DAFTAR PUSTAKA

Aditya, D. M. N. (2020). Anosmia pada COVID-19: Studi Neurobiologi. *KELUWIH: Jurnal Kesehatan dan Kedokteran*, *2*(1), 50-55.

Ahmed, M. U., Hanif, M., Ali, M. J., Haider, M. A., Kherani, D., Memon, G. M., Karim, A. H., & Sattar, A. (2020). Neurological Manifestations of COVID19 (SARS-CoV-2): A Review. *Frontiers in Neurology*, *11*(May), 1–9. https://doi.org/10.3389/fneur.2020.00518

Baig, A. M., Khaleeq, A., Ali, U., & Syeda, H. (2020). Evidence of the COVID19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. *ACS Chemical Neuroscience*, *11*(7), 995–998. https://doi.org/10.1021/acschemneuro.0c00122

Brann, D. H., Tsukahara, T., Weinreb, C., Lipovsek, M., Van Den Berge, K., Gong, B., Chance, R., Macaulay, I. C., Chou, H. J., Fletcher, R. B., Das, D., Street, K., De Bezieux, H. R., Choi, Y. G., Risso, D., Dudoit, S., Purdom, E., Mill, J., Hachem, R. A., … Datta, S. R. (2020). Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *Science Advances*, *6*(31), 1–20. https://doi.org/10.1126/sciadv.abc5801

Bianco, M. R., Modica, D. M., Drago, G. D., Azzolina, A., Mattina, G., De Natale, M., Rossi, G., Amata, M., Canzoneri, G., Manganaro, G., Di Gregorio, F., Russo, R., Pricoco, S., Saita, V., & Allegra, E. (2021). Alteration of Smell and Taste in Asymptomatic and Symptomatic COVID-19 Patients in Sicily, Italy. *Ear, nose, & throat journal*, *100*(2_suppl), 182S–185S. https://doi.org/10.1177/0145561320981447

Dev, N., Sankar, J., Gupta, N., Meena, R. C., Singh, C., Gupta, D. K., & Sen,M. K. (2021). COVID-19 with and without anosmia or dysgeusia: A case-control study. *Journal of medical virology*, *93*(4), 2499–2504. https://doi.org/10.1002/jmv.26784

Dağl, H. Y., Akcan, O. M., Pekcan, S., Gençeli, M., Özdemir, H. S., Uğurlu, B., Özbek, U. S., Parlatan, H., Akın, F., Yazar, A., Kılıç, A. O., Özdemir, M., Taşbent, F. E. (2021). Uncommon Presentation of COVID-19 in Pediatric Patients: Anosmia, 16: 80-84. DOI https://doi.org/ 10.1055/s-0041-1723974. ISSN 1305-7707.

Gane, S. B. C., Kelly, C., & Hopkins, C. (2020). Isolated Sudden onset anosmia in COVID-19 infection. A novel syndrome? *Rhinology*, *58*(3), 299–301. https://doi.org/10.4193/Rhin20.114

Grace, C. (2020). Manifestasi Klinis dan Perjalanan Penyakit pada Pasien Covid- 19. *Majority*, *9*, 49–55.

Hopkins, C., Surda, P., & Kumar, B. N. (2020). *Presentation of new onset anosmia during the COVID-19 pandemic*. *9*, 3–6.

Kesehatan, K. (2020). Pedoman Pencegahan dan Pengendalian Corona Virus deases (Covid-19).*KementrianKesehatan*,*5*,178. https://covid19.go.id/storage/app/media/Protokol/REV05_Pedoman_P2_COVID-19_13_Juli_2020.pdf

Klopfenstein, T., Kadiane-Oussou, N. J., Toko, L., Royer, P. Y., Lepiller, Q.,Gendrin, V., & Zayet, S. (2020). Features of anosmia in COVID-19. *Medecine et Maladies Infectieuses*, *50*(5), 436–439. https://doi.org/10.1016/j.medmal.2020.04.006

Lechien, J. R., Chiesa-Estomba, C. M., De Siati, D. R., Horoi, M., Le Bon, S. D., Rodriguez, A., Dequanter, D., Blecic, S., El Afia, F., Distinguin, L., Chekkoury-Idrissi, Y., Hans, S., Delgado, I. L., Calvo-Henriquez, C., Lavigne, P., Falanga, C., Barillari, M. R., Cammaroto, G., Khalife, M., … Saussez, S. (2020). Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID- 19): a multicenter European study. *European Archives of Oto-RhinoLaryngology*, *277*(8), 2251–2261. https://doi.org/10.1007/s00405-020- 05965-1

Kumar, L., Kahlon, N., Jain, A., Kaur, J., Singh, M., & Pandey, A. K. (2021). Loss of smell and taste in COVID-19 infection in adolescents. *International journal of pediatricotorhinolaryngology*, *142*,110626.https://doi.org/10.1016/j.ijporl.2021.110626

Moein, S. T., Hashemian, S. M. R., Mansourafshar, B., Khorram-Tousi, A., Tabarsi, P., & Doty, R. L. (2020). Smell dysfunction: a biomarker for COVID-19. *International Forum of Allergy and Rhinology*, *10*(8), 944–950. https://doi.org/10.1002/alr.22587

Michael Eliezer, M., Charlotte Hautefort, M., Anne-Laure Hamel, M., Benjamin Verillaud, M., Philippe Herman, MD, P., Emmanuel Houdart, MD, P., Corinne Eloit, M., & Depart, A. A. (2020). Sudden and Complete Olfactory Loss of Function as a Possible Symptom of COVID-19. *Journal of Medical Virology*, *92*(6), 552–555. https://doi.org/10.1002/jmv.25728

Netland, J., Meyerholz, D. K., Moore, S., Cassell, M., & Perlman, S. (2008). Severe Acute Respiratory Syndrome Coronavirus Infection Causes Neuronal Death in the Absence of Encephalitis in Mice Transgenic for Human ACE2. *Journal of Virology*, *82*(15), 7264–7275. https://doi.org/10.1128/jvi.0073708

Patients, L., Taylor, D., Lindsay, A. C., & Halcox, J. P. (2020). Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. *The New England Journal of Medicine*, 0–3.

Russell, B., Moss, C., Rigg, A., Hopkins, C., Papa, S., & Van Hemelrijck, M. (2020). Anosmia and ageusia are emerging as symptoms in patients with COVID-19: What does the current evidence say? *Ecancermedicalscience*, *14*, 9–10. https://doi.org/10.3332/ecancer.2020.ed98

Sari, M. K. (2020). Sosialisasi tentang Pencegahan Covid-19 di Kalangan Siswa Sekolah Dasar di SD Minggiran 2 Kecamatan Papar Kabupaten Kediri. *Jurnal Karya Abdi*, *4*(1), 80–83.

S, M. N. T. N., & Belladonna, M. (2018). Hubungan Paparan Inhalasi Karbon Monoksida Dengan Fungsi Penghidu (Studi Analitik Observasional Pada Pekerja Tukang Sate Di Kota Semarang). *Diponegoro Medical Journal (Jurnal Kedokteran Diponegoro)*, *7*(2), 1617–1621.

Suxin Wan, Qingjie Yi, Shibing Fan, Jinglong Lv, Xianxiang Zhang, Lian Guo, Chunhui Lang, Qing Xiao, Kaihu Xiao, Zhengjun Yi, Mao Qiang, Jianglin Xiang, Bangshuo Zhang, Y. C. (2020). Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). *MedRxiv*, *165*, 1–13.

Swanson, P. A., & McGavern, D. B. (2015). Viral diseases of the central nervous system. *Current Opinion in Virology*, *11*, 44–54. https://doi.org/10.1016/j.coviro.2014.12.009

WHO. (2020a). *Modes of transmission of virus causing COVID-19: implications for IPCprecautionrecommendations*.https://www.who.int/news16room/commentaries/detail/modes-of-transmission-of-virus-causing-covid19implications-for ipc-precaution-recommendations

WHO. (2020b). Tatalaksana klinis infeksi saluran pernapasan akut berat (SARI) suspek penyakit COVID-19. *World Health Organization*, *4*(March), 1–25.

LAMPIRAN 1 : Jurnal Studi Inklusi 1

Clinical Study: Smell & Taste Manifestations

Alteration of Smell and Taste in Asymptomatic and Symptomatic COVID-19 Patients in Sicily, Italy

Maria Rita Bianco, MD[1] , Domenico M. Modica, MD[2] , Gaetano D. Drago, MD[3],
Alfio Azzolina, MD[4], Gianfranco Mattina, MD[2], Massimo De Natale, MD[4],
Giuseppe Rossi, MD[4], Marta Amata, MD[5], Gaspare Canzoneri, MD[2],
Giovanni Manganaro, MD[4], Francesco Di Gregorio, MD[2], Rosario Russo, MD[4],
Salvatore Pricoco, MD[4], Vincenzo Saita, MD[4], and Eugenia Allegra, MD[1]

Abstract

Objectives: Alteration of smell and taste has been reported in patients with coronavirus disease 2019 (COVID-19). The incidence and clinical-symptomatic manifestation of COVID-19 is different between northern and southern Italy. This study aims to evaluate the onset of alteration of smell and taste in asymptomatic and symptomatic patients in Sicily (extreme south of Italy). **Methods:** This prospective cross-sectional study was performed on asymptomatic and symptomatic COVID-19 patients tested for severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) from May 1 to May 15, 2020. A questionnaire was used for evaluating the prevalence of smell and taste disorders in COVID-19 patients before performing nasopharyngeal swab. **Results:** Of the total 292 patients, 242 (83.2%) were negative for SARS-CoV-2 and 50 were positive (16.8%). Twenty-six of the 50 (52%) SARS-CoV-2 positive patients reported smell/taste disorders. Twenty-eight of the 50 (57.1%) SARS-CoV-2 positive patients were hospitalized (group A), and 22 (42.9%) were nonhospitalized (group B). The mean age in group A and group B was 45.4 $\pm$ 13.7 years and 57.0 $\pm$ 15.0, respectively ($P = .007$). The symptoms reported by hospitalized patients were fever (71.4%), cough (64.2%), fatigue (82.1%), and dyspnea (100%), while in nonhospitalized patients, the most reported symptoms were sore throat (72.7%), rhinorrhea (77.2%), and altered smell (81.8%). Anosmia/hyposmia reported in group A and group B was 28.5% and 81.8%, respectively ($P = .001$). **Conclusion:** These preliminary results indicate that the majority of SARS-Cov-2 positive patients in southern Italy did not require hospitalization and presented with milder symptoms or no symptoms and the alterations in smell and taste occurred.

Keywords
COVID-19, SARS-CoV-2, olfactory disorders, smell disorders, taste disorders

Introduction

The epidemic, coronavirus disease 2019 (COVID-19) that appeared in December 2019 in the city of Wuhan, China, as atypical pneumonia, is caused by a novel coronavirus called severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2).[1] The infection rapidly spread from China affecting the whole world, which was declared as global pandemic by the World Health Organization in March 2020. In Italy, the spread of the disease had a very different trend based on the population in north and south. According to a recent report,[2] the weekly incidence reported on May 5, 2020, was 19.07 in Italy, but the average incidence in the

[1] Otolaryngology, Department of Health Science, University of Catanzaro, Italy
[2] Public Health, Epidemiology and Preventive Medicine, ASP Trapani, Italy
[3] Infectious Diseases Unit, Cannizzaro Hospital, Catania, Italy
[4] Otolaryngology Unit, Cannizzaro Hospital, Catania, Italy
[5] Department of Biomedicine and Internal and Specialistic Medicine (DIBIMIS), University of Palermo, Palermo, Italy

Corresponding Author:
Maria Rita Bianco, MD, Otolaryngology–Head and Neck Surgery, Department of Health Sciences, University Magna Graecia of Catanzaro, Viale Europa, Germaneto, 88100, Catanzaro, Italy.
Email: mrbianco@unicz.it

regions of central and northern Italy reached an average of 39.5, while in the south and islands, the average was 2.28. The rapid spread of COVID-19 pandemic is mainly related to the mode of transmission through respiratory droplets. The disease may present with flu-like symptoms characterized by cough, fever, chills, sore throat, or with more severe symptoms such as shortness of breath or difficulty in breathing, nausea, vomiting, or diarrhea, and most cases can be asymptomatic. Symptoms related to the alteration of smell and taste in COVID-19 patients have not been reported from China, where the disease originated. Smell disorders in COVID-19 were initially reported as case reports.[3] Bagheri et al,[4] for the first time, reported that the symptoms of smell and taste alterations in Iranian patients with COVID-19 could show up early. In Italy, in addition to the variations in the spread of the pandemic, the symptomatological manifestation may also have been different. Of the total patients hospitalized, patients admitted to intensive care units in each Italian region at the end of April 2020 showed differences in the incidence of alteration of smell and taste ranging from 5.04% to 20.7%,[2] with higher values observed in the regions of northern Italy. The studies conducted so far in Italy on the onset of symptoms of smell and taste alterations are mainly reported in the northern Italian population.[5,6] Since the course of the disease has shown a difference in terms of incidence and clinical-symptomatic manifestation between northern and southern Italy, this study aims to evaluate the appearance of alteration of smell and taste in asymptomatic and symptomatic patients in Sicily (extreme south of Italy).

