Caspian Journal of Neurological Sciences
"Caspian J Neurol Sci"

Journal Homepage: http://cjns.gums.ac.ir

Research Paper

Olfactory Dysfunction and Phantosmia in Patients With COVID-19 in Northern Iran

Shadman Nemati[1], Ali Faghih Habibi[1*], Makan Shalchizadeh[1], Tofigh Yaghubi Kalurazi[2], Heydar Ali Balou[3], Mehryar Mashouf[4], Seyed Hamidreza Bagheri[5], Vahid Aghsaghloo[1], Yasaman Hosseinzadeh Lakhani[1]

1. Oto-Rhinolaryngology Research Center, Department of Otorhinolaryngology, Head and Neck Surgery, Amiralmomenin Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.
2. Department of Health, Nutrition and Infectious Diseases, School of Medicine Razi Hospital, Guilan University of Medical Sciences, Rasht, Iran.
3. Department of Internal Medicine, School of Medicine, Gastrointestinal and Liver Disease Research Center, Guilan University of Medical, Sciences, Rasht, Iran.
4. International Fellow of the American Association of Neurological Surgeons, Arya Hospital, Rasht, Iran.
5. Oto-Rhinolaryngologist, Pars Hospital, Rasht, Iran.

Use your device to scan and read the article online

Citation Nemati S, Faghih Habibi A, Shalchizadeh M, Yaghubi Kalurazi T, Ali Balou H, Mashouf M, et al. Olfactory Dysfunction and Phantosmia in Patients with COVID-19 in Northern Iran. Caspian J Neurol Sci. 2022; 8(3):171-177. https://doi.org/10.32598/CJNS.8.30.8

Running Title Olfactory Dysfunction in Patients with Covid-19

https://doi.org/10.32598/CJNS.8.30.8

Article info:
Received: 12 Jan 2022
First Revision: 05 Apr 2022
Accepted: 10 Apr 2022
Published: 01 Jul 2022

ABSTRACT

Background: One of the most common symptoms of COVID-19 infection is Olfactory Dysfunction (OD).

Objectives: This study aims to investigate OD and phantosmia in COVID-19 cases from northern Iran.

Materials & Methods: In this cross-sectional study, participants were 400 patients with COVID-19 infection in Rasht, Iran from March 2019 to September 2020. All the patients were evaluated in terms of OD and then followed up for 3 months face-to-face, by telephone call, or online.

Results: Among 400 patients, 37.75% had OD (19% hyposmia, 10.75% primary phantosmia, and 8% anosmia) during the initiation of the disease, but 121 (30.25%) including nearly 65% of anosmic and/or hyposmic cases reported phantosmia at different time intervals of follow-up visits. Moreover, 65.38% of patients reported acute onset of OD. The prevalence of OD was significantly higher in patients aged <40 years (P=0.001) and in females (P=0.002). OD improved in about 90% of patients within 3 months. Peripheral oxygen saturation was better in anosmic cases and C-reactive protein level was higher in normosmic cases at their first visit. No significant difference was found in terms of other laboratory results.

Conclusion: OD is a common complication of COVID-19 infection, but seems not to be permanent. It is more common in young patients, females, and those with mild COVID-19 infection.

Keywords: Anosmia, COVID-19, Olfaction Dysfunction

*** Corresponding Author:**
Ali Faghih Habibi.
Address: *Oto-Rhinolaryngology Research Center, Department of Otorhinolaryngology, Head and Neck Surgery, Amiralmomenin Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.*
Tel: *+98 (13) 3323 8306 ,* ***Fax:*** *+98 (13) 33225242*
E-mail: *dr.fagih.habibi@gmail.com*

Highlights

- Olfactory dysfunction is common in patients with COVID-19 in Northern Iran which includes hyposmia, phantosmia, and anosmia cases.
- Both primary and secondary phantosmia are common during the initiation of COVID-19 infection, where secondary phantosmia is more common.
- The prevalence of olfactory dysfunction is significantly higher in patients under 40 years of age and in females.
- Olfactory recovery occurs in about 90% of patients with COVID-19 within 3 months.

Introduction

A new coronavirus was found in Wuhan, China in 2019, which is known as COVID-19 or SARS-COV-2. This virus causes acute respiratory infection and pneumonia, and can involve multiple body organs. Based on serological findings, the prevalence of COVID-19 was 10 times more than other reported diseases, because only acute cases are diagnosed and those with mild cases do not attend medical centers [1]. Disease transmission starts before the onset of symptoms and continues 7-10 days after the end of symptoms. The rate of transmission is higher at the beginning of the disease course [2].

Olfactory Dysfunction (OD), which consists of anosmia (loss of sense of smell), hyposmia (reduced ability to smell), and phantosmia (distorted sense of smell), affects almost 14-22% of people over 60 years old [3]. Nasal and paranasal sinus diseases (i.e. chronic rhinosinusitis with or without nasal polyps) and viral Upper Respiratory Tract Infections (URTI) are the most common causes of OD [4]. Head trauma, aging, and neurodegenerative disorders such as parkinsonism and Alzheimer's disease are other causes of OD [5]. OD usually improves after infection; 83% of patients with OD after viral URTI, recover within 2 years after infection [6]. Spinato et al. in a study on 202 patients with COVID-19, reported the prevalence of OD and dysgeusia (distorted sense of taste) as 52% and 44%, respectively [7]. In Leichen et al.'s study, OD or dysgeusia was observed in 64% of patients with mild COVID-19 infection, and in 24% of patients with severe infection. OD or dysgeusia was the only symptom of COVID-19 infection in 3% of patients. In 12% of patients, it was the first symptom [8]. Based on Meinhardt's study, OD related to COVID-19 infection was almost transient and 89% of patients recovered completely or partially within 4 weeks after infection [9].

This study aims to determine the prevalence of OD in patients with COVID-19 in northern Iran. Most of the previous studies evaluated the relationship between COVID-19 and hyposmia or anosmia. To our knowledge, this is the first study that evaluates phantosmia prevalence, in addition to anosmia and hyposmia, in patients hospitalized due to COVID-19 infection. As OD has a great effect on the quality of life of patients, we followed up the patients for three months to evaluate the recovery rate of OD among them.

Materials and Methods

Study design and participants

In this cross-sectional study, 418 patients who were hospitalized in the hospitals in Rasht, Iran due to COVID-19 infection from March 2019 to September 2020 were screened for OD, associated clinical symptoms, underlying diseases, and laboratory results. The Covid-19 diagnosis was made based on standard diagnostic kits, symptoms, and positive lung CT scan and according to specialists in infectious diseases or lung and respiratory diseases. The inclusion criteria were age 15-80 years and hospitalization in Rasht city due to COVID-19 infection from March 2019 to September 2020. The patients who were intubated or had decreased level of consciousness, having any past medical history of nasal and paranasal sinus disorders, endoscopic sinus surgery, or rhinoplasty surgery, those with central nervous system disorders (e.g., Alzheimer's, epilepsy, Parkinson, or tumor), and psychologic problems were excluded from the study.

Assessments

First, the researcher explained the study design and objectives to the patients and asked them to read and sign an informed consent form for participation. Then, their demographic information (age, gender, occupation, and

place of residence), clinical information (the time of starting and the severity of hyposmia and phantosmia, if any), and any accompanied gustatory and neurologic symptoms were recorded. Moreover, the presence of dysgeusia, headache, URTI symptoms, past medical history, documented Covid-19 infection, any improvement in OD, and history of contact with a stimulus (cigarette or any detergent stimulus except soap) were examined. Laboratory data including C-Reactive Protein (CRP) level, Erythrocyte Sedimentation Rate (ESR), White Blood Cell (WBC) count, the ratio of Neutrophil to Lymphocyte (Neu/Lym), Absolute Neutrophil Count (ANC), Absolute Lymphocyte Count (ALC), Body Temperature (BT), and peripheral oxygen saturation were also collected at baseline. The severity of hyposmia was evaluated using the Visual Analogue Scale (VAS) in a range from 0 to 10; a score of 1-3 indicates mild hyposmia; 4-6, moderate; 7-8, severe hyposmia; 9-10, anosmia. The VAS was administrated by an ENT specialist.

Statistical analysis

The collected data were entered into IBM SPSS v. 22 software (IBM Corp., Armonk, NY) for the statistical analysis. Descriptive data were presented by frequency (percentage) at 95% confidence interval. Kolmogorov-Smirnov test was used for evaluating the normal distribution of quantitative data. Numeric variables were described using Median. Mann–Whitney U test was used for qualitative data analysis, while chi-square test was used for numerical data analysis. Multiple linear regression analysis was used to evaluate the factors (such as contact with detergents and stimuli, history of recent URTI, tobacco use) affecting OD in patients. A $P<0.05$ was considered statistically significant.

Results

Of 418 patients, 18 patients were excluded due to loss of follow-up because of reasons such as travel, low level of consciousness, and etc. Their age and gender information are presented in Table 1. It was found that 62.25% of patients had a normal olfactory function, and 37.75% had OD, including mild hyposmia (2.75%), moderate hyposmia (11%), severe hyposmia (5.25%), primary phantosmia (10.75%), and anosmia (8%). More specially, phantosmia was reported in 30.25% of patients. 64.46% of phantosmia cases were secondary to hyposmia and anosmia while 35.54% had primary phantosmia. Furthermore, 65.38% of participants reported acute onset of OD.

The Kolmogorov-Smirnov test for data related to any improvement in OD, showed abnormal distribution; therefore, Wilcoxon signed-rank test was used to evaluate the improvement of OD over time. Based on the results, OD was improved significantly in 86% of patients in three months of follow-up without any specific treatment (VAS score reached from 7.9 to 3.8); in more than 50% it reached to normal olfactory function during this 3-month period. The recovery from phantosmia was a little different compared to hyposmia and anosmia; about 65% of patients reported some degrees of improvement , but only about 27% reported full recovery in three months without any specific treatment.

The prevalence of OD caused by COVID-19 was significantly more in females ($P=0.002$). In terms of age, the prevalence of OD was higher in youth (<30 years), which was statistically significant ($P=0.001$). In terms of clinical symptoms (fever, myalgia, dyspnea, coughing, sneezing, rhinorrhea, sore throat, postnasal discharge, dysgeusia, gustatory symptoms, headache), there was no any significant difference between the groups with and without OD ($P>0.05$); the most common clinical symptoms were cough (67%), dyspnea (60.2%), weakness (57.5%), fever (39.5%), and headache (14.3%). Peripheral oxygen saturation was higher in groups with hyposmia in comparison with the normosmic group ($P<0.05$). In terms of laboratory data, only CRP level was higher in the group with normosmia ($P=0.008$); there were no significant difference between normosmic and hyposmic groups in other data (ESR, WBC count, Neu/Lym, ANC, ALC, and BT) ($P>0.05$). In terms of history of contact with a stimulus (cigarette or any detergents except soap), there was not a statistically significant difference between the two groups ($P>0.05$). The most common underlying diseases were hypertension (23.3%), diabetes mellitus (20.8%), and cardiac problems (14.2%); none of them had a statistically significant relationship with hyposmia ($P>0.05$) (Table 2).

Discussion

One of the symptoms of COVID-19 is OD. One of the leading causes of OD is hyposmia after infection, but its incidence rate was not reported in our study. The increased rate of OD during the COVID-19 pandemic can be due to excessive attention to this infection or due to other viruses [10]. The SARS-Cov-2 virus can reach the central nervous system via the olfactory neurons. Inflammatory cell infiltration and axonal damage have been found in pathologic studies, but the damage seems not to be directly due to the virus. Transient anosmia can be due to inflammation through the olfactory pathway.

Table 1. Age and gender of patients with COVID-19 infection (n=400)

Variables		No. (%)			P
		Total	With OD	Without OD	
Gender	Female	181(45.20)	43(62.31)	138(41.69)	0.002
	Male	219(54.80)	26(37.68)	193(58.30)	
Age	<30 years	30(7.50)	11(36.66)	19(63.33)	0.001
	30-39	65(16.25)	22(33.84)	43(66.15)	
	40-49	69(17.25)	16(23.19)	53(76.81)	
	50-59	71(17.75)	8(11.26)	63(88.73)	
	≥60 years	165(41.25)	12(7.27)	153(92.72)	

Obstruction of the nasal cavity in some patients with anosmia due to COVID-19 has been reported [11]. OD is currently treated by the treatment of nasal obstruction and accompanied infections (glucocorticoids, antihistamines, and leukotriene inhibitors which reduce the inflammation and edema), and olfactory training [12].

In our study, participants were 400 patients with COVID-19 infection with a mean age of 55.21±16.72 years. Most of them were older than 50 years, which can be due to more severe COVID-19 infection in older people. OD was higher among younger patients (<40 years old). OD was present in 68.4% of patients aged <40 years and in 28.2% patients aged >40 years. Consistent with this result, in Speth et al.'s study, OD was more common at young patients [10], while there was no difference in OD among different age groups in Vaira's study [13]. In studies by Mercante et al. and Lee et al., OD was more common in older patients [14, 15]. Olfactory function decreases with aging. On the other hand, OD has other causes such as other infectious diseases and nasal and paranasal sinus disorders which can be different in various study settings. There are different methods to evaluate the severity of OD, which can influence the results [5, 6].

In our study, 37.75% of patients with COVID-19 had OD (19% with hyposmia, 8% with anosmia, and 10.75% with primary phantosmia). In Moein et al.'s study, 25% of patients with COVID-19 infection had OD [16]. In Lee et al.'s study, 31% of patients had OD; which is close to its prevalence rate in our study [15]. In Speth et al.'s study, 61.2% of patients had OD which was moderate to severe [10]. In Vaira et al.'s study, OD was present in 56.1% of patients; but this rate was reduced significantly after re-assessment by quantitative olfactory function tests [13]. It seems that different rates of OD incidence among patients with COVID-19 in various studies can be due to various assessment methods of OD severity. Another explanation for discrepancy in results is that OD occurrence can be different between inpatients and outpatients, because their disease severity and age are different.

Most patients in our study had almost normal olfactory function after three months of follow-up without any treatment (86% of patients with anosmia and hyposmia, 65% of patients with primary phantosmia). This is similar to the results of Samimi Ardestani et al. which reported almost full recovery of OD over one month [17]. Lee also reported similar results as most cases of OD were recovered within 3 weeks [15]. In our study, most of patients were female, and OD was significantly more common in females than in males (54.4% to 24.2%). In Leichen et al.'s study, OD was also more common in female patients [8], while there was no difference in OD incidence rate between men and women in studies by Vaira et al. and Moein et al. [13, 16]. In these studies, quantitative methods were used to evaluate the olfactory function, which can be the cause of different results compared to our study.

The most common accompanying clinical symptoms were cough (67%), dyspnea (60.2%), weakness (57.5%), fever (39.5%), and headache (14.3%). None of them had a statistically significant relationship with the severity of OD. Consistent with our study, Speth et al. also found that none of the clinical symptoms had a meaningful relationship with the severity of OD [10]. In Mercante et al.'s study, rhinorrhea and nasal congestion were related to the severity of hyposmia [14]. In Leichen et al.'s

Table 2. Clinical characteristics of patients with COVID-19 infection (n=400)

Variables	Groups	N (%)	P
Olfactory function	Normosmia	249(62.25)	-
	Mild hyposmia	11(2.75)	
	Moderate hyposmia	44(11)	
	Severe hyposmia	21(5.25)	
	Anosmia	32(8)	
	Phantosmia	Primary: 43(10.75) Secondary: 78(19.5)	
Headache	With OD	77(50.9)	0.165
	Without OD	149(59.8)	
		Median (Q1-Q3)	
BT	With OD	37.53 (37-38)	0.248
	Without OD	37.69 (37.0-38.1)	
WBC count	With OD	6000 (7850 – 4550)	0.586
	Without OD	6350 (8350 – 4600)	
ANC	With OD	3959 (5793 – 2941)	0.275
	Without OD	4480 (6314 – 3064)	
ALC	With OD	1238 (1869 -942)	0.547
	Without OD	1290 (1699 -925)	
Neu/Lym	With OD	3.21 (2.34 – 4.32)	0.966
	Without OD	3.7 (2.5-5)	
ESR	With OD	70.5 (31.5- 123.75)	0.422
	Without OD	51 (82-27)	
CRP level	Without OD	26 (2-72)	0.008
	With OD	15 (2-30)	
Peripheral oxygen saturation	Without OD	93 (90-95)	0.001
	With OD	96 (94-97)	

Q1= First quarter, Q3= Third quarter

CJNS

study, nasal congestion was related to the severity of OD [8]. In our study, patients with chronic rhinosinusitis and past history of nasal and sinus disorders were excluded, which can be the reason for discrepancy in results between our study and their studies.

The most common underlying diseases in patients were hypertension, diabetes mellitus, and cardiac problems. None of them had a significant relationship with OD. In Leichen et al.'s study, allergic disorders were the most common underlying diseases [8], while in Klopfenstein et al.'s study, hypertension and diabetes mellitus were more common among patients with OD [18]. In

studies by Lee et al. and Moien et al., there was no any significant relationship between underlying diseases and OD [15, 16]. Consistent with our study, Speth et al. and Mercanta et al. showed no relationship between history of contact with stimulus (cigarette or any detergents except soap) and the severity of OD [10, 14]. In our study, peripheral oxygen saturation was lower and CRP level was higher in the normosmic group in comparison with the hyposmic group at baseline. Both parameters indicate more severe forms of the disease; it seems that OD is not more common in patients with severe COVID-19 infection. This can be due to the less attention of these patients to less important symptoms such as OD. The higher CRP levels in the normosmic group can be due to more immune system reaction against COVID-19 infection; which leads to preventing damage to the olfactory neurons by the virus. Indeed one may think OD is mainly due to the neurotropic property of COVID-19 virus, while other more intense involvements, such as pulmonary infection or other organ dysfunctions may be due to the host immunological reactions against COVID-19 virus. In patients with and without OD, peripheral oxygen saturation levels were above 90%, but there was no significant difference between them.

To the best of our knowledge, the present study is a first study that surveyed phantosmia in patients with COVID-19. The relationship between peripheral blood oxygen saturation and the severity of OD has not been investigated yet; therefore, further studies are recommended for its assessment. One of the limitations in our study was the short-term follow-up of patients with OD, especially phantosmia cases. For future studies, we recommend using quantitative and more objective tests to screen OD and its changes more exactly over time. Clinical trials with different treatment modalities, including olfactory re-training therapies are also recommended.

Conclusion

OD is common in patients with COVID-19 infection in northern Iran, which includes hyposmia, phantosmia, and anosmia cases. Both primary and secondary phantosmia are common during the initiation of the disease, where secondary phantosmia is more common. The prevalence of OD is significantly higher in patients with COVID-19 aged <40 years and in females. Olfactory recovery occurs in about 90% of these patients within 3 months.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the ethical committee of Guilan University of Medical Sciences (Code:IR.GUMS.REC.1399.063). All study procedures complied with the ethical guidelines of the 2013 Declaration of Helsinki.

Funding

This article was extracted from the PhD dissertation of. the third author. It received no funding from any organizations.

Authors contributions

Conceptualization: Ali Faghih Habibi; Methodology: Shadman Nemati, Seyed Hamidreza Bagherim, and Vahid Aghsaghloo; Writing-original draft: Makan Shalchizadeh, Tofigh Yaghubi Kalurazi, and Heydar Ali Balou; Writing-review & editing: Mehryar Mashouf and Yasaman Hosseinzadeh Lakhani

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors would like to thank to the staff of Amir Almomenin, Arya, and Razi hospitals in Rasht, Iran as well as patients for their cooperation during this study.

References

[1] Stringhini S, Zaballa ME, Pullen N, Perez-Saez J, de Mestral C, Loizeau AJ, et al. Seroprevalence of anti-SARS-CoV-2 antibodies 6 months into the vaccination campaign in Geneva, Switzerland, 1 June to 7 July 2021. Euro Surveill. 2021; 26(43):2100830. [DOI:10.2807/1560-7917.ES.2021.26.43.2100830] [PMID] [PMCID]

[2] He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med. 2020; 26(5):672-5. [DOI:10.1038/s41591-020-0869-5] [PMID]

[3] Bhattacharyya N, Kepnes LJ. Contemporary assessment of the prevalence of smell and taste problems in adults. Laryngoscope. 2015; 125(5):1102-6. [DOI:10.1002/lary.24999] [PMID]

[4] Konstantinidis I, Haehner A, Frasnelli J, Reden J, Quante G, Damm M, et al. Post-infectious olfactory dysfunction exhibits a seasonal pattern. Rhinology. 2006; 44(2):135-9. [PMID]

[5] Gerami H, Nemati S, Abbaspour F, Banan R. Brain single photon emission computed tomography in anosmic subjects after closed head trauma. Acta Med Iran. 2011; 49(1):13-7. [PMID]

[6] Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: A cross-sectional study. Clin Infect Dis. 2020; 71(15):889-90. [DOI:10.1093/cid/ciaa330] [PMID] [PMCID]

[7] Spinato G, Fabbris C, Polesel J, Cazzador D, Borsetto D, Hopkins C, et al. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. JAMA. 2020; 323(20):2089-90. [DOI:10.1001/jama.2020.6771] [PMID] [PMCID]

[8] Lechien JR, Chiesa-Estomba CM, Hans S, Barillari MR, Jouffe L, Saussez S. Loss of smell and taste in 2013 European patients with mild to moderate COVID-19. Ann Intern Med. 2020; 173(8):672-5. [PMID] [PMCID]

[9] Meinhardt J, Radke J, Dittmayer C, Franz J, Thomas C, Mothes R, et al. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. Nat Neurosci. 2021; 24(2):168-75. [DOI:10.1101/2020.06.04.135012]

[10] Speth MM, Singer-Cornelius T, Oberle M, Gengler I, Brockmeier SJ, Sedaghat AR. Olfactory dysfunction and sinonasal symptomatology in COVID-19: prevalence, severity, timing, and associated characteristics. Otolaryngol Head Neck Surg. 2020; 163(1):114-20. [PMID] [PMCID]

[11] Meng X, Deng Y, Dai Z, Meng Z. COVID-19 and anosmia: A review based on up-to-date knowledge. Am J Otolaryngol. 2020; 41(5):102581. [PMID] [PMCID]

[12] Whitcroft KL, Hummel T. Clinical diagnosis and current management strategies for olfactory dysfunction: A review. JAMA Otolaryngol Head Neck Surg. 2019; 145(9):846-53. [PMID]

[13] Vaira LA, Deiana G, Fois AG, Pirina P, Madeddu G, De Vito A, et al. Objective evaluation of anosmia and ageusia in COVID-19 patients: Single-center experience on 72 cases. Head Neck. 2020; 42(6):1252-8. [PMID] [PMCID]

[14] Mercante G, Ferreli F, De Virgilio A, Gaino F, Di Bari M, Colombo G, et al. Prevalence of taste and smell dysfunction in coronavirus disease 2019. JAMA Otolaryngol Head Neck Surg. 2020; 146(8):723-8. [PMID] [PMCID]

[15] Lee Y, Min P, Lee S, Kim SW. Prevalence and duration of acute loss of smell or taste in COVID-19 patients. J Korean Med Sci. 2020; 35(18):e174. [DOI:10.3346/jkms.2020.35.e174] [PMID] [PMCID]

[16] Moein ST, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: A biomarker for COVID-19. Int Forum Allergy Rhinol. 2020; 10(8):944-50. [PMID] [PMCID]

[17] Samimi Ardestani SH, Mohammadi Ardehali M, Rabbani Anari M, Rahmaty B, Erfanian R, Akbari M, et al. The coronavirus disease 2019: The prevalence, prognosis, and recovery from olfactory dysfunction (OD). Acta Otolaryngol. 2021; 141(2):171-80. [PMID]

[18] Klopfenstein T, Kadiane-Oussou NJ, Toko L, Royer PY, Lepiller Q, Gendrin V, et al. Features of anosmia in COVID-19. Med Mal Infect. 2020; 50(5):436-9. [PMID]