61)	6 (10.2)
Chi-square test *P* value		0.662		

OGDs are frequent symptoms according to French and European studies rather than Asian studies. Incidence of OGDs was higher in European (34%–86%), North America (19%–71%) and middle east (36%–98%) as compared to Asian population (11%–15%).[16] According to the data of our study, the presence of OGDs is comparatively less as compare to other European studies, but more than the study conducted by Mao *et al*. in China. This clinical difference in patients may be due to variation of affinity of SARS-CoV-2 to different tissue sites in different ethnic group, as explained by Lechien *et al*. or alternatively genomic mutation in Europe and North America could be the possibility.[12] Patients with OGDs have 6–10 fold odds of having COVID-19.[16]

Females (72.8%) were significantly more affected by OGDs than males (48%) ($P < 0.001$) being in consensus with another studies.[12,17] No significant difference was noticed in our study according to age group. All age groups were almost equally affected. However, the recovery of OGDs was faster in younger age group (<40 age), which was significant ($P < 0.001$). According to most of studies, younger group, female population and mild symptomatic patients are more frequently affected by OGDs.[11,17] Females being observed more prone to OGDs could possibly due to gender-related difference in inflammatory reaction process.[12,17,19]

These symptoms can be first presenting symptoms, concomitantly or after the onset of general symptoms of cough, fever, sore throat, myalgia and shortness of breath. Around 11.8%–64% appears before the onset of general symptoms.[12,15-20] In our study, 26.8% reported it as presenting complaint, 58.2% as with the other typical symptoms and 11.1% after the appearance of other symptoms which was consistent with other studies.

OGDs mostly persist for a period of about 7–10 days with majority improving after 2 weeks and complete recovery rate of 44% within 5–8 days.[12,15-18] In our study, 88.9 recovered with these symptoms within 10 days and only 11.1 took more than 10 days.

In a prevalence study of 115 patients, 70% reported olfactory and gustatory disorders without nasal obstruction or rhinorrhea, more frequently in the female and young population.[17] In this study, among 153 patients of olfactory and gustatory disorders, only two patients were with rhinorrhea.

OGDs complaints in COVID 19 patients were almost twice that of non-COVID-19 patients. Nearly 65.1% COVID-19 patients have olfactory and gustatory dysfunctions as compared to non-COVID-19 patients who have only 21.2%.[16]

The pathophysiology of olfactory and gustatory disorder in COVID-19 is remaining unclear.

SARS-CoV-2 uses ACE-2 as the receptor for host cell entry mainly through endocytosis and uses the transmembrane serine protease 2 (TMPRSS2) for S protein priming along with activation. Loss of smell without any significant nasal inflammation in COVID-19 may be due to (1) direct damage of olfactory receptor neurons located on olfactory epithelium by virus, (2) cytokine storm (uncontrolled or marked increase of immune cells and cytokine release) and affect nervous system include sensory organs of smell and (3) nonneuronal cells located in the olfactory epithelium express both, ACE-2 and TMPRSS2 protein receptors, required for efficient SARS-CoV-2 infection in humans.[21]

Primary infection of nonneuronal cell types may be the cause of anosmia in COVID-19 patients possibly by three ways – local infection of supporting cells and vascular pericytes that modulate the function of olfactory sensory or bulb neurons, supporting cell damage that impair signaling from olfactory sensory neuron to brain and last is damage to sustentacular cells and Bowman's gland cells in mice models which can damage the entire olfactory epithelium diffusely.[21,22]

According to Hu *et al*., SARS-CoV-2 may have an effect on taste buds receptors directly because high ACE 2 receptors expression on the oral cavity mucosa and epithelial cells of tongue.[23]

Loss of taste might be associated to binding between SARS-CoV-2 and sialic acid receptors, a component of saliva that protects the glycoproteins responsible for the transport of molecules stimulating taste in the taste pores that can lead to degradation of taste particles with an alteration of taste sensation.[22,24]

The ability to separate flavors, including odor's smell, taste, temperature and texture, depends on the retronasal stimulation pathway. Some authors say, loss of taste can be linked to loss of smell because the brain combines the perceptions of taste from mouth, so mostly loss of taste due to retronasal olfactory dysfunction.[21,24]

In COVID-19, dysregulated immune system responds by secreting cytokines (small proteins interleukin [IL]-6, IL-8, IL-10, tumor necrosis factor-alpha, IL1 β, IL-18 and IL-33) in an uncontrolled manner leads to cytokine storm which can develop into a severe acute respiratory distress syndrome lead to multiple organ damage. It has been suggested that IL-6 is the most common type of cytokine released by activated macrophages and rise sharply in the severe cases of COVID-19. Study on 67 patients demonstrates a specific correlation between the level of IL-6 and taste and smell dysfunctions. Reduction of disturbances is accompanied by a progressive reduction of IL-6 level which returns to normal value when disturbance disappear.[24,25]

To summarize, OGDs were more prevalent in females, and recovery was faster in younger age group which being consistent with other studies. All age groups are almost equally affected by OGDs. OGDs may appear just before, concomitantly or immediately after onset of typical symptoms of COVID-19 and most patients recovered within 7–10 days. Mostly appeared as olfactory dysfunction, but both OLGs were also present together.

Our study has few limitations which were shared by similar researches. First, it was retrospective study, and we could not distinguish whether OGDs caused by COVID-19 virus directly or by neurological damage or other infections indirectly, so nasal endoscopy, specific imaging or objective evaluation is required to know exact pathogenesis behind this. Second, it is a single-center study, so zonal bias can be there on the basis of localities, so multicenter studies would contribute more specific results. Third, we have included self-reported evaluation of loss of taste and smell; however, according to previous studies, subjective evaluation of sense of smell is specific but less sensitive than objective evaluation. The strength of the study was that it provides the presence, the onset before other typical symptoms or with symptoms or after the symptoms and recovery in COVID-19 patients related to olfactory and gustatory dysfunctions. We have included all adult patients, and sample size is quite representative.

CONCLUSION

Considering the seriousness of ongoing pandemic and concurrent limitations of testing and contact tracing potentials, prevalence of such prominent symptoms of sudden onset of OGDs in COVID-19 patients can for sure be paramount tool for all clinicians and health-care persons to assist isolation recommendation and prevent hazardous uncontrolled community transmission of the COVID-19 pandemic. Altogether, these findings can possibly act pivot screening or diagnostic tool for the COVID-19 pandemic subjected to further advanced studies and research related to the association of chemosensory loss and recovery according to viral contamination and hence to justifiably segregate and identify the tip of disastrous glacier named COVID-19.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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APPENDIX

Appendix 1

Questionnaire

Patient identification number

Age

Sex

Symptoms: Yes/no

Onset duration

- Cough
- Fever
- Dyspnea
- Sore throat
- Myalgia.

History of olfactory and gustatory dysfunction specific questions: yes/no

1. Loss of taste
   First symptom
   Along with other symptoms
   After other symptoms

2. Loss of smell
   First symptom
   Along with other symptoms
   After other symptoms

3. Loss of taste and smell
   First symptom
   Along with other symptoms
   After other symptoms.

Duration of recovery of anosmia and ageusia

<5 days-

5–10 days-

>10 days-