Olfactory and Gustatory Dysfunction in Coronavirus Disease 19 (COVID-19)

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Abstract

Objective: To evaluate the recovery rate and duration of olfactory and gustatory dysfunction of patients over a period of two months in the Iranian population.

Methods: In this study, 305 patients with COVID-19 were enrolled and followed over a duration of 2 months. Binary logistic regression was employed to assess the association between olfactory and gustatory dysfunction with clinical manifestations and past medical history of patients.

Results: Olfactory-gustatory dysfunction was reported in 103 (33.7%) patients. Of them, approximately 54.5% and 56.9% of patients did not recover from olfactory and gustatory dysfunction before 10 days, respectively. In addition, almost 21.8% and 20.1% of the patients did not recover from olfactory and gustatory dysfunction after two-month follow-up, respectively. Severe form of olfactory and gustatory dysfunction was reported in 93% and 74.7% of patients, respectively.

Conclusion: We found that the majority of patients had olfactory and gustatory dysfunction for more than 10 days and about one fifth of patients did not recover after 60 days. Also, longer recovery time from olfactory and gustatory dysfunction was seen in patients who experienced the symptoms of weakness and dyspnea during the time of their disease.

Introduction

Currently, the world is in the middle of a pandemic of an infectious Human coronavirus which was discovered in Wuhan, China. Over 140 million people have been diagnosed with this infection and it has caused nearly 3 million deaths worldwide, according to Center for Disease Control and Prevention (CDC) (1). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is identified to be the causative agent for this disease which results in a variable range of symptoms in affected individuals and is transmitted by direct human contact (2-7). While the symptoms can be non-existent, mild, or severe, common respiratory manifestations are dry cough, fever, dyspnea, and weakness (2, 3, 8). Other less common symptoms include nausea, vomiting, diarrhea and abdominal pain (9-12). Moreover, olfactory and gustatory dysfunction have been increasingly reported as symptoms of COVID-19 in several countries (8,9), with olfactory disorder being more prevalent than gustatory dysfunction (2,10). Interestingly, some studies also suggest that onset anosmia, the loss of sense of smell, appears in the absence of other clinical symptoms associated with COVID-19 (13). Because of the rising number of recent reports regarding olfactory dysfunction as a potential early symptom of COVID-19, the CDC has added "new loss of taste or smell" to its list of symptoms that may appear 2 to 14 days after exposure to the virus (11). Whereas anosmia has been reported to be present in 73% of cases before laboratory diagnosis of COVID-19, it appeared as the presenting symptom in nearly 26.6% of cases (12). As the exact pathogenesis of COVID-19 remains to be uncertain (22), a thorough understanding of the variety of symptoms it causes is important to facilitate early diagnosis.

In several COVID-19 self-report studies, estimations of prevalence olfactory impairment are between 5 to 85%, depending on the severity of cases; this suggests a higher overall prevalence of COVID-related olfactory impairment compared to COVID-19-independent post-viral olfactory loss (13-20). The prevalence of olfactory impairment using the psychophysical odor identification tests appeared to range from 76% in Europe using the Sniffin' Sticks (17) to 98% in Iran using the UPSIT(21). Considering that these study cohorts may not be representative of the larger population and that it is not clear whether the appearance of olfactory and gustatory dysfunction symptoms are associated with other COVID-19 comorbidities, further research is needed. In the present study, recovery rate and duration of olfactory and gustatory dysfunction in a two-month follow-up of covid-19 patients was investigated.

Methods

Study population

This study was conducted in Saveh, Iran via a questionnaire designed by Ear, Nose, Throat and Head and Neck Surgery Research Center affiliated with Iran University of Medical Sciences from March 15th to June 1st, 2020. Three hundred and five patients with COVID-19, based on the laboratory-confirmed (reverse transcription polymerase chain reaction, RT-PCR) diagnosis of SARS-CoV-2 infection who were hospitalized, were enrolled into this study and were followed over a duration of 2 months. Patients who had reported pre-existing olfactory dysfunction were excluded from the study.

Assessment of patients' symptoms and comorbidities

Data was collected by a trained interviewer via a questionnaire and checklist (appendix 1) during the time of COVID-19 infection and after 2 months. The interview during two-month follow up was performed by the same interviewer. The questionnaire contained 200 questions about all COVID-19 signs and symptoms based on previous studies with an emphasis on olfactory and gustatory dysfunction, past medical histories, habitual history (smoking and Hookah use), Use of medications, family history of olfactory and gustatory dysfunction, and history of ICU admission during their follow ups. The participants were asked to rank their ability to taste and smell prior to, during and after contracting covid-19 on three different horizontal 100-point visual analogue scales (VAS).

Ethical approval

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected by a priori approval by the institution's Human Research Committee. This study protocol was also approved by the local ethics committee of the Saveh University of Medical Sciences. Informed consent about data collection was obtained from all participants prior to their enrolment.

Statistical analysis

SPSS software version 25 for Windows was employed for statistical analysis. We used Kolmogorov–Smirnov and Shapiro-Wilk normality tests, P-P plot, and histogram to test the normality of our study

population. The normality of all of the variables were approved as their respective null hypothesis was rejected. To assess the association between olfactory and gustatory dysfunction and different variables (i.e., clinical manifestations and past medical history of patients with COVID-19), univariable analysis of potential continuous and categorical risk factors was performed using t-test and chi-square, respectively. Data are reported as mean $\pm$ standard deviation (SD) for continuous variables and as proportions for categorical variables. An adjustment was made for confounding variables. Binary logistic regression was employed to assess the association between olfactory and gustatory dysfunction with clinical manifestations and past medical history of patients. To reject the null hypothesis, a 2-sided p value <0.05 was considered necessary.

Results

Prevalence of clinical manifestation and past medical history of COVID-19 patients and its association with olfactory and gustatory dysfunction

The most common clinical manifestations of the patients were fever and myalgia (both with 51.8% prevalence), dyspnea (39.7%), fatigue (21.6%), dry cough (20.7%), anorexia (20.7%), and asthenia (18.7%). Among the COVID-19 patients, 18% and 17.4% had diabetes mellitus and hypertension (**Table1**). The mean duration of patients' admission was 10 ± 3.1 days.

Among COVID-19 patients, 103(33.7%) experienced olfactory-gustatory dysfunctions; of which 25.2 % had isolated hyposmia, 16.5% had isolated hypogeusia 13.6% isolated ageusia, and 6.8% isolated anosmia. 16.5% had hyposmia and hypogeusia, 13.6% hyposmia and ageusia, 7.8% anosmia and dysgeusia and 1.9% had anosmia and ageusia.

When comparing two groups with and without olfactory dysfunction, positive family history, and presence of postnasal discharge were statistically significant different. When comparing patients with and without gustatory dysfunction, sex, positive family history, cheek pain, presence of postnasal discharge, use of mask and overuse of sanitizers were statistically significantly different between the two groups. Most patients (more than 60 %) reported loss of sweet and salty taste more than other tastes. 19 (6.6%) and 14 (4.6%) patients reported olfactory and gustatory dysfunction as the first presentation, respectively.

Numerical scaling of olfactory and gustatory dysfunction in patients with olfactory-gustatory manifestations of COVID-19

Among patients with olfactory manifestations of COVID-19, numerical scaling of olfactory dysfunction varied from 1 to 7 out of 10. A noticeable proportion of the patients (17.8%) gave a score of 0 or 1 to their olfactory sensation at the time of infection. 18.8% of the patients had a score of 2 and 3 while the majority (33.7%), gave a 4. Further, 7% of the patients had a score between 5 to 7.

Among patients with gustatory manifestations of COVID-19, numerical scaling of gustatory varied from 1 to 8 out of 10. 20% of the patients gave a score of 0 and 1 to their gustatory sensation at the time of infection. Overall, 10.7% of the patients had a score of 2 and 3 while 18.7% of the patients had a score of 4. The score mentioned most frequently was 5 with prevalence of 25.3%. Lastly, 25.3% of the patients gave a score between 6 to 8 to their gustatory sensation at the time of COVID-19 infection.

Prevalence of clinical manifestations before and after the onset of olfactory and gustatory dysfunction

In terms of olfactory dysfunction, headache, dyspnea, vomiting, diarrhea and sneezing all happened before the onset of olfactory dysfunction in 5.3%, 18.7%, 2.7%, 1.3% and 2.7% of the patients with COVID-19, respectively. Symptoms including sore throat, pneumonia, myalgia, weakness, cough and fever were present either before or after, but predominantly before onset of olfactory dysfunction. Facial fullness and sinus pain was only present after the onset of olfactory dysfunction in 1.3% of the patients with COVID-19.

In terms of gustatory dysfunction, headache, facial fullness and sinus pain, vomiting, diarrhea and sneezing all happened before onset of gustatory dysfunction in 5.9%, 1%, 5%, 1% and 1% of the patients. Moreover, symptoms such as dyspnea, pneumonia, sore throat, myalgia, weakness, cough and fever were reported after or predominantly before the onset of gustatory dysfunction.

Recovery time of olfactory and gustatory dysfunction and its association with clinical manifestations and past medical history

Recovery time of olfactory dysfunction happened more than 10 days among 54.5% of the patients with olfactory manifestations of COVID-19. 21.8% of the patients had not yet recovered from olfactory dysfunction after two months post-infection.

Recovery time from gustatory dysfunction happened more than 10 days among 56.9% of the patients with gustatory manifestations of COVID-19. Recovery from gustatory dysfunction had not occurred in 20.1% of the patients before two months.

Time of recovery from olfactory dysfunction was found to be significantly associated with presence of fatigue (p-value=0.043), dyspnea (p-value=0.032), and pneumonia (p-value=0.046) (**Table2**). Time of recovery from gustatory dysfunction demonstrated a statistically significant association with presence of fatigue (p-value=0.046) and dyspnea (p-value=0.038) (**Table3**).

Discussion

In the present study, it was found that of 305 enrolled participants, 33.7% reported olfactory-gustatory dysfunction from whom 54.4% had this problem for more than 10 days. Moreover, symptoms such as headache, vomiting, diarrhea and sneezing happened before onset of olfactory and gustatory dysfunction in most of the patients. It was determined that patients who had history of pneumonia had longer recovery times from olfactory dysfunction. Also, patients who experienced the symptoms of

weakness and dyspnea during the time of their disease experienced longer recovery time from olfactory and gustatory dysfunction. Furthermore, the statistical analysis of the questionnaire indicates that most of the patients self-reported severe form of olfactory and gustatory dysfunction during COVID-19 disease (VAS less than 5).

Olfactory dysfunction is a common consequence of viral infections that is usually caused by an inflammatory reaction in the nasal mucosa which further leads to the development of rhinorrhea. The most familiar agents of such viral infections are rhinovirus, parainfluenza, Epstein-Barr virus, and some coronaviruses. While the overall spontaneous improvement rates after upper respiratory tract infections have been estimated to be between 35-67% in post viral infections, over 80% of the patients reported subjective recovery after a year post viral infection (22); in this study, the olfactory dysfunction was recovered completely after two months in 78.2% of patients.

The specific pathophysiology of the olfactory dysfunction following viral infections is not thoroughly understood yet. However, since SARS-CoV-2, like other respiratory viruses, primarily attaches and infects the respiratory epithelium, it is not surprising that COVID-19 affects the olfactory neuro-epithelium and consequently impairs the sense of smell and taste (13, 23). Due to these similarities, there are no specific upper respiratory symptoms to allow COVID-19 to be distinguished from other potential viral respiratory infections.

Olfactory dysfunction is found to be associated with several other disease states including congenital causes, post infectious disorders, sinonasal diseases, traumatic brain injuries, and neurodegenerative disorders (24, 25). A cause of post-viral upper respiratory infection is identified to be a combined conductive and sensorineural/inflammatory disorder (26). Sinonasal diseases including allergic rhinitis or rhinosinusitis may cause anatomic barriers to give rise to conductive and inflammatory disorders, preventing odorants from reaching the olfactory receptors (27, 28). Smell impairment associated with disease severity is frequently reported such that a study suggested that that two out of three patients with the common cold or post-viral acute rhinosinusitis have impaired smell associated with disease severity(26).

Additionally, due to the association between long-term pharmacological treatments such as aminoglycosides, tetracycline, opioids, cannabinoids, and sildenafil and olfactory dysfunction (36), the participants were asked about past history of treatment with the mentioned substances; none of the patients with olfactory dysfunction had previously used these kinds of drugs. Other confounding factors that potentially promotes the development of olfactory dysfunction are potassium-sparing diuretics, antiplatelet drugs, α - and β -blockers, and calcium channel blockers. In the case of potassium-sparing diuretics, it can be speculated that these drugs interfere with olfactory receptor activity since they contain a large class of G-protein-coupled receptors which can potentially trigger neuronal activity, once activated (29). In the present study, no association was found between the olfactory dysfunction and the participants' use of these medications.

Angiotensin-converting enzyme 2 (ACE2) was identified as the main receptor for SARS-CoV-2 virus, in January 2020. ACE 2 is a class of receptors that are commonly present on the cells of multiple human organs such as the skeletal muscles, and the central nervous system (CNS). Because of the specified expression and distribution of ACE2, it can be deduced that the SARS-CoV-2 virus may cause some neurologic manifestations directly or indirectly due to the direct damage of cranial nerve endings or the possibility of retrograde invasion of CNS (olfactory bulb, solitary nucleus). Olfactory and gustatory dysfunction raises the issue of retrograde invasion of CNS. However, no evidence of direct invasion of cranial nerves may be present. Accordingly, olfactory and gustatory dysfunction could depend only on damage of olfactory epithelial cells that exhibit ACE2 receptor on surface.

Autopsy results from COVID-19 patients demonstrated that the brain tissue appeared to be hyperemic and edematous, with some neurons looking degenerated (30, 31). In addition, previous studies have determined that SARS-CoV is capable of causing neuronal death in mice through the invasion of the brain via the nose close to the olfactory epithelium (32). Based on an experimental study, because of the high expression of ACE2 in taste organs of mouse, ACE2 could potentially play an important role in the development of taste dysfunction in COVID-19 patients (33). Similarly in humans, ACE2 receptors has been identified in the oral cavity with high expression level in the tongue during an infection with COVID-19 (9). Therefore, a possible explanation deduced from the evidences could be that the SARS-CoV-2 spreads into and infects the nerve ending of the taste buds in the oral cavity resulting in gustatory dysfunction or the impairment of salty, sweet, bitter and sour tastes. Pure taste disorders are rarely reported with only a 5% representation in specialized smell and taste consultations (34, 35).

In the present study, approximately 16 percent of patients reported only gustatory dysfunction without any olfactory symptoms. The presented finding conforms to the hypothesis that viral infection and inflammatory response may lead to disruption of saliva composition, normal taste transduction or the continuous renewal of taste buds which helps explaining the pathogenic mechanism underlying anosmia and ageusia in COVID-19.(36). Although upper respiratory tract infection is reported as a very frequent suspected etiology in patients with gustatory dysfunction (34), only a few patients with gustatory dysfunction in this study had upper respiratory tract symptoms before presenting with gustatory dysfunction.

The prevalence of olfactory dysfunction in COVID-19 patients varies greatly in previous studies, ranging from approximately 5 to 85 percent (13, 17, 20, 37-42). At the beginning of the COVID-19 outbreak, studies reported a fewer number of self-reported olfactory and gustatory dysfunction in the general population. For instance the first European study included 59 hospitalized patients in Italy with twenty of them (33.9%) reporting at least taste or olfactory disorders, and 11 (18.6%) presenting with both symptoms(43). One possible explanation for this phenomenon is the lack of knowledge on the effect of COVID-19 on other organs apart from the lungs. Most of our patients who reported these problems were admitted at the beginning of the first outbreak in Iran.

As an emerging infectious disease, it is vital to discover the main clinical characteristics of COVID-19 patients to allow for early diagnosis, and isolation of infected individuals and consequently reducing the

spread of the disease.

A major strength of the present study was evaluating approximately all symptoms and comorbidities of the COVID-19 with olfactory and gustatory dysfunction, while a limitation of this study was the self-reporting of olfactory and gustatory function which may suffer from a low validity because of reporting biases of the participants. Further research is needed to evaluate olfactory and gustatory dysfunction via psychophysical odor and taste identification tests to find the association between olfactory and gustatory dysfunction and other COVID-19 symptoms and comorbidities.

Conclusions

Most patients with COVID-19 recovered from olfactory and gustatory dysfunction after 10 days post-infection and patients experienced symptoms such as headache, vomiting, diarrhea and sneezing before the onset of olfactory and gustatory dysfunction in the course of the infection. Additionally, we determined that patients with previous history of pneumonia experienced an increased duration of recovery from olfactory dysfunction. Symptoms of weakness and dyspnea during the course of disease was also found to be associated with longer recovery time from olfactory and gustatory dysfunction. Lastly, it is important to mention that most of the patients in this study reported severe form of olfactory and gustatory dysfunction during COVID-19 disease.

Declarations

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Declaration of interest:

The authors declare that they have no competing interest.

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All the authors approved the final version and have the agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Data availability: All data generated or analysed during this study are included in this submitted article.

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Tables

Table 1. Clinical manifestations and past medical history of the study population, ARDS: Acute respiratory distress syndrome, DM: Diabetes mellitus, HTN: Hypertension, CVD: Cardiovascular disease, PND: Purulent nasal discharge, QOL: Quality of life , ICU: intensive care unit

		Frequency	percentage
Gender	Male	189	62
	Female	116	38
Fever		158	51.8
Dry cough		63	20.7
Anorexia		63	20.7
Diarrhea		31	10.2
Pharyngalgia		18	5.9
Abdominal pain		13	4.3
Dizziness		16	5.2
Headache		43	14.1
Impaired consciousness		5	1.6
Ataxia		2	0.7
Myalgia		158	51.8
Fatigue		66	21.6
ARDS		10	3.3
Dyspnea		121	39.7
Sore throat		12	3.9
Arthralgia		14	4.6
Asthenia		57	18.7
Rhinorrhea		3	1
Sneezing		7	2.3
PND		2	0.7
Vomiting		36	11.8
Nasal congestion		2	0.7
Nasal stiffness		1	0.3
Facial fullness and sinus pain		3	1

Otalgia	5	1.6
Cheeks pain	2	0.7
Mild flu like symptoms lasting<24 hours	22	7.2
Delirium	2	0.7
Chest pain	50	16.4
Hoarse voice	1	0.3
Vertigo	9	3
Flu-like syndrome before anosmia	1	0.3
Parosmia	0	0
Phantosmia	2	0.7
Unilateral facial palsy	2	0.7
History of diabetes mellitus	55	18
History of hyperthyroidism	5	1.6
History of hypothyroidism	6	2
History of asthma	3	1
History of Hypertension	53	17.4
History of Cardiovascular disease	27	8.9
History of Immunocompromised Condition	3	1
Chemotherapy or immune therapy	4	1.3
Nasal polyps	1	0.3
Head trauma	1	0.3
Kidney disease	4	1.3
Use of Enalapril	3	1
Use of Losartan	33	10.8
Use of Valsartan	2	0.7
Medicine use (aminoglycosides, tetracycline, opioids, cannabinoids, sildenafil, metronidazole, chlorpheniramine, allopurinol, methimazole, baclofen, levodopa, codein, morphin, carbamazepine, lithium, phenytoin, amphetamine, iron, vitamin D)	0	0
Corticosteroid spray to treat olfactory dysfunction	0	0
Olfactory dysfunction in family members	30	9.9

Gustatory dysfunction in family members	19	6.2
Effect of olfactory dysfunction on quality of life	42	13.8
Effect of gustatory dysfunction on quality of life	16	5.2
Smoking	14	4.6
Use of mask	123	40.3
Nasal drop use for olfactory dysfunction	0	0
Overuse of sanitizers and alcohol	10	3.3
ICU admit	11	3.6
Ventilator use during hospitalization	1	0.3

Table 2. Association between clinical manifestations and past medical history and recovery time of olfactory dysfunction; Data are presented as mean (SD). ARDS: Acute respiratory distress syndrome, DM: Diabetes mellitus, HTN: Hypertension, CVD: Cardiovascular disease, PND: Purulent nasal discharge

	Recovery time of olfactory dysfunction (days)	P-value
Myalgia	8.10± 6.75	0.701
Fever	8.40± 7.44	0.431
Dry cough	8.52± 10.10	0.729
Anorexia	6.43± 7.15	0.351
Diarrhea	4.58± 8.38	0.140
Abdominal pain	10.66± 9.01	0.538
Dizziness	7.50± 7.54	0.936
Headache	9.33± 6.84	0.435
Fatigue	4.54 ± 8.35	0.043
ARDS	3.50± 4.43	0.046
Dyspnea	7.17± 7.40	0.032
Sore throat	10.50± 14.84	0.638
Arthralgia	9.14± 6.41	0.656
Asthenia	7.92± 6.19	0.935
Rhinorrhea	10± 14.14	0.702
Sneezing	10.25± 11.84	0.542
PND	5± 7.07	0.620
Vomiting	5.66± 7.12	0.327
Otalgia	15± 21.21	0.711
Cheek pain	15± 21.21	0.711
Mild flu like symptoms lasting<24 hours	8.20± 8.72	0.915
Chest pain	8.35 ± 6.14	0.746
Vertigo	4± 6.73	0.337
History of DM	5.4± 5.79	0.210
History of hyperthyroidism	9.66± 10.01	0.690
History of HTN	9.75± 5.56	0.381

History of CVD	14	<0.001
History of Losartan use	11.37± 4.56	0.196
History of Valsartan use	7± 9.89	0.885

Table 3. Association between clinical manifestations and past medical history and recovery time of gustatory dysfunction. ARDS: Acute respiratory distress syndrome, DM: Diabetes mellitus, HTN: Hypertension, CVD: Cardiovascular disease, PND: Purulent nasal discharge, QOL: Quality of life, ICU: intensive care unit

	Recovery time of gustatory dysfunction (days)	P-value
Myalgia	8.10± 6.75	0.701
Fever	8.81± 7.80	0.589
Dry cough	8.31± 10.02	0.986
Anorexia	6.64± 7.62	0.358
Diarrhea	4.58± 8.38	0.099
Abdominal pain	10.66± 9.01	0.637
Dizziness	6.25± 6.84	0.620
Headache	8.92± 7.25	0.793
Impaired consciousness	13± 1.41	0.442
Ataxia	8.85± 6.89	0.579
Fatigue	6.18± 9.33	0.046
Dyspnea	8 ± 7.96	0.038
Sore throat	7 ± 12.12	0.784
Arthralgia	8 ± 7.34	0.927
Asthenia	9.23± 6.37	0.687
Rhinorrhea	10± 14.14	0.785
Sneezing	10.25± 11.84	0.653
Purulent nasal discharge	5± 7.07	0.307
Vomiting	5.77± 7.44	0.344
Facial fullness and sinus pain	9.5± 0.70	0.849
Otalgia	15 ± 21.21	0.271
Cheek pain	15± 21.21	0.271
Mild flu like symptoms lasting<24 hours	8.2± 8.72	0.969
Chest pain	9.91± 6.24	0.495
Vertigo	4.6± 8.08	0.454
History of DM	5.83± 6.01	0.273

History of Hypothyroidism	14.5± 7.77	0.309
History of HTN	10.25± 5.89	0.512
History of CVD	7.5± 8.10	0.841
History of Losartan use	14	0.179
History of Valsartan use	7 ± 9.89	0.824

Supplementary Files

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- [Appendix1.docx](#)