Materials and Methods

This prospective cross-sectional study was performed with COVID-19 asymptomatic and symptomatic patients, submitted to a nasopharyngeal swab for SARS-CoV-2 from May 1 to May 15, 2020. Patients were recruited from the Otolaryngology Unit and Infectious Disease Unit of Cannizzaro Hospital, Catania and Public health, Epidemiology and Preventive Medicine, ASP Trapani, Italy. The exclusion criteria were age <18 years, physical or cognitive inability to cooperate, patients admitted to intensive care units, patients with a previous history of hypo/anosmia or taste disturbances. A questionnaire was used for evaluating the prevalence of smell disorders in the context of SARS-CoV-2 infection using the questions included in the COVID-19 Anosmic Reporting Tool of the American Academy of Otolaryngology Head and Neck Surgery,[7] (supplemental materials) which was translated into Italian (See Supplemental Material online). This questionnaire was administered by a physician before performing the nasopharyngeal swab. Severe acute respiratory syndrome-coronavirus-2 infection was diagnosed with a positive reverse transcription-polymerase chain reaction test. Demographic and clinical data were collected anonymously together with the relative responses from a specific database. The study was performed according to the Guidelines for Biomedical Studies Involving Human Subjects (Helsinki Declaration). All patients provided written informed consent. According to the institutional review board of the University of Catanzaro, Italy, this study was exempt from ethical committee approval because the study was based on anonymized data.

Statistical Analyses

Statistical analyses were performed with MedCalc software using the chi-square test and Fisher's exact test. Correlations between the groups and clinical data were examined with the Mann-Whitney U test. A *P* value of <.05 was considered statistically significant.

Results

Overall, 434 patients were recruited; 142 were excluded for incomplete questionnaire. Finally, 292 patients with an average age of 47.6 $\pm$ 13.7 years were included in the study, with 180 men (61.6%) and 112 women (38.4%). While performing the nasopharyngeal swab, 241 (82.5%) patients were asymptomatic and 51 (17.4%) symptomatic. Thirty-nine patients (13.4%) were hospitalized, and 253/292 (86.6%) were nonhospitalized. Of the 253 nonhospitalized patients, 52 were quarantined, 48 were health workers, and 153 patients, defined as not at risk, underwent nasopharyngeal swab for different reasons (hospitalization for other causes, outpatient visit). Of the total of 292 patients, 242 (83.2%) were negative for SARS-CoV-2, and 50 were positive (16.8%). Twenty-six of the 50 (52%) SARS-CoV-2 positive patients reported smell/taste disorders. Twenty-eight of the 50 (57.1%) SARS-CoV-2 positive patients were hospitalized (group A), and 22 (42.9%) were nonhospitalized (group B). The mean age in group A and group B was 45.4 $\pm$ 13.7 years and 57.0 $\pm$ 15.0, respectively (*P* = .007). The univariate analysis did not reveal any other significant differences in the anamnestic and clinical characteristics between the 2 groups of patients (Table 1).

The symptoms most reported by hospitalized patients were fever (71.4%), cough (64.2%), fatigue (82.1%), and dyspnea (100%), while in the group of nonhospitalized patients, the most reported symptoms were sore throat (72.7%), rhinorrhea (77.2%), and altered smell (81.8%). Anosmia/hyposmia reported in group A and group B was 28.5% and 81.8%, respectively (*P* = .001).

The univariate analysis showed a statistically significant difference between the 2 groups in relation to the symptoms of fever, dyspnea, and fatigue, mostly reported in group A, while rhinorrhea, alteration of smell and taste were significantly reported in group B (Table 2).

The multivariate analysis showed that age was the only predictive factor associated with hospitalization (*P* = .018). Considering the alteration of the sense of smell, the multivariate logistic analysis showed that the alteration of the taste was significantly associated with the smell disorders (*P* = .002). An inverse correlation was instead found between alteration of the sense of smell and hospitalization status (*P* = .015).

Table 1. Anamnestic and Clinical Characteristics of Group A and Group B.[a]

Patient characteristics	Group A = 28, N (%)	Group B = 22, N (%)	P-value
Age			
Mean ± SD	57.03 ± 15.0	45.4 ± 13.7	0.007
Range	27-87	27-68	
Sex			
Male	14 (50)	15 (68.2)	0.25
Female	14 (50)	7 (31.8)	
Tobacco use			
No	6 (21.5)	4 (18.2)	1.00
Yes	22 (78.5)	18 (81.8)	
Alcohol use			
No	22 (78.5)	15 (68.2)	0.52
Yes	6 (21.5)	7 (31.8)	
Hypertension			
No	19 (67.8)	15 (68.2)	1.00
Yes	9 (32.2)	7 (31.8)	
Diabetes mellitus			
No	19 (67.9)	19 (86.4)	0.18
Yes	9 (32.1)	3 (13.6)	
Chronic pulmonary disease			
No	25 (89.3)	21 (95.5)	
Yes	3 (10.7)	1 (0.5)	0.62
Asthma			
No	24 (85.7)	21 (95.5)	0.36
Yes	4 (14.3)	1 (0.5)	

Abbreviation: SD, standard deviation.
[a]Group A: hospitalized; Group B: nonhospitalized.

Table 2. Self-Reported Symptoms of the 2 Groups of SARS-CoV-2 Positive Patients.[a]

Symptoms	Group A = 28, N (%)	Group B = 22, N (%)	P-value
Fever			
No	8 (28.6)	16 (72.8)	0.003
Yes	20 (71.4)	6 (27.2)	
Cough			
No	10 (35.8)	11 (50)	0.39
Yes	18 (64.2)	11 (50)	
Dyspnea			
No	17 (60.8)	22 (100)	0.001
Yes	11 (39.2)	0 (0)	
Fatigue			
No	5 (17.9)	12 (54.5)	0.01
Yes	23 (82.1)	10 (45.5)	
Sore throat			
No	14 (50)	6 (27.3)	0.14
Yes	14 (50)	16 (72.7)	
Rhinorrhea			
No	18 (64.3)	5 (22.8)	0.004
Yes	10 (35.7)	17 (77.2)	
Anosmia/hyposmia			
No	20 (71.5)	4 (18.2)	0.001
Yes	8 (28.5)	18 (81.8)	
Dysgeusia			
No	23 (82.2)	9 (41.0)	0.003
Yes	5 (17.8)	13 (59.0)	

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.
[a]Group A: hospitalized; Group B: nonhospitalized.

Discussion

Our study considered asymptomatic and symptomatic patients who underwent nasopharyngeal swab for SARS-CoV-2. The preliminary results showed that 16.8% of all examined patients tested positive for SARS-CoV-2; this result reflects the epidemiological data on the spread of the pandemic in Sicily. Of the SARS-CoV-2 positive patients, 52% had smell/taste disorders, and 81.8% of them were not hospitalized. Hospitalized patients presented mainly fever, fatigue, and dyspnea. In the nonhospitalized group, the most frequent symptomatology was the alteration of the sense of smell, rhinorrhea, and dysgeusia. Regarding the prevalence of disorders of smell and taste in Europe, a multicenter study[8] conducted on a total of 417 hospitalized or quarantined patients found smell/taste disorders in 85.6% of cases. Giacomelli et al[5] conducted a study on 59 patients affected by COVID-19 and hospitalized in the "Sacco" hospital in Milan, Italy, of which 33.9% were affected by smell/taste disorders, and 72.8% of them had an atypical pneumonia. From a recent study by Paderno et al,[6] in a total of 508 positive SARS-CoV-2 patients with 58% of hospitalized patients and 42% of quarantined patients, a prevalence of smell and taste disorders were detected in 73.4% of hospitalized patients and in 93.1% of nonhospitalized patients. Our results are similar to those reported by Paderno et al,[6] probably because the sample of SARS-CoV-2 positive patients is very similar to ours, consisting of a similar percentage of hospitalized and nonhospitalized patients. Recently, Yan et al[9] reported that hospitalized patients with COVID-19 are 10 times less likely to report hyposmia/anosmia than SARS-CoV-2 positive outpatients. This would confirm the earliness of the onset of smell and taste disorders in nonhospitalized COVID-19 patients, where the prevalence of these symptoms is more significant than that in hospitalized patients with more serious symptoms. Moreover, the sense of smell and taste disorders was also reported in several patients hospitalized in intensive care units or with infectious diseases, but the severity of the symptomatology that occurred subsequently influenced the answers given by the patient on the previous symptomatology. The data collected in Italy on the smell/taste symptomatology in patients affected by the COVID-19 are few and concern the population of northern Italy. This can be attributed to the variations in the geographical spread of COVID-19 infection in Italy. Recently, Adorni et al[10] conducted a study on nonhospitalized Italian patients and found that participants in a web-based survey on self-reported symptoms of COVID-19 infection were mostly from northern regions. This reflects the higher incidence of COVID-19 outbreak in the northern regions than in the southern regions. In addition to the higher incidence of the spread of infection in the regions of northern Italy, an increase in mortality owing to COVID-19 was

observed. Stortichini et al[11] found an increase in mortality attributable to COVID-19 infection in some northern provinces that was 400% greater than the rest of country. Mortality rates were lower in central Italy and minimal or absent in the south and the islands. The different spread of the infection between the north and south could be attributed to different climatic and socioeconomic conditions. Cai et al[12] reported an association between the SARS-CoV-2 outbreak and metrological factors, including temperature, humidity, wind velocity, and air pollution. Higher temperature and humidity reduce SARS-CoV-2 transmission rate owing to their impact on the viral growth rate.[13,14] The higher relative humidity and high wind velocity decrease the suspending time of the viruses in the air. In the southern regions, the weather is warmer, and there are more sunny days during the year than in the northern regions; therefore, the exposure to the ultraviolet light is higher. It is known that the ultraviolet light promote vitamin D production, which through several mechanisms increases the immune system and reduces the risk of virus infections.[15] For this reason, the southern population could acquire an immune resistance to the SARS-CoV-2.[16] In contrast, the northern regions of Italy present a socioeconomic contest, with industrialization and urbanization favoring air pollution. In these conditions, the air is less rarefied and can contribute to the persistence of the droplets of SARS-CoV-2 in the air.[16] For these reasons, both the type and severity of the symptoms could be different in different regions of Italy. Our study is still ongoing, and there are several hypothesis for the interpretation of this data. It is possible that in patients who regain a sense of smell, an antibody response develops early, which avoids the patient's more serious symptomatology that requires hospitalization. However, a lack of objective olfactory testing represents a limitation of our study and further studies have been done to confirm this our hypothesis.

Conclusion

In summary, these preliminary results indicate that the majority of SARS-Cov-2 positive patients in Sicily did not require hospitalization were presenting with milder symptomatology, and the disturbances of smell and taste represent prodromal symptoms of the infection.

Declaration of Conflicting Interests

Funding

ORCID iD

Maria Rita Bianco ⬤ https://orcid.org/0000-0003-4512-1378
Domenico M. Modica ⬤ https://orcid.org/0000-0003-2016-4101
Eugenia Allegra ⬤ https://orcid.org/0000-0002-5202-4333

Supplemental Material

Supplemental material for this article is available online.

References

1. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-1911-march-2020

2. Accessed May 11, 2020. https://web.unicz.it/it/news/85338/andamento-della-diffusione-del-sars-cov-2

3. Brookes NR, Fairley JW, Brookes GB. Acute olfactory dysfunction—a primary presentation of COVID-19 infection. *Ear, Nose & Throat J*. 2020;99(9):94-98.

4. Bagheri SH, Asghari A, Farhadi M, et al. Coincidence of COVID-19 epidemic and olfactory dysfunction outbreak in Iran. *Med J Islam Repub Iran*. 2020;34(1):446-452.

5. Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clin Infect Dis*. 2020;71(15):889-890.

6. Paderno A, Schreiber A, Grammatica A, et al. Smell and taste alterations in Covid19: a cross sectional analysis of different cohorts. *Int Forum Allergy Rhinol*. 2020;10(8):955-962.

7. American Academy of Otolaryngology–Head and Neck Surgery. COVID-19 Anosmia Reporting Tool for Clinicians. 2020. https://www.entnet.org/content/reporting-tool-patients-anosmia-related-covid-19

8. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a Multicenter European Study. *Eur Arch Otorhinolaryngol*. 2020;277(8):2251-2261.

9. Yan CH, Faraji F, Prajapati DP, Ostrander BT, De Conde AS. Self-reported olfactory loss associated with outpatient clinical course in COVID-19. *Int Forum Allergy Rhinol*. 2020;10(7):821-883.

10. Adorni F, Prinelli F, Bianchi F, et al. Self-reported symptoms of SARS-CoV-2 infection in a nonhospitalized population in Italy: cross-sectional study of the EPICOVID19 web-based survey. *JMIR Public Health Surveill*. 2020;6(3):e21866.

11. Scortichini M, Schneider Dos Santos R, De' Donato F, et al. Excess mortality during the COVID-19 outbreak in Italy: a two-stage interrupted time-series analysis [published online October 14, 2020]. *Int J Epidemiol*. 2020;dyaa169.

12. Cai QC, Lu J, Xu QF, et al. Influence of meteorological factors and air pollution on the outbreak of severe acute respiratory syndrome. *Public Health*. 2007;121(4):258-265.

13. Sarkodie SA, Owusu PA. Impact of meteorological factors on COVID-19 pandemic: evidence from top 20 countries with confirmed cases. *Environ Res*. 2020;191:110101.

14. Chan KH, Peiris JS, Lam SY, et al. The effects of temperature and relative humidity on the viability of the SARS coronavirus. *Adv Virol*. 2011;2011:734690.

15. Schwalfenberg GK. A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency. *Mol Nutr Food Res*. 2011;55(1):96-108.

16. Merow C, Urban MC. Seasonality and uncertainty in global COVID-19 growth rates. *Proc Natl Acad Sci U S A*. 2020; 202008590.

LAMPIRAN 2 : Jurnal Studi Inklusi 2

Loss of smell and taste in COVID-19 infection in adolescents

Lakshit Kumar [a], Namrata Kahlon [b], Avani Jain [a,*], Jasleen Kaur [a], Mitasha Singh [c], A.K. Pandey [b]

[a] Department of ENT, ESIC Medical College and Hospital, Faridabad, India
[b] Department of Physiology, ESIC Medical College and Hospital, Faridabad, India
[c] Department of Community Medicine, ESIC Medical College and Hospital, Faridabad, India

ARTICLE INFO

ABSTRACT

Objectives: To study the prevalence, clinical course and outcomes of olfactory and taste dysfunction in COVID-19 positive adolescents.
Methods: This prospective study was carried out from May to August 2020. The adolescents, aged 10–19 years, who were detected COVID-19 positive by RT-PCR with mild to moderate disease were included in the study. The following epidemiological and clinical outcomes were studied: age, sex, general symptoms, olfactory and taste dysfunction.
Results: Out of 141 patients included in the study, there were 83 males (58.9%) and 58 females (41.1%). The age varied from 10 to 19 years with an average of 15.2 years. Forty patients (28.4%) had olfactory or taste dysfunction. Out of these 40 patients, 28 patients (19.8%) had both olfactory and taste dysfunction. Of the 34 patients (24.1%) who complained of olfactory dysfunction, 16 patients complained of hyposmia and 18 patients complained of anosmia. Dysgeusia was reported by 34 patients (24.1%). The duration of OTD varied from 2 to 15 days with an average of 5.7 days.
Conclusion: Loss of smell and taste are common symptoms in COVID-19 positive adolescents. It recovers spontaneously within a few weeks, along with the resolution of other symptoms.

1. Introduction

COVID-19, an ongoing global pandemic, results from infection with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). There are varied clinical presentations of the disease in children. They may be asymptomatic, mildly symptomatic with symptoms similar to common viral respiratory tract infections, or it may manifest as multisystem inflammatory syndrome. However, it has been reported that the infection in most children is mild, and some are completely asymptomatic, and are less likely to be hospitalized as compared to adults [1, 2]. The possible causes for less severe disease in children as compared to adults are: decreased expression of angiotensin converting enzyme 2 (the receptor for SARS-CoV-2), less intense immune responsivity and potential viral interference by co-infecting viruses [3,4].

There is increasing evidence that olfactory and taste dysfunction can present in COVID-19 patients. Recognizing this dysfunction can help in identifying asymptomatic individuals who may act as carriers, and thereby prevent further spread of the disease. Although olfactory and taste dysfunction has been reported in COVID-19 adult patients, there is limited data on its occurrence in children and adolescents. The main objective of this study was to determine the prevalence of olfactory and taste dysfunction in adolescents and its outcomes.

2. Methodology

We evaluated the olfactory and taste dysfunction in adolescent COVID-19 patients at ESIC Medical College and Hospital, Faridabad from May to August 2020. This was a prospective study and was approved by the Institutional Ethics Committee. The data was collected during ENT consultation or over the phone. The inclusion criteria was adolescents, aged 10–19 years, who were detected COVID-19 positive by RT-PCR during the study period with mild to moderate disease [5]. Those patients who could not be contacted even after 3 attempts were excluded from the study. The exclusion criteria were: patients with severe disease or those on assisted ventilation, psychiatric or neurological disorders, previous surgery or radiation of the nasal or oral cavity, chronic rhinosinusitis, pre existing smell or taste disturbances.

All the adolescents with influenza like illness (ILI) who presented to the study centre during the study period underwent COVID-19 testing by RT-PCR of nasopharyngeal swabs. The patients who were COVID-19

positive and matching the inclusion criteria were included in the study. After COVID-19 positive report, these patients were further contacted and detailed history was taken.

At the time of presentation, the demographic characteristics of the patients were noted. Clinical history was taken from the parent or the patient. The onset and duration of the symptoms were noted, including loss of smell and taste. The patients were asked to rate their smell sensation at its worst point during the infection, as normal, partial (hyposmia) or complete (anosmia) loss of smell. All the patients were asked if they had any alteration in taste (dysgeusia) or not. The order of appearance of symptoms was noted. The duration of loss of smell and/or taste was noted in a follow up ENT consultation or by telephone contact. The patients were followed up till their OTD recovered or COVID-19 negative report, whichever was later.

Data analysis was done using Epi info version 7 software. Differences between groups were assessed using chi square test for qualitative data and "p" value less than 0.05 was considered as statistically significant.

3. Results

A total of 141 patients were included in the study, including 83 males (58.9%) and 58 females (41.1%). The age ranged from 10 to 19 years with a mean of 15.2 years. The symptoms of the patients recorded were: malaise in 20 patients (14.2%), sore throat in 28 patients (19.9%), cough in 29 patients (20.6%), fever in 68 patients (48.2%), diarrhoea in 8 patients (5.7%), nasal discharge in 5 patients (3.5%) and headache in 8 patients (5.7%).

Out of 141 patients, 40 patients (28.4%) reported olfactory or taste dysfunction. Olfactory dysfunction was reported by 34 patients (24.1%), taste dysfunction was reported by 34 patients (24.1%) and, both olfactory and taste dysfunction was reported by 28 patients (19.8%). Of the 34 patients who reported olfactory dysfunction, 16 patients complained of hyposmia and 18 patients complained of anosmia. The OTD reported by the two age groups 10–14 years and 15–19 years was 26% and 29.7%, respectively. This difference between the two age groups was not statistically significant (p = 0.644). OTD was reported by 30.1% males and 25.9% females. This difference was not statistically significant (p = 0.581).

OTD was first noticed before the appearance of other symptoms in 19 patients (13.5%) and after the appearance of other symptoms in 21 patients (14.9%). The duration of OTD varied from 2 to 15 days with an average of 5.7 days. In only three patients the OTD persisted following recovery from COVID-19 infection, that is, after COVID-19 negative report. Out of these three patients, the duration of OTD was 10 days in two patients and 15 days in one patient. The chemosensory dysfunction of all the patients recovered completely.

The association of OTD with other symptoms is shown in Table 1. It was found that OTD had significant positive association with patients having fever (Odds ratio = 10.60, p = 0.001) and diarrhoea (Odds ratio = 4.86, p = 0.027).

4. Discussion

Early reports from China, Italy and United States of America indicated that children were underrepresented among COVID-19 cases, especially among severe and fatal cases [2,6,7]. However, a study by Bi et al. suggested that children are just as likely as adults to be infected by SARS-CoV-2, but are less likely to be symptomatic or develop severe or critical disease [8]. Children have milder clinical symptoms than adults, which could be responsible for reduced testing for SARS-CoV-2 in children as compared to adults [9]. Children, who are asymptomatic or mildly symptomatic, may play a role in community transmission of the virus [10]. Most of the children infected have been part of a family cluster outbreak. Also, the symptoms of other common viral respiratory tract infections in children, such as influenza and respiratory syncytial virus may overlap and pose additional diagnostic challenges.

Table 1
Association of OTD and general symptoms.

	Olfactory or taste dysfunction	
Malaise	No (n = 101)	Yes (n = 40)
No	89	32
Yes	12	8
Odds ratio, p value	1.55, 0.213	
Sore throat		
No	85	28
Yes	16	12
Odds ratio, p value	3.61, 0.057	
Cough		
No	83	29
Yes	18	11
Odds ratio, p value	1.64, 0.200	
Fever		
No	61	12
Yes	40	28
Odds ratio, p value	10.60, 0.001	
Diarrhoea		
No	98	35
Yes	3	5
Odds ratio, p value	4.86, 0.027	

In adults, the most frequently reported clinical features of COVID-19 are fever, cough, shortness of breath, myalgia, fatigue and headache [10]. Studies have found similar symptoms in children. A review by Hoang et al. [11] reported that the most common clinical manifestations in children were fever (59.1%), cough (55.9%), rhinorrhoea (20.0%) and myalgia/fatigue (18.7%). Children rarely progressed to severe or critical disease, unlike adults [12]. The prevalence of gastrointestinal symptoms varies in various studies.

Sudden loss of smell and taste have also been reported as symptoms of COVID-19 infection. The exact pathophysiology of OTD in COVID-19 patients is still unknown. The possible hypotheses are direct extension via angiotensin-converting enzyme 2 (ACE2) receptor on the nasal epithelium and/or direct invasion of the olfactory bulb and central nervous system [13]. ACE2 is highly expressed on the oral mucosa and tongue, which may be a possible mechanism for gustatory dysfunction. In adults, anosmia and dysgeusia in COVID-19 patients has been widely reported in literature with a varying prevalence. There is a difference in the prevalence of olfactory and taste dysfunction between the Asian [14–16] and European population [17–22]. This may be due to increased expression of ACE2 in the European population as compared to the Asian population [23]. In a review and meta analysis by von Bartheld et al. [24], the prevalence of olfactory and/or gustatory dysfunction in the East Asian and European populations was found to be 23.4% and 54.7%, respectively.

Although there are multiple reports on the prevalence of OTD in adult patients with COVID-19, there is limited data regarding its occurrence in the paediatric population. This may be due to the fact that the diagnosis of olfactory disorders in young children is challenging. PQ Mak et al. [25] reported three children aged- 14 years, 15 years and 17 years, with COVID-19 infection who presented with anosmia and/or ageusia. In a multicentric study by Qiu et al. [16], out of 27 COVID-19 positive children, ten children (37%) reported olfactory or gustatory dysfunction. The age of these ten children ranged from 15 to 17 years, and six were male. Gaborieau et al. [26] reported anosmia/dysgeusia in seven out of 157 children (4.5%) who were positive for SARS-CoV-2 by RT-PCR test. In a study by Somekh et al. [27], in the age group 11–17 years, eight out of twenty children (40%) had altered smell or taste, and in the age group 5–11 years, no children had altered smell or taste. One of the possible mechanisms for OTD in COVID-19 patients is the ability of SARS CoV-2 to bind to ACE2 in the nasal and oral mucosa. Somekh et al. [27] correlated the difference in the impairment of sensation in different age groups with ACE2 expression in the corresponding age groups. They reported that the sensory impairment was significantly lower in children as compared to adult COVID-19 positive patients. This

2

significant difference supports the data that showed age dependent expression of ACE2 in the nasal epithelium. This could possibly explain that the differences in the sensory impairment may be due to distribution and expression of ACE2 in the oral cavity and nasal epithelium. However, in our study there was no significant difference in the OTD in different age groups.

In our study, the OTD lasted for 2–15 days, with an average of 5.7 days. Three patients reported persisting OTD following recovery from COVID-19 infection, that is, after COVID-19 negative report. Out of these three patients, the OTD was reported for a total duration of 10 days in two patients and 15 days in one patient. However, all the patients reported complete recovery of their smell and taste sensations. This rapid and spontaneous recovery of OTD has also been reported in adult COVID-19 patients. Some studies report that chemosensory loss in COVID-19 adult patients recovers in about 1–2 weeks of onset, in conjunction with improvement of infection [14,17]. This short duration and spontaneous recovery supports the findings that SARS-CoV-2 targets the non neural olfactory epithelial cells. This knowledge of spontaneous recovery of chemosensory dysfunction helps in reassuring patients. Meini et al. [21], reported a complete and near complete recovery in 83% of the studied patients in a month from the hospital discharge (mean recovery time for females was 26 days and for males 14 days). Lechien et al. [17] reported that the olfactory dysfunction persisted after the resolution of other symptoms in 63.0% of cases. The short-term olfaction recovery rate, which was assessed in 59 clinically cured patients, was 44.0%.

This prospective study reports olfactory and taste dysfunction in adolescent COVID-19 patients. Out of the 141 patients included in the study, 28.4% (40 patients) reported OTD. Although the prevalence of OTD in COVID-19 adult patients has been reported in literature, limited research has been published on OTD in children. This study has several limitations. Firstly, in our patients, there was no objective evaluation of olfactory and taste dysfunction, such as psychophysical tests or electrophysiological methods, because of the risk of exposure to health care workers. All the symptoms were self reported by the patients. Secondly, this study included only patients with mild to moderate disease. Patients with severe disease were not included in the study. Additionally, smell and taste disorders are confounded if not separately measured [28].

5. Conclusion

Loss of smell and taste are common symptoms in COVID-19 patients and may be the only symptoms in some patients. These symptoms may help in early diagnosis of COVID-19 patients and in reducing the spread of infection. There is limited data on the prevalence of OTD in children and adolescents. In our study, the prevalence of OTD in COVID-19 adolescent patients was 28.4%. OTD resolves spontaneously in around 1–2 weeks of onset.

Conflicts of interest and source of funding (for all the authors)

None declared.

References

[1] E. Wang, K. Brar, COVID-19 in children: an epidemiology study from China, J Allergy Clin Immunol Pract 8 (2020) 2118–2120.
[2] N. Parri, M. Lenge, D. Buonsenso, Coronavirus Infection in pediatric emergency departments (CONFIDENCE) research group. Children with Covid-19 in pediatric emergency departments in Italy, N. Engl. J. Med. 383 (2020) 187–190.
[3] S. Bunyavanich, A. Do, A. Vicencio, Nasal gene expression angiotensin-converting enzyme 2 in children and adults, J. Am. Med. Assoc. 323 (2020) 2427–2429.
[4] P. Brodin, Why is COVID-19 so mild in children? Acta Paediatr. 109 (2020) 1082–1083.
[5] Covid-19 Treatment Guidelines Panel, Coronavirus disease 2019 (COVID-19) treatment guidelines. National institutes of health, Available at: https://www.covid19treatmentguidelines.nih.gov/. (Accessed November 2020).
[6] Y. Dong, X. Mo, Y. Hu, X. Qi, F. Jiang, Z. Jiang, et al., Epidemiology of COVID-19 among children in China, Pediatrics 145 (2020), e20200702.
[7] Cdc Covid-19 Response Team, Coronavirus disease 2019 in children—United States, february 12–april 2, 2020, Morb. Mortal. Wkly. Rep. 69 (2020) 422–426.
[8] Q. Bi, Y. Wu, S. Mei, et al., Epidemiology and transmission of COVID-19 in 391 cases and 1,286 of their close contacts in in Shenzhen China: a retrospective cohort study, Lancet Infect. Dis. 20 (2020) 911–919.
[9] P. Zimmermann, N. Curtis, Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children, Pediatr. Infect. Dis. J. 39 (2020) 355–368.
[10] W.J. Guan, Z.Y. Ni, Y. Hu, W.H. Liang, C.Q. Ou, J.X. He, et al., Clinical characteristics of coronavirus disease 2019 in China, N. Engl. J. Med. 382 (2020) 1708–1720.
[11] A. Hoang, K. Chorath, A. Moreira, M. Evans, F. Burmeister-Morton, F. Burmeister, et al., COVID-19 in 7780 pediatric patients: a systematic review, EClinicalMedicine 24 (2020) 100433.
[12] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (2020) 497–506.
[13] R. Pellegrino, K.W. Cooper, A. Di Pizio, P.V. Joseph, S. Bhutani, V. Parma, Coronaviruses and the chemical senses: past, present, and future, Chem. Senses 45 (2020) 415–422.
[14] A. Jain, L. Kumar, J. Kaur, T. Baisla, P. Goyal, A.K. Pandey, A. Das, L. Parashar, Olfactory and taste dysfunction in coronavirus disease 2019 patients: its prevalence and outcomes, J. Laryngol. Otol. (2020 Nov 16) 1–5.
[15] L. Mao, H. Jin, M. Wang, Y. Hu, S. Chen, Q. He, et al., Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China, JAMA Neurol 77 (2020) 683–690.
[16] C. Qiu, C. Cui, C. Hautefort, A. Haehner, J. Zhao, Q. Yao, et al., Olfactory and gustatory dysfunction as an early identifier of COVID-19 in adults and children: an international multicenter study, Otolaryngol. Head Neck Surg. (2020 Jun 16), 194599820934376.
[17] J.R. Lechien, C.M. Chiesta-Estomba, D.R. De Siati, M. Horoi, S.D. Le Bon, A. Rodriguez, et al., Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study, Eur. Arch. Oto-Rhino-Laryngol. 277 (2020) 2251–2261.
[18] M.M. Speth, T. Singer-Cornelius, M. Oberle, I. Gengler, S.J. Brockmeier, A. R. Sedaghat, Olfactory dysfunction and sinonasal symptomatology in COVID-19: prevalence, severity, timing, and associated characteristics, Otolaryngol. Head Neck Surg. 163 (2020) 114–120.
[19] A. Patel, E. Charani, D. Ariyanayagam, A. Abdulaal, S.J. Denny, N. Mughal, et al., New-onset anosmia and ageusia in adult patients diagnosed with SARS-CoV-2 infection, Clin. Microbiol. Infect. 26 (2020) 1236–1241.
[20] V. Gorzkowski, S. Bevilacqua, A. Charmillon, R. Jankowski, P. Gallet, C. Rumeau, D.T. Nguyen, Evolution of olfactory disorders in COVID-19 patients, Laryngoscope (2020 Jul 2), https://doi.org/10.1002/lary.28957.
[21] S. Meini, L.R. Suardi, M. Busoni, A.T. Roberts, A. Fortini, Olfactory and gustatory dysfunctions in 100 patients hospitalized for COVID-19: sex differences and recovery time in real-life, Eur. Arch. Oto-Rhino-Laryngol. 4 (2020) 1–5.
[22] A. Haehner, J. Draf, S. Dräger, K. de With, T. Hummel, Predictive value of sudden olfactory loss in the diagnosis of COVID-19, ORL J Otorhinolaryngol Relat Spec 82 (2020) 175–180.
[23] Y. Cao, L. Li, Z. Feng, S. Wan, P. Huang, X. Sun, et al., Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations, Cell Discov 6 (2020) 11.
[24] C.S. von Bartheld, M.M. Hagen, R. Butowt, Prevalence of chemosensory dysfunction in COVID-19 patients: a systematic review and meta-analysis reveals significant ethnic differences, Preprint. *medRxiv* (2020) 2020, https://doi.org/10.1101/2020.06.15.20132134, 06.15.20132134. Published 2020 Jun 17.
[25] P.Q. Mak, K.S. Chung, J.S. Wong, C.C. Shek, M.Y. Kwan, Anosmia and ageusia: not an uncommon presentation of COVID-19 infection in children and adolescents, Pediatr. Infect. Dis. J. 39 (2020) e199–e200.
[26] L. Gaborieau, C. Delestrain, P. Bensaid, A. Vizeneux, P. Blanc, A. Garraffo, et al., Epidemiology and clinical presentation of children hospitalized with SARS-CoV-2 infection in suburbs of paris, J. Clin. Med. 9 (2020) 2227.
[27] I. Somekh, H. Yakub Hanna, E. Heller, H. Bibi, E. Somekh, Age-dependent sensory impairment in COVID-19 infection and its correlation with ACE2 expression, Pediatr. Infect. Dis. J. 39 (2020) e270–e272.
[28] D.A. Deems, R.L. Doty, R.G. Settle, V. Moore-Gillon, P. Shaman, A.F. Mester, et al., Smell and taste disorders, a study of 750 patients from the university of Pennsylvania smell and taste center, Arch. Otolaryngol. Head Neck Surg. 117 (1991) 519–528.

Check for updates

RESEARCH ARTICLE

JOURNAL OF
MEDICAL VIROLOGY WILEY

COVID-19 with and without anosmia or dysgeusia: A case-control study

Nishanth Dev[1] | **Jhuma Sankar**[2] | **Nitesh Gupta**[3] | **Ramesh Chand Meena**[1] | **Charanjit Singh**[1] | **D. K. Gupta**[1] | **M. K. Sen**[3]

[1]Department of Medicine, VMMC & Safdarjung Hospital, Delhi, India

[2]Department of Pediatrics, All India Institute of Medical Sciences, Delhi, India

[3]Department of Pulmonology and critical care, VMMC & Safdarjung Hospital, Delhi, India

Correspondence
Nishanth Dev, Department of Medicine, VMMC & Safdarjung Hospital, Delhi 110029, India.
Email: devnishant@gmail.com

Abstract

Various new clinical signs and symptoms, such as dysfunction of smell (anosmia) and taste (dysgeusia) have emerged ever since the coronavirus disease 2019 (COVID-19) pandemic begun. The objective of this study was to identify the clinical presentation and factors associated with 'new loss/change of smell (anosmia) or taste (dysgeusia)' at admission in patients positive by real time polymerase chain reaction for SARS-CoV-2 infection. All adult COVID-19 patients with new onset anosmia or dysgeusia at admission were included in study group. Equal number of age and gender matched COVID-19 patients without anosmia or dysgeusia at admission were included in the control group. A total of 261 COVID-19 patients were admitted during the study period of which 55 (21%) had anosmia and or dysgeusia. The mean (*SD*) age was 36 (13) years and majority were males (58%, *n* = 32). Comorbidity was present in 38% of cases (*n* = 21). Anosmia and dysgeusia were noted in more than 1/5th of the cases. Anosmia (96%, *n* = 53) was more common than dysgeusia (75%, *n* = 41). Presence of both ansomia and dysgeusia was noted in 71% of patients (*n* = 39). On comparing the cases with the controls, on univariate analysis, fever (higher in cases), rhinitis (lower in cases), thrombocytopenia, elevated creatinine and bilirubin (all higher in cases) were significantly associated with anosmia or dysgeusia. On multivariate analysis, only rhinitis (odds ratio [OR]: 0.28; 95% confidence interval [CI]: 0.09–0.83; *p* = .02) thrombocytopenia (OR: 0.99; 95% CI: 0.99–0.99; *p* = .01) and elevated creatinine (OR: 7.6; 95% CI: 1.5–37.6; *p* = .01) remained significant. In this retrospective study of COVID-19 patients, we found anosmia and dysgeusia in more than 1/5th of the cases. Absence of rhinitis, low platelet counts and elevated creatinine were associated with anosmia or dysgeusia in these patients.

KEYWORDS

anosmia, COVID-19, dysgeusia, rhinitis, SARS-CoV-2

1 | INTRODUCTION

The current pandemic of coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to evolve and perplex the clinicians across the globe.

Various new clinical signs and symptoms have emerged ever since the pandemic begun. The expanding list of various clinical manifestations also includes dysfunction of smell and taste i.e. anosmia and dysgeusia.[1] Various case reports and case series have highlighted the same and explored its pathophysiology.[2]

wileyonlinelibrary.com/journal/jmv
2499

Although the exact pathophysiology of these symptoms has not been established, various animal models have demonstrated high levels of angiotensin converting enzyme (ACE2) proteins expression by nasal and olfactory support cells which is used by the SARS-CoV-2 to infect the cells.[3] Many believe these symptoms to be part of the neurological manifestations of COVID-19 with evidence suggesting propagation of the virus through the olfactory pathway.[4]

The increasing evidence of olfactory or gustatory dysfunction as potential early symptoms of COVID-19 infection has also prompted the Centers for Disease Control and Prevention to add "new loss of taste or smell" to its list of COVID-19 symptoms.[5] Despite the recognition of anosmia and dysgeusia as an important clinical symptom and sign of COVID-19, there is paucity of data describing various clinical features, co-morbidities and clinical outcome associated with anosmia and dysgeusia in patients with COVID-19. In this retrospective case control study, we aim to identify clinical presentation and factors associated with of new onset anosmia and/or dysgeusia at admission in COVID-19 patients admitted to a tertiary care center in North India.

2 | MATERIALS AND METHODS

Design and setting: We conducted this retrospective case control study of prospectively collected data at our tertiary care center Medical college and hospital in North India between May 1st and June 15th, 2020.

2.1 | Participants

Cases: All laboratory confirmed COVID-19 patients greatert than 17 years of age with clinical presentation of "new loss/change of taste or smell" at admission during the study period were included in the study group.

Controls: Equal number of age and gender matched COVID-19 patients without clinical presentation of "new loss/change of taste or smell" at admission were included in the control or comparison group.

We excluded those with pre-existing history of anosmia and/or dysgeusia, nasal or oral illness, neurodegenerative disorder, on chemotherapy or radiotherapy. Patients who were unable to give history, transferred out, absconded were also excluded from the study. The study was approved by the Institutional Ethics Committee and patient consent was waived off owing to the retrospective nature of the study.

2.2 | Definitions used in the study

- Anosmia was defined as temporary or permanent loss of the ability to detect one or more smells.
- Dysgeusia was defined as distortion of the sense of taste.

Methods: Case records of patients with SARS-CoV-2 infection admitted to the COVID wards from May 1st to June 15th, 2020 were retrieved. Information retrieved included demographic features, such as age, gender, duration of illness, signs, and symptoms at admission, laboratory parameters, treatment received, and discharge or death from hospital were recorded.

Statistical analysis: Data were entered into Microsoft Excel 2013 and analyzed using Stata 11 (Stata Corp.). Missing values of clinical and laboratory variables were assumed to be normal for the purpose of statistical analysis. Continuous variables are presented as mean (SD), or median (interquartille range [IQR]) as appropriate. Categorical variables are presented as absolute numbers (%). Continuous variables were compared using either independent Student's t test or Wilcoxon rank-sum test (based on the distribution of the data). Categorical data were compared using χ^2 test or Fischer's exact test as appropriate. For assessing the factors associated with anosmia or dysgeusia (we combined anosmia and/or dysgeusia for this purpose), univariate analysis followed by multivariate analysis of key variables including age, gender, presence of underlying co-morbidities, key clinical features and laboratory parameters was performed. In the multivariate model by logistic regression, only those variables that were clinically relevant and did not result in multicollinearity were included as the independent variables.[6]

3 | RESULTS

3.1 | Baseline characteristics

The case records of 261 COVID-19 patients were screened during the study period. A total of 55 patients who were eligible were enrolled in the study group. An equal number of age and gender matched patients fulfilling the inclusion and exclusion criteria were enrolled in the control group. The baseline characteristics of the enrolled patients are described in Table 1. The mean (SD) age was

TABLE 1 Demographic profile of the cases and control

Variables	Case n = 55	Control n = 55	p Value
Age (years) (mean, SD)	36 (13)	36 (13)	.96
Gender (male)	32 (58%)	32 (58%)	1
History of contact with COVID-19 patient	16 (29%)	17 (31%)	.9
Comorbidity			
• Diabetes	02 (3.6%)	04 (7%)	.06
• Hypertension	07 (13%)	03 (5%)	
• Diabetes and hypertension	05 (9%)	03 (5%)	
• Hypothyroidism	07 (13%)	01 (2%)	
• Tuberculosis	00	01 (2%)	
• Chronic Kidney disease	00	01 (2%)	
• Bronchial asthma	00	03 (5%)	
• None	34 (62%)	39 (71%)	
Lifestyle			
• Smoker	14 (25%)	10 (18%)	.35
• Alcoholic	12 (22%)	06 (11%)	.12

Abbreviation: COVID-19, coronavirus disease 2019.

TABLE 2 Clinical, laboratory features, treatment details, and outcomes

Variables	Case, n = 55	Control, n = 55	p Value
Clinical features			
• Fever	41 (75%)	28 (51%)	.01
• Cough	29 (53%)	23 (42%)	.25
• Dyspnoea	15 (27%)	15 (27%)	1
• Rhinitis	09 (16%)	20 (36%)	.017
• Anosmia	53 (96%)	00	–
• Dysgeusia	41 (75%)	00	–
• Anosmia and dysgeusia	39 (71%)	00	–
Duration in days (mean, SD)			
• Anosmia	07 (3)	–	–
• Dysgeusia	07 (2)	–	–
Laboratory features			
• Haemoglobin (g/dl) (mean, SD)	12 (2)	13 (2)	.07
• Total leucocyte count/mm^3 (median, IQR)	5600 (4500, 7800)	5900 (4800, 6800)	.84
• Platelets (in lakh)/mm^3 (median, IQR)	1.5 (1, 2.2)	1.94 (1.53, 2.56)	.0009
• Creatinine (mg/dl) (median, IQR)	0.9 (0.8, 1.2)	0.8 (.6, 0.9)	.0001
• Bilirubin (mg/dl) (mean, SD)	0.9 (0.25)	0.6 (0.2)	<.0001
• Chest X-ray (infiltrates)	13 (24%)	15 (27%)	.66
Treatment received			
• Oxygen therapy	10 (18%)	12 (22%)	.63
• Antibiotics	34 (62%)	31 (56%)	.56
Duration of hospital stay in days (mean, SD)	11 (02)	13 (03)	.001
Discharged	55 (100%)	55 (100%)	1

Abbreviation: IQR, interquartile range.

36 (13) years and majority were men (n = 32, 58%) in both the groups. Comorbidities was present in 38 per cent (n = 21) of patients in the study group and 29 percent (n = 16) in the comparison group (p = .06). Hypertension and hypothyroidism were the commonest co-morbidity in the study group (13% each) where as diabetes mellitus was the commonest in the control group (7%). Twenty five percent of the study subjects (n = 14) and 18% percent (n = 10) of the control group had history of smoking. Twenty two percent in the study group (n = 12) and 11% in the comparison group (n = 06) consumed alcohol. There was no difference in the baseline characteristics between the groups. History of contact with a COVID-19 patient was found in 29% (n = 16) and 31% (n = 17) in cases and control respectively.

3.2 | Comparison of clinical and laboratory parameters between the "cases" and "controls"

On evaluation of the 55 patients with olfactory and gustatory symptoms, anosmia (96%, n = 53) was more common than dysgeusia (75%, n = 41). Presence of both ansomia and dysgeusia was noted in 71% of the patients (n = 31). Fever was present in 75% (n = 41) and 51% (n = 28) in the "cases" and "controls," respectively (p = .01). Rhinitis was higher in controls (n = 20, 36%) as than cases (n = 09, 16%; p = .017). The clinical and laboratory features of the cases and

controls are described in Table 2. The median (IQR) duration of anosmia and dysgeusia was 7 (4, 10) days and 7 (5, 2) days in the "cases" and "controls," respectively.

The mean (SD) of serum bilirubin was 0.9 mg/dl (0.25) in the study group and 0.6 mg/dl (0.2) in the comparison group (p < .0001). Serum creatinine level was higher in the "cases" with median (IQR) value of 0.9 mg/dl (0.8, 1.2) as compared to 0.8 mg/dl (0.6, 0.9) (p = .0001). A statistically significant difference was also seen in the platelet count (p = .0009). The median (IQR) platelet count was lower in the "cases" (1.5 lakh/mm^3 [1, 2.2]) as compared to "controls" (1.94 lakh/mm^3 [1.53, 2.56]). About 1/4th of the patients had an abnormal chest X-ray in both the groups.

The disease severity of patients enrolled was comparable in both the groups. The cases had 18% (n = 10) in the moderate category as compared to 22% (n = 12) in the control group with p = .63. None of the subjects in either category had severe disease. The presence of moderate category disease was not found to be significantly associated with development of anosmia and/or dysgeusia (odds ratio [OR], 0.79; 95% confidence interval [CI], 0.31–2.03; p = .64).

On comparing cases with controls, in univariate analysis, fever (higher in cases), rhinitis (lower in cases), thrombocytopenia, elevated creatinine and bilirubin (all higher in cases) were significantly associated with anosmia or dysgeusia as described in Table 3.

TABLE 3 Univariate analysis of factors associated with anosmia or dysgeusia

Variables	Anosmia/dysgeusia, n = 55	No anosmia/dysgeusia, n = 55	p Value
Baseline			
Age (years) (mean, SD)	36 (13)	36 (13)	1
Gender (male)	32 (58)	32 (58)	1
Comorbidity (yes/no)	21 (38%)	16 (29)	.08
Lifestyle			
• Smoker	14 (25%)	10 (18%)	.35
• Alcoholic	12 (22%)	06 (11%)	.12
Clinical features			
• Fever	41	28	.01
• Cough	29	23	.25
• Dyspnoea	15	15	1
• Rhinitis	09	20	**.01**
Laboratory features			
• Haemoglobin (g/dl) (mean, SD)	12 (2)	113 (2)	.07
• Total leucocyte count/mm^3 (median, IQR)	5600 (4500, 7800)	5900 (4800, 6800)	.84
• Platelets (in lakh)/mm^3 (median, IQR)[b]	1.5 (1, 2.2)	1.94 (1.53, 2.56)	.0009
• Creatinine (mg/dl) (median, IQR)	0.9 (0.8, 1.2)	0.8 (0.6, 0.9)	**.0001**
• Bilirubin (mg/dl)[a] (mean, SD)	0.9 (0.25)	0.6 (0.2)	<.0001
• Chest X-ray (infiltrates)	13 (24%)	15 (27%)	.66

Note: Data presented as number (%) unless specified otherwise.

Abbreviation: IQR, interquartile range.

[a]Elevated in "3 cases" and "1 control," respectively.

[b]27 "cases" and 13 "controls" had thrombocytopenia.

3.3 | Multivariate analysis of factors associated with anosmia or dysgeusia

On multivariate analysis of factors associated with anosmia or dysgeusia we found rhinitis (OR, 0.28; 95% CI, 0.09–0.83); *p* = .02) thrombocytopenia (OR, 0.99; 95% CI, 0.99–0.99; *p* = .01) and elevated creatinine (OR, 7.6; 95% CI, 1.5–37.6; *p* = .01) to be factors significantly associated with anosmia or dysgeusia as described in Table 4.

3.4 | Treatment and clinical course

About two-third of the cases (62%, *n* = 34) and half (56%, *n* = 31) of the controls received antibiotics. About one-fifth (20%) of patients required oxygen supplementation in both groups. The mean (*SD*) duration of hospital stay in the "cases" was 11 days (02) as compared to 13 days (03) in the "controls" (*p* = .001). No mortality occurred in either groups.

4 | DISCUSSION

COVID-19 is mostly asymptomatic with an estimated figure of 40%–45%.[7] The common presenting features are fever, cough, sore throat, dyspnea, and myalgia.[8] New signs or symptoms including olfactory and gustatory dysfunctions are increasingly being observed. Our study highlights the presence of these two dysfunctions in patients with COVID-19 in almost 21% of patients. The reported prevalence of olfactory dysfunction in various case series have ranged from 5.14% to as high as 98.33% whereas the reported prevalence of gustatory dysfunction has ranged from 5.61% to 92.65%.[9] In a Chinese cohort the frequency of neurological manifestations was noticed in 214 COVID-19 patients, anosmia in 11 (5.1%) patients and ageusia in 12 (5.6%) patients.[10] Presence of gustatory and olfactory dysfunction was found in 19.38% cases in a case series which is similar to our study.[11] However, olfactory and gustatory dysfunction was reported in 75% and 92.65% respectively by Bénézit et al.[12] The significantly higher figures could be attributed to the fact that fewer number of patients included in the study. Highly variable figures of taste and smell dysfunction may also be attributed to presence of variable strains of SARS-CoV-2 in various countries as well as varying pathogenicity for the nasal cavity by different strains. A meta-analysis has also reported that higher prevalence was demonstrated when validated instruments were used and self-reports generally underestimated its incidence.[9]

While most studies have been either case series or cross sectional, only two case control studies have been done on the subject till date. Moein et al.[13] conducted olfactory function tests on 60 COVID-19 patients and compared with age and gender matched

TABLE 4 Multivariate analysis of factors associated with anosmia or dysgeusia

Variables	Anosmia/ dysgeusia (n = 55)	No anosmia/no dysgeusia (n = 55)	Adjusted OR (95% CI), p value	p Value
o Age in years (mean, SD)	36 (13)	36 (13)	0.98 (0.94,1.02)	.38
o Gender (male) (n, %)	32 (58%)	32 (58%)	1.09 (0.41, 2.9)	.85
o Co-morbidity (yes/no)	21 (38%)	16 (29%)	0.9 (0.68, 1.19)	.47
o Fever	41 (75%)	28 (51%)	2.28 (0.87, 5.9)	.09
o Rhinitis	09 (16%)	20 (36%)	0.28 (0.09, 0.83)	.02
o Haemoglobin (g/dl) (mean, SD)	12 (2)	13 (2)	0.84 (0.66, 1.08)	.18
o Platelets (in lakh)/mm^3 (median, IQR)	1.5 (1, 2.2)	1.94 (1.53, 2.56)	0.99 (0.99, 0.99)	.01
o Creatinine (mg/dl) (median, IQR)	0.9 (0.8, 1.2)	0.8 (0.6, 0.9)	7.6 (1.5, 37.6)	.01

Abbreviations: CI, confidence interval; IQR: Interquartile range; OR, odds ratio.

historical control from a previous study. Although pronounced olfactory dysfunction was demonstrated, no meaningful relationships between olfactory function test scores and sex, disease severity, or comorbidities could be demonstrated. In another case control study which included 79 COVID-19 cases and 40 controls (patients positive for influenza polymerase chain reaction (historical control sample), new onset taste and smell dysfunction were significantly higher amongst cases (31, 39.2%) than in the control group (5, 12.5%) (adjusted OR, 21.4; CI, 2.77–165.4; p = .003)].[14] While these studies have made attempts to study certain factors associated with olfactory dysfunctions, our study is probably the first attempt to identify various demographic and clinical factors associated with olfactory and gustatory dysfunction. Thrombocytopenia and elevated serum creatinine levels were associated significantly with presence of anosmia or dysgeusia. While renal derangements have been associated with these dysfunctions, its sudden onset in COVID-19 patients remains unanswered. Another feature identified in the current study is significantly lower incidence of rhinitis in patients with anosmia or dysgeusia. Rhinitis was also found to have significant associated on multivariate analysis as well. While anosmia or dysgeusia have been found to be higher in patients with rhinitis due to nasal congestion and obstruction, certain other studies have suggested affinity of certain viruses for structures of the olfactory sensory epithelium as a causative mechanism.[15] Its lower incidence in COVID-19 patients with rhinitis in our study also suggests towards a complex pathophysiology which is yet to be elucidated.

Anosmia has already been reported in various viral illnesses including other coronavirus infections; however, it has been identified only recently as a presenting manifestation in COVID-19 patients.[16] The exact pathophysiology is not clear till date, with various hypothesis and animal models suggesting trans-neural penetration through the olfactory bulb.[17] It has also been demonstrated that ACE-2 receptor used by SARS-CoV-2 to bind and penetrate into the cell, is also expressed on the epithelial cells of the oral cavity.[18] Another plausible mechanism involves cellular receptor neuropilin-1, which is abundantly expressed in the respiratory and olfactory epithelium.[19] It has been demonstrated to significantly potentiate SARS-CoV-2 infectivity.

Our study demonstrates that anosmia and dysgeusia are fairly frequent in patients with SARS-CoV-2 infection and may precede the onset of full-blown clinical disease. From an epidemiological perspective during a pandemic, further investigations using validated tools on nonhospitalized infected patients are required to ascertain if these symptoms, although nonspecific, can prove to be an important tool in identification of asymptomatic COVID-19 patients.

Ours is the first case control study from one of the worst effected countries from COVID-19. It is also the first attempt to study various factors associated with anosmia/and or dysgeusia in COVID-19 patients. Limitation of the study includes non-usage of validated tool to assess theses dysfunctions.

5 | CONCLUSION

Anosmia and dysgeusia are fairly common in patients with SARS-CoV-2 infection and may precede the onset of full-blown clinical disease. Prospective study with large sample size using validated tools is required to identify the true incidence and various factors associated with these clinical presentations.

ORCID

Nishanth Dev http://orcid.org/0000-0003-2486-6725

Jhuma Sankar https://orcid.org/0000-0002-9807-6550

REFERENCES

1. Giacomelli A, Pezzati L, Conti F, 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):889-890.

2. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multi-center European study. *Eur Arch Otorhinolaryngol.* 2020;277(8): 2251-2261.

3. Brann DH, Tsukahara T, Weinreb C, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *Sci Adv.* 2020; 6(31):eabc5801.

4. Wu Y, Xu X, Chen Z, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun.* 2020;87:18-22.

5. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19). https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Accessed September 08, 2020.

6. Feske SK, Martin AS. *Office Practice of Neurology.* 2nd ed. Churchill Livingstone; 2003.

7. Oran DP, Topol EJ. Prevalence of asymptomatic SARS-CoV-2 infection: a narrative review. *Ann Intern Med.* 2020:M20-3012.

8. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020;382:1708-1720.

9. Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T. The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg.* 2020; 163(1):3-11.

10. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* 2020;77(6):1.

11. Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and Ageusia: common findings in COVID-19 patients. *Laryngoscope.* 2020;130(7): 1787.

12. Bénézit F, Le Turnier P, Declerck C, et al. Utility of hyposmia and hypogeusia for the diagnosis of COVID-19. *Lancet Infect Dis.* 2020; S1473-3099(20):30297-30298.

13. 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):944-950.

14. Beltrán-Corbellini Á, Chico-García JL, Martínez-Poles J, et al. Acute-onset smell and taste disorders in the context of COVID-19: a pilot multicentre polymerase chain reaction based case-control study. *Eur J Neurol.* 2020. https://doi.org/10.1111/ene.14273

15. Suzuki M, Saito K, Min WP, et al. Identification of viruses in patients with postviral olfactory dysfunction. *Laryngoscope.* 2007;117: 272-277.

16. Seiden AM. Postviral olfactory loss. *Otolaryngol Clin North Am.* 2004; 37:1159-1166.

17. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol.* 2008;82(15):7264-7275.

18. Hamming I, Timens W, Bulthuis M, Lely A, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus: a first step in understanding SARS pathogenesis. *J Pathol.* 2004;203(2):631-637.

19. Cantuti-Castelvetri L, Ojha R, Pedro LD, et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. *Science.* 2020; 370(6518):856-860.

LAMPIRAN 4 : Jurnal Studi Inklusi 4

80 Original Article

Uncommon Presentation of COVID-19 in Pediatric Patients: Anosmia

Hatice Y. Dağlı[1]   Özge M. Akcan[2]   Sevgi Pekcan[3]   Mustafa Gençeli[4]   Hüseyin S. Özdemir[4]
Betül Uğurlu[4]   Ümmü S. Özbek[4]   Havva Parlatan[4]   Fatih Akın[4]   Abdullah Yazar[4]   Ahmet O. Kılıç[4]
Mehmet Özdemir[5]   Fatma E. Taşbent[6]

[1] Department of Pediatrics, Faculty of Medicine, Necmettin Erbakan
University Meram, Konya, Turkey
[2] Department of Pediatric Infectious Diseases, Necmettin Erbakan
University Meram Faculty of Medicine, Konya, Turkey
[3] Department of Pediatric Pulmonology, Necmettin Erbakan
University Meram Faculty of Medicine, Konya, Turkey
[4] Department of Pediatrics, Necmettin Erbakan University Meram
Faculty of Medicine, Konya, Turkey
[5] Division of Medical Virology, Department of Medical Microbiology,
Necmettin Erbakan University Meram Faculty of Medicine, Konya,
Turkey
[6] Department of Medical Microbiology, Necmettin Erbakan University
Meram Faculty of Medicine, Konya, Turkey

Address for correspondence Hatice Y. Dağlı, MD, Department of
Pediatrics, Meram Medical Faculty, Necmettin Erbakan University,
42080 Meram, Konya, Turkey (e-mail: serhatice@hotmail.com).

J Pediatr Infect Dis 2021;16:80–84.

Abstract

Objective   The novel coronavirus disease 2019 (COVID-19) infection was declared as a
pandemic by the World Health Organization on March 11, 2020. Although the
complaint of anosmia is well described in adult patients, there is limited knowledge
in pediatric patients. We aim to evaluate the epidemiological characteristics and
clinical findings of children with anosmia in COVID-19-positive pediatric patients.

Methods   Patients diagnosed with COVID-19 infection at 1 month to 18 years of age,
who admitted to Meram Faculty of Medicine of Necmettin Erbakan University between
March and June 2020, were retrospectively reviewed, and the patients who had
anosmia or developed anosmia during follow-up were then included in the study.
The diagnosis was established by polymerase chain reaction (PCR).

Results   A total of 71 patients were diagnosed with COVID-19 and 14 (19.7%) of them
had anosmia. Mean patient age was 14.07 (range: 10–16) years. Six of our 14 (42.8%)
patients had anosmia at the time of diagnosis and anosmia developed in the follow-up
among eight patients. The mean duration of anosmia in our patients was 6.9 ± 3.8
days. Recovery time was 1 to 4 days in four patients (28.5%), 5 to 8 days in four patients
(28.5%), and 9 to 14 days in six patients (42.8%).

Conclusion   In this article, it was emphasized that anosmia can be the sole manifes-
tation or concomitant with other symptoms in children with COVID-19 disease. Care
and attention is important to identify COVID-19 patients at an early stage of the disease
and limit the spread of the virus.

Keywords
► anosmia
► COVID-19
► polymerase chain
   reaction
► children

Introduction

A cluster of cases of severe pneumonia of unknown etiology emerged in Wuhan City of Hubei province in China in December 2019.[1] A new coronavirus, named severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), was isolated from samples from the lower respiratory tract as the causative agent.[2] The current outbreak of infections with SARS-CoV-2 is termed as novel coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO).[3] COVID-19 rapidly spread into at least 114 countries and killed more than 4,000 people by March 11, 2020, after which WHO officially declared COVID-19 as a pandemic on March 11, 2020.[4] In Turkey, 500,865 laboratory confirmed COVID-19 cases and 13,746 deaths have been reported up to November 30, 2020.[5] Overall, 14,388 cases in children under 15 years of age (7.3%) have been reported in Turkey up to June 28, 2020.[6]

Compared with adult patients, pediatric patients with COVID-19 infection are usually asymptomatic or present with mild symptoms such as fever; dry cough; fatigue; upper respiratory symptoms including nasal congestion and runny nose; and gastrointestinal symptoms including abdominal discomfort, nausea, vomiting, abdominal pain, and diarrhea. Prognosis of infected children has been reported as favorable in the literature.[7,8] Anosmia is one of the clinical manifestations in COVID-19 infection and has been reported in adult population in the literature with limited data for children.[9–12] The aim of this study was to evaluate the epidemiological characteristics, as well as clinical findings of children with anosmia in COVID-19-positive pediatric patients.

Materials and Methods

This was an observational descriptive case series with retrospective study of pediatric patients (<18 years) who were admitted to the Emergency Department (ED) of the Meram Faculty of Medicine of Necmettin Erbakan University in Turkey between March and June 2020 with confirmed SARS-CoV-2 infection with the complaint of anosmia. The Meram Faculty of Medicine of Necmettin Erbakan University is a university hospital and was declared as a pandemic hospital after the first case of coronavirus in Turkey was identified in March 2020. Our hospital is a tertiary pandemic hospital where COVID-19 patients are followed-up as inpatients and outpatients and also referred from other hospitals. To prevent possible transmission during the pandemic period, a new outpatient clinic was set up in the emergency room where suspected cases were admitted. A separate follow-up system was established for polymerase chain reaction (PCR)-positive patients in our clinic. A follow-up form was filled in for inpatients during their hospitalization and daily follow-up was made by using telemedicine technique for outpatients. To monitor the COVID-19 pandemic and its impact on children, patients were followed for at least 14 days or, if symptoms were ongoing

at 14 days, then they were followed-up as long as symptoms persisted. Demographic data, epidemiological history, complaints, physical examination, and therapies were recorded. Families were informed about the isolation measures at home and contact tracing was performed. Contact tracing is the process of scanning the contact chain for an infectious disease. The diagnosis of COVID-19 infection was established by PCR. During this time, nasal–throat swabs were taken from patients and then transferred to the Medical Molecular Laboratory of Meram Faculty of Medicine in a viral transport medium within 30 minutes. During this period, the samples that could not be delivered to the laboratory or could not be studied immediately were stored in the refrigerator at 2 to 8°C. First, manual extraction was performed for all samples in laboratory. Amplification process was performed by using COVID-19 quantitative (Q) reverse transcription-PCR (Bio-speedy, Istanbul, Turkey) kit on the resulting extract. Rotor gene-q (Qiagen, Germany) device was used, and the resulting amplification curves were monitored on the computer screen and then evaluated according to the criteria recommended by the kit manufacturer. This kit provides rapid diagnosis with real-time PCR in one step targeting the RNA-dependent RNA polymerase gene fragment. Our study obtained an ethics committee approval in accordance with the decisions numbered T09_42_13 by Ministry of Health and numbered 2020/2631 by Necmettin Erbakan University Meram Faculty of Medicine.

Pediatric patients who had a positive nasal PCR sample and had the complaint of anosmia or developed anosmia during follow-up were included in the study. The presence of anosmia was identified in the questionnaire. An objective test could not be used because of the pandemic period and so all patients were questioned subjectively about an osmia such as smelling onions or cologne. Azithromycin was given to all patients (5 mg/kg/day, periorally) for 5 days, in accordance with the algorithms specified by the ministry of health and 4 of 14 patients were treated with oseltamivir until influenza tests were concluded.

Responses to the survey were recorded in an electronic spread sheet. Anosmia was recorded as positive or negative. The overall results of this study were expressed as percentages for categorical variables, means ± standard deviation (SD) and as medians for continuous variables.

Results

A total of 71 pediatric patients were diagnosed with COVID-19 in this pandemic period and only 14 (19.7%) of them had the complaint of anosmia. Mean patient age was 14.07 (range: 10–16) years. Because the study was based on history taking and due to lack of an objective test, our youngest patient who could give a reliable history was 10 years of age. As anosmia could not be appropriately described in the younger age group, a 5-year-old patient who failed to give a reliable history was not included in the study. All patients included in the study had a history of contact with a known COVID-19-positive person, and six

34

Table 1 Summary of COVID-19 pediatric patients with anosmia

Patient ID	Age (y)	Sex	Additional complaints	Duration of anosmia (d)	Day of illness when anosmia was present (starting–finishing)	Family members with COVID-19	Anosmia history in family members
1	16	F	–	14	0–14	Mother, father	+
2	14	F	–	9	0–9	Mother, father	+
3	12	F	–	9	0–9	Mother, father	+
4	14	F	–	4	3–7	Brother in law	–
5	13	F	Fever	2	2–4	Mother, father, brother	+
6	16	F	Fever, cough	9	2–11	Mother, father, 2 brothers, sister	+
7	10	F	Fever, cough, fatigue	4	4–8	Mother, father	+
8	14	M	Fever, cough	5	6–11	Mother, father	+
9	12	M	–	5	2–7	Mother	+
10	16	F	Cough	11	0–11	Aunt	–
11	13	F	Fever, sore throat	14	2–16	Mother	+
12	16	M	Fever, fatigue	2	3–5	Aunt	–
13	15	F	Ageusia	6	0–6	Cousin	–
14	16	M	Cough, ageusia	6	0–6	Mother, father	+

Abbreviations: COVID-19, novel coronavirus 2019; F, female; M, male.

patients attended the emergency department at the onset of anosmia due to pandemic concerns. The complaint of anosmia was developed in the follow-up of eight patients and two of those patients had a contact history. The epidemiological factors, clinical findings, duration of anosmia, time of onset, and family history of anosmia are listed in ►**Table 1**.

Patients 1, 2, and 3 and patients 8 and 9 are siblings. It was noted that seven out of 14 patients had a family history of anosmia. The grandfathers of the patients' number 8 and 9 had died of COVID-19 infection. The mean duration of anosmia of our patients was 6.9 ± 3.8 days. Recovery time was 1 to 4 days in four patients (28.5%), 5 to 8 days in four patients (28.5%), and 9 to 14 days in six patients (42.8%). All patients were followed-up as an outpatient. All patients were cured without sequelae.

Discussion

Although anosmia is a well-defined clinical finding in adult patients with COVID-19, data in the literature for children is limited. There are only case reports in the literature in the English language.[9,10] Smell dysfunction is known to be common in viral infections. Several viruses can cause loss of smell via inflammatory reaction in nasal mucosa, leading to rhinorrhea. In a study of 24 patients with sudden onset of smell loss, 10 patients were evaluated with viral PCR analysis and only one patient tested positive for human coronavirus 229E.[13] In a multicenter study from 12 European hospitals 85.6% of 417 patients with COVID-19

had smell disorder, with 23.6% of patients with smell disorder also developing taste disorder during the pandemic period. The pathophysiology of anosmia still remains unknown but this finding is not related significantly to rhinorrhea or nasal congestion.[13,14] In another study, there was a significant association between COVID-19 and disorders of taste/smell, and chemosensorial disorder also was 10 times more common in SARS-CoV-2 positive patients.[15] In a study of COVID-19 patients, symptoms were particularly examined and 36.4% of patients had neurological symptoms. The symptoms were listed as disorders of central nervous system, peripheral nervous system, and muscle–skeletal system. The patients with peripheral nervous system disorders had complaints of hypogeusia (5.6%) and hyposmia (5.1%). Most of the neurological symptoms developed in the early term of the disease (mean duration was 1–2 days after admission to the hospital). The patients with no typical symptoms (fever, cough, anorexia, and diarrhea) of COVID-19 infection could only have neurological symptoms when admitted to hospital.[11] In patients with neurological symptoms at admission to hospital, COVID-19 infection should be considered as a cause and history must be taken carefully. Olfactory dysfunction developed before onset of other symptoms in 11.8% of cases in a multicenter adult study, in which it was found that 40% of the patients had anosmia at the time of diagnosis. In a multicenter study, the adult patients with anosmia had the following recovery times; 1 to 4 days in 20.3%, 5 to 8 days in 47.5%, 9 to 14 days in 28.8%, and more than 15 days in 3.4% of patients.[14] In our

35

study, the recovery time was 1 to 4 days in four patients (28.5%), 5 to 8 days in four patients (28.5%), and 9 to 14 days in six patients (42.8%), with no patients with a recovery time longer than 15 days. In a retrospective study with 326 adult patients with COVID-19, it has been showed that xerostomia, olfactory, and gustatory dysfunctions are common symptoms reported as concomitant and in some cases, the sole manifestation of COVID-19.[12] In our report, three patients had only anosmia and one patient had anosmia and ageusia as a manifestation.

Angiotensin-converting enzyme 2 (ACE-2) was determined as the functional receptor for SARS-COV-2 and the organs having this receptor are targeted.[16] Although the pathophysiology of anosmia in COVID-19 is still unknown, sensorineural inflammation of the olfactory neuroepithelium may play a more major role than conductive olfactory loss in causing anosmia, because it is possible that the virus may preferably target olfactory neurons in the upper respiratory tract.[9] The entrance receptor, known as ACE-2, is more predominantly found in nasal epithelial cells, particularly in goblet and ciliated cells.[17] It was demonstrated that virus enters the brain primarily via the olfactory bulb and the infection results in a rapid transneuronal spread to connected areas of the brain in a mouse model transgenic for ACE-2.[18] Anosmia in COVID-19 infection can be explained by this condition. In recent studies, it was suggested that ACE-2 could be specific to some populations and the level of expression in different tissues might be critical for the susceptibility to the symptoms and outcomes of COVID-19 infection.[19] The incidence of anosmia in COVID-19-positive family members of COVID-19 positive children was 71% (10/14) and this high rate was a notable point in our study, which may be linked to same ACE-2 gene polymorphism in family members.

Most publications that discussed treatment in children with COVID-19 suggested supportive treatment, including oxygen therapy and antibiotics for bacterial superinfections, while antiviral treatment is recommended by some researchers.[20] In our study, none of the children had an indication for hospitalization or supportive treatment. In terms of secondary bacterial infection, azithromycin treatment was given to all patients and oseltamivir was given as antiviral treatment until they have a negative influenza PCR result.

The limitations of the study are dependence on history taking for diagnosis of anosmia and lack of an objective test, the inability of young children to describe anosmia, and the small number of younger patients.

Conclusion

It is considered that the patients who neglect their anosmia spread the disease easily without knowing being infected, so that this symptom should be taken into consideration to detect the patients in early period. It is also important for source detection and prevention of dissemination of the pandemic COVID-19 infection. In this article, it was emphasized that anosmia can be the first manifestation of the COVID-19 infection in the pandemic period, so every child

with isolated anosmia should be treated as a potential COVID-19 case.

Funding
None.

Conflict of Interest
None declared.

References

1 Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. J Med Virol 2020;92(04):401–402

2 Paraskevis D, Kostaki EG, Magiorkinis G, Panayiotakopoulos G, Sourvinos G, Tsiodras S. Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event. Infect Genet Evol 2020;79:104212

3 World Health Organization. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. Accessed 11 February 2020 at: https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020

4 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Accessed 11 June 2020 at: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020

5 TR Ministry of Health. COVID-19 status report. Accessed November 30, 2020 at: https://covid19.saglik.gov.tr/

6 Republic of Turkey, Ministry of Health. COVID-19 situation report, Turkey. Accessed June 30, 2020 at: https://dosyamerkez.saglik.gov.tr/Eklenti/37743,covid-19-situation-report-v4pdf.pdf?

7 Hoang A, Chorath K, Moreira A, et al. COVID-19 in 7780 pediatric patients: a systematic review. EClinicalMedicine 2020;24:100433

8 Götzinger F, Santiago-García B, Noguera-Julián A, et al; ptbnet COVID-19 Study Group. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health 2020;4(09):653–661

9 Mak PQ, Chung KS, Wong JS, Shek CC, Kwan MY. Anosmia and ageusia: not an uncommon presentation of COVID-19 infection in children and adolescents. Pediatr Infect Dis J 2020;39(08):e199–e200

10 Rusetsky YY, MeYtel Y, Babayan AR, Malyavina US. [Otorhinolaryngological aspects of the disease course in children infected with SARS-CoV-2 virus] (in Russian). Vestn Otorinolaringol 2020;85(02):63–66

11 Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77(06):683–690

12 Fantozzi PJ, Pampena E, Di Vanna D, et al. Xerostomia, gustatory and olfactory dysfunctions in patients with COVID-19. Am J Otolaryngol 2020;41(06):102721

13 Suzuki M, Saito K, Min WP, et al. Identification of viruses in patients with postviral olfactory dysfunction. Laryngoscope 2007;117(02):272–277

14 Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020;277(08):2251–2261

15 Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS. Association of chemosensory dysfunction and COVID-19 in patients presenting with influenza-like symptoms. Int Forum Allergy Rhinol 2020;10(07):806–813

16 Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. Biochem Biophys Res Commun 2020;526(01):135–140

17 Sungnak W, Huang N, Bécavin C, et al; HCA Lung Biological Network. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med 2020;26(05):681–687

18 Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuro-nal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol 2008;82(15):7264–7275

19 Li W, Zhang C, Sui J, et al. Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. EMBO J 2005;24(08):1634–1643

20 Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr 2020;109(06):1088–10951

LAMPIRAN 5 : Jurnal Studi Inklusi 5

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

New-onset anosmia and ageusia in adult patients diagnosed with SARS-CoV-2 infection

A. Patel [1], E. Charani [2, *], D. Ariyanayagam [3], A. Abdulaal [1], S.J. Denny [1, 4], N. Mughal [1, 2, 4], L.S.P. Moore [1, 2, 4]

[1] Chelsea and Westminster NHS Foundation Trust, 369 Fulham Road, London, SW10 9NH, UK
[2] Imperial College London, NIHR Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, Hammersmith Campus, Du Cane Road, London, W12 0NN, UK
[3] Imperial College London School of Medicine, Kensington, London, SW7 2DD, UK
[4] North West London Pathology, Fulham Palace Road, London, W6 8RF, UK

ARTICLE INFO

ABSTRACT

Objectives: We investigated the prevalence of anosmia and ageusia in adult patients with a laboratory-confirmed diagnosis of infection with severe acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2).

Methods: This was a retrospective observational analysis of patients infected with SARS-CoV-2 admitted to hospital or managed in the community and their household contacts across a London population during the period March 1st to April 1st, 2020. Symptomatology and duration were extracted from routinely collected clinical data and follow-up telephone consultations. Descriptive statistics were used.

Results: Of 386 patients, 141 (92 community patients, 49 discharged inpatients) were included for analysis; 77/141 (55%) reported anosmia and ageusia, nine reported only ageusia and three only anosmia. The median onset of anosmia in relation to onset of SARS-CoV-2 disease (COVID-19) symptoms (as defined by the Public Health England case definition) was 4 days (interquartile range (IQR) 5). Median duration of anosmia was 8 days (IQR 16). Median duration of COVID-19 symptoms in community patients was 10 days (IQR 8) versus 18 days (IQR 13.5) in admitted patients. As of April 1, 45 patients had ongoing COVID-19 symptoms and/or anosmia; 107/141 (76%) patients had household contacts, and of 185 non-tested household contacts 79 (43%) had COVID-19 symptoms with 46/79 (58%) reporting anosmia. Six household contacts had anosmia only.

Conclusions: Over half of the positive patients reported anosmia and ageusia, suggesting that these should be added to the case definition and used to guide self-isolation protocols. This adaptation may be integral to case findings in the absence of population-level testing. Until we have successful population-level vaccination coverage, these steps remain critical in the current and future waves of this pandemic. **A. Patel, Clin Microbiol Infect 2020;26:1236**

Introduction

Since the outbreak of the severe acute respiratory syndrome coronavirus (SARS-CoV-2) pandemic—reported first from Wuhan, China in December 2019—there have been increasing reports of anosmia (total or partial loss of smell) and ageusia (total or partial loss of taste) amongst patients presenting with suspected or confirmed infection [1]. Early reports from Italy and South Korea showed anosmia in up to 34% of patients [2–4]. A more recent cross-European analysis looking at patients with mild to moderate SARS-CoV-2 disease (COVID-19) put this number at 85.6% [5].

Anosmia can occur in a wide range of viral infections; published literature estimates the prevalence of olfactory disorders, including anosmia, to be 11–40% [1,6–8]. The higher estimates (20–40%) were generated using data from patients in specialized smell and

* Corresponding author. E. Charani, NIHR Health Protection Research Unit, Healthcare Associated Infections and Antimicrobial Resistance, Hammersmith Campus, London, W12 ONN, UK.
E-mail address: e.charani@imperial.ac.uk (E. Charani).

taste centres, and the lower estimate (11%) was based on data from general ear, nose, and throat clinics [8]. SARS-CoV-2 does not generate clinically significant nasal congestion or rhinorrhoea that would typically be associated with anosmia in other upper respiratory tract infections, and it has also been observed that anosmia manifests either early in the disease process or in patients with mild symptoms [1]. Early analysis of the 'Anosmia Reporting Tool' by the American Academy of Otolaryngology showed anosmia in 73% of patients prior to COVID-19 diagnosis, and was the initial symptom in 26.6%, suggesting that anosmia may be a presenting symptom of COVID-19 [9]. In the absence of a widespread population testing strategy, understanding the symptomatology of this new illness is critical to ensuring that the correct advice is given to patients and the public in relation to self-isolation leading to reduced population transmission.

In the United Kingdom (UK), the transmission of SARS-CoV-2 was first confirmed in February 2020. From March 1, SARS-CoV-2 was reported across England, Wales, Scotland and Ireland, indicating widespread community transmission. Public Health England guidance currently recognizes symptoms of COVID-19 to include fever ≥37.8°C and at least one of the symptoms persistent cough (with or without sputum), hoarseness, nasal discharge or congestion, shortness of breath, sore throat, wheezing or sneezing [10]. To date, anosmia and ageusia are not recognised symptoms in the disease case definition. However, there is increasing evidence of these symptoms presenting in patients who are otherwise asymptomatic, highlighting the possibility that new-onset anosmia and/or ageusia may be useful as a component of screening for the virus [4]. This is critical at this stage in the pandemic, as adding olfactory symptoms to the case definition of COVID-19 would be especially useful should anosmia and/or ageusia be shown to present early and in otherwise asymptomatic patients who may go on to require hospital admission.

In this retrospective analysis of both community and secondary-care patients in a London population diagnosed with SARS-CoV-2 infection, we aimed to establish the prevalence of new-onset anosmia and ageusia and place them within disease symptom progression. We also investigated whether the olfactory symptoms experienced by COVID-19 patients are accompanied by other nasal symptoms (congestion or rhinorrhoea) as with other post-viral olfactory disorders. Additionally, we investigated the presence of COVID-19 symptoms, anosmia and ageusia in the household contacts of these patients.

Methods

Ethics approval and consent to participate

Data were collected as part of routine care by the responsible clinical team. No patient-identifiable data are reported in this analysis. The need for written informed consent was waived by the Research Governance Office of Chelsea and Westminster NHS Foundation Trust.

Study design and participants

This was a retrospective, observational analysis of patients diagnosed either as inpatients at a 430-bed London acute teaching hospital or in the surrounding community. As well as receiving unwell patients warranting admission, the hospital adopted a community testing strategy to identify suspected COVID-19 cases. Unwell patients were screened through call centres and general practitioners, who referred patients suspected of having COVID-19 to a centralized response team. Depending on mobility, these patients were either directed to drive through SARS-CoV-2 testing clinics or visited at home by community testing teams. Patients were also assessed through a bespoke section of the emergency department. This community testing ceased on March 13th, 2020.

Nasopharyngeal and oral swabs were taken from all patients (both community and secondary care) and tested at a central reference laboratory using real-time reverse transcriptase polymerase chain reaction (PCR) (initially using a proprietary assay run by Public Health England, then from March 6th, 2020 onwards a commercial assay from AusDiagnostics®, Australia) for SARS-CoV-2. Patients who were considered to be clinically stable were allowed to self-isolate at home. Community patients were informed of their result by telephone. Inpatients had their symptoms and clinical course documented in their electronic healthcare record (Millennium: Cerner Corporation, Kansas City, Missouri, USA) by the admitting clinical team. Demographic and clinical data were collected from electronic health records for all patients included in the analysis. Details of onset of COVID-19 symptoms, anosmia and/or ageusia were extracted where present.

All patients with a laboratory diagnosis of COVID-19 between March 1 and April 1, 2020 were identified. Patients were included if they (a) had a positive diagnosis for COVID-19 based on real-time PCR detection of SARS-CoV-2, and (b) were tested in the community OR admitted to and discharged from hospital. Patients were excluded if they (a) died post-diagnosis, (b) were <16 years of age, (c) did not have an accurate record of symptom history (e.g. due to confusion or lack of memory), or (d) were readmitted to hospital or transferred to another healthcare facility. We excluded current inpatients because a large proportion had current oxygen requirements either through nasal cannulae or via face-masks. These devices could influence the assessment of anosmia. Additionally, these patients were in isolation wards with only essential care being given to limit onward transmission, which made them inaccessible for the purposes of this study.

Between April 13th and April 17th, 2020, telephone consultations were conducted with all identified patients to verify symptomatology and timeline to resolution of clinical symptoms. All patients were asked a series of standardized questions on the presence of COVID-19 symptoms and also diarrhoea, vomiting, myalgia, and any change in their sense of smell and taste. If changes in smell and/or taste were reported, further standardized questions were asked regarding time of onset relative to onset of COVID-19 symptoms, duration of change, and whether these symptoms had resolved. Only complete recovery from anosmia was considered as resolution of the symptom. Partial recovery was considered as hyposmia. At the time of this study there was little evidence associating anosmia and COVID-19, therefore the primary outcome was new-onset anosmia and the questionnaire was not scored [11]. Details of the presence of household contacts and their symptomatology were also routinely collected in line with public health guidance. Specifically, patients were asked whether household contacts had experienced COVID-19 symptoms and whether any of them had experienced anosmia.

Study outcome measures

The primary outcome measure was the prevalence of new-onset anosmia and/or associated ageusia. Secondary outcome measures included analysis of duration of COVID-19 symptoms (as outlined by the current Public Health England case definition) [10] and new-onset anosmia and/or associated ageusia. Clinical presentation was defined as mild versus severe depending on whether patients were admitted to hospital or isolated in the community. An additional outcome measure was the prevalence of new-onset anosmia amongst household contacts.

Results

Between March 1st and April 1st 2020, 386 patients were diagnosed as SARS-CoV-2-positive using real-time PCR detection (Fig. 1). Of these, 167 were excluded as they did not fit the study inclusion criteria. Of the remaining 219, 74 were not contactable for the follow-up telephone consultations after three attempts across multiple dates. The final analysis included 141 patients. Of these, 92 were treated in the community and 49 were admitted to and discharged from hospital.

Table 1 summarizes the most commonly reported COVID-19 symptoms. Of the 141 patients, 77 (55%) reported anosmia and ageusia. Three patients reported only anosmia. Nine patients reported only ageusia. No patients reported pre-existing anosmia. Nasal congestion was reported in 39/80 patients (49%) with anosmia and 43/89 patients (48%) with ageusia. Nasal symptoms in the absence of anosmia and/or ageusia were reported in 16/52 patients (31%).

Table 2 shows the median duration of COVID-19 symptoms and anosmia (duration of symptoms was not normally distributed). The data in the table exclude 14 patients who were clear about the presence of both COVID-19 symptoms and anosmia but were unable to give an accurate duration of the anosmia. Fig. 2 charts the onset and duration of anosmia in relation to onset of COVID-19 symptoms. The onset of anosmia ranged between 1 and 21 days, and the duration was reported to be between 1 and 30 days with 32/81 patients experiencing ongoing anosmia or hyposmia at the end of the study period.

Of the 141 patients, 107 (76%) had one or more household contacts (total number of household contacts = 195) during their isolation period. Five households contained two study participants
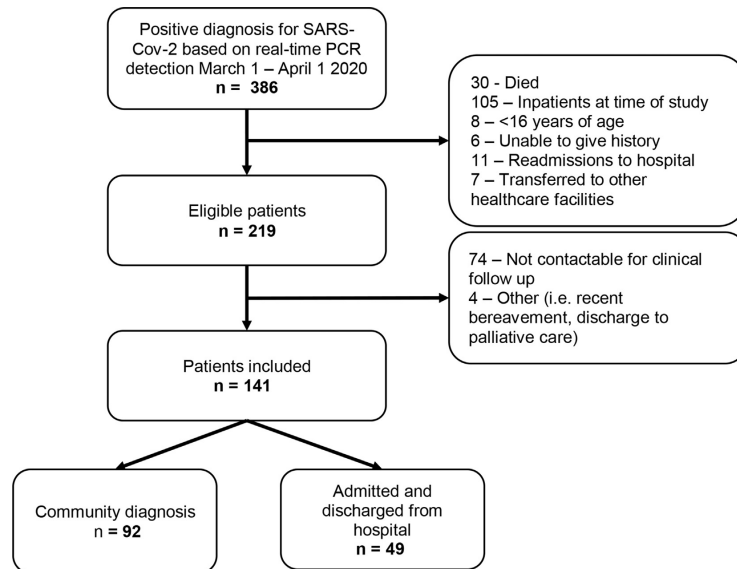
Table 1
Patient demographics and frequency of COVID-19 symptoms in patients from a London community and secondary-care population between March 1st and April 1st, 2020

	Total	Community	Admitted
n	141	92 (65.2%)	49 (34.8%)
Mean age (range)	45.6 (20—93)	40.7 (20—87)	54.9 (22—93)
Sex (male/female)	83/58	58/34	27/22
Most common reported symptoms			
Fever	111 (75.7%)	70 (76.1%)	41 (83.7%)
Cough	102 (72.3%)	68 (73.9%)	34 (69.4%)
Myalgia	93 (66.0%)	67 (72.8%)	26 (53.1%)
Ageusia	89 (63.1%)	57 (62.0%)	32 (65.3%)
Shortness of breath	86 (61.0%)	54 (58.7%)	32 (65.3%)
Anosmia	80 (56.7%)	56 (60.9%)	24 (49.0%)
Nasal congestion	60 (42.6%)	43 (46.7%)	17 (34.7%)
Diarrhoea	45 (31.9%)	23 (25.0%)	22 (44.9%)
Vomiting	19 (13.5%)	11 (12.0%)	8 (16.3%)

each (*n* = 10), leaving 185 non-tested household contacts. Of these, 79 (43%) had COVID-19 symptoms and 46 (58%) had anosmia. Six household contacts had anosmia in the absence of other symptoms (Fig. 3).

Discussion

This analysis reports that over half of patients with COVID-19 experienced anosmia and/or ageusia. These findings are important as they support the increasing evidence associating anosmia and ageusia with SARS-CoV-2. They also represent a snapshot of the community setting at the early stages of the spread of this

Fig. 1. Flow diagram of participant selection for patients positive for severe acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2) from a London community and a secondary-care population between March 1st and April 1st, 2020.
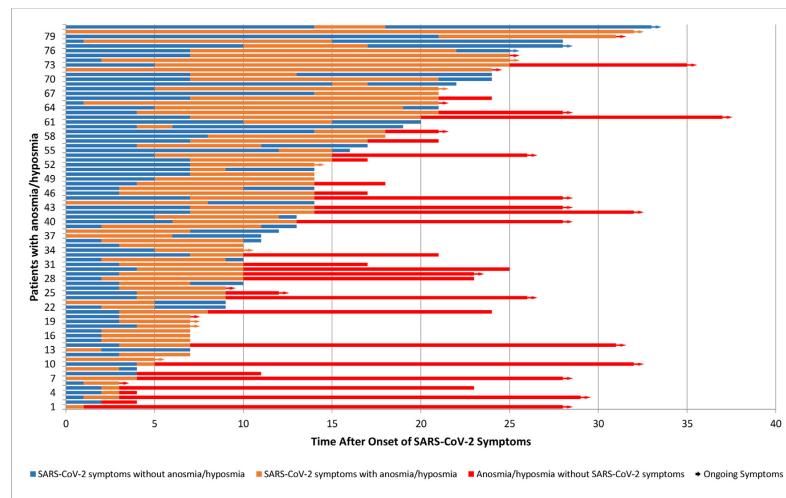
Table 2
Natural history of COVID-19 symptoms and anosmia in patients from a London community and secondary-care population between March 1st and April 1st, 2020

	Total	Community	Admitted
Patients with resolved COVID-19 symptoms	114	83	31
Patients with unresolved COVID-19 symptoms	13	6	7
Median duration of COVID-19 symptoms in days (interquartile range)	12 (11.5)	10 (8)	118 (13.5)
Patients with resolved anosmia	49	34	15
Patients with unresolved anosmia/ongoing hyposmia	32	21	11
Median lag for onset of anosmia in days (IQR)	4 (5)	3 (3)	5 (4)
Median duration of anosmia in days (IQR)	8 (16)	14 (16)	7 (8.5)

IQR, interquartile range.

Fig. 2. Onset and duration (in days) of anosmia in relation to COVID-19 symptoms in patients from a London community and a secondary-care population between March 1st and April 1st, 2020. Arrow indicates ongoing symptoms at the time of telephone consultations.

pandemic in the UK, which is valuable given the early cessation of community testing.

The prevalence of anosmia in post-viral respiratory tract infections seen in specialist clinics is greater than in general ear nose and throat clinics [8]. This suggests that the pickup rates in specialist clinics are higher. Our analysis, though more comparable to that of a general clinic setting, found the prevalence of anosmia to be greater than that found in specialist anosmia clinics. This higher prevalence of anosmia in COVID-19 is broadly in line with the current literature, where anosmia has been identified as one of the most predictive symptoms of COVID-19 [12]. Of all patients with anosmia, the majority (52%) did not report concurrent nasal congestion. This supports data from a large cross-European analysis that showed olfactory disorders are prevalent in COVID-19 patients, who may not have nasal symptoms [5].

Patients who reported ageusia only could not accurately differentiate between losing their sense of taste or their sense of smell. This may be due to retronasal olfactory function being labelled as taste [13]. The gustatory system (transmitted via the glossopharyngeal, facial and vagal nerves) only recognizes the basic tastes (sweet, sour, salty, bitter and umami), but most of the culinary experiences are recognized by the olfactory nerve [14]. Indeed,

there is a close association between anosmia and ageusia, which may make it difficult for patients to differentiate between the two [15]. In our analysis we therefore made the assumption that ageusia was unlikely to be present in the absence of anosmia, and we therefore considered these patients to have anosmia also.

In this study a sizeable proportion of patients reported anosmia and ageusia extending beyond the resolution of COVID-19 symptoms. Additionally, three patients reported anosmia in the absence of any other symptoms. Mild community-treated patients were more likely to report anosmia than those admitted to hospital, which supports emerging evidence associating new-onset anosmia with mild or absent COVID-19 symptoms [1,5]. Prospective studies are needed to investigate the epidemiological significance of this in the context of potential spread of disease by individuals with mild atypical presentations.

The relative short time span of onset of anosmia in relation to other COVID-19 symptoms suggests that anosmia may be a useful early diagnostic factor in this viral disease and may subsequently have a role in guiding isolation practice. Duration and time of onset of anosmia were twice as long in the hospital group, although this analysis was not powered to investigate the significance of the variation in findings between hospitalized and community
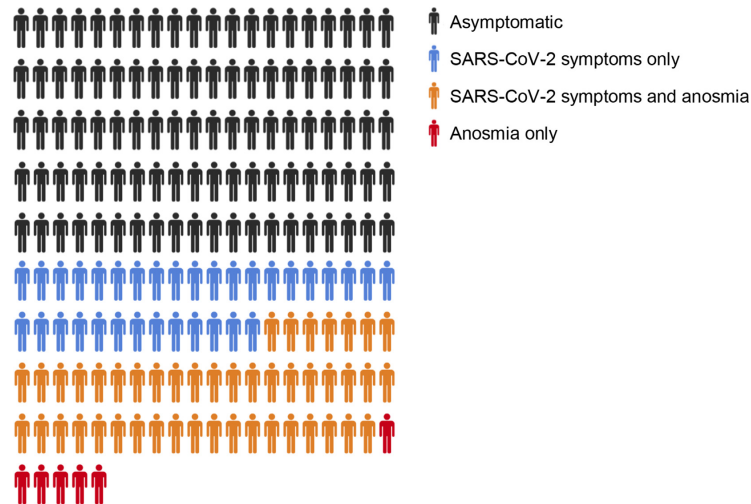
Fig. 3. The presence of COVID-19 symptoms and anosmia in non-tested household contacts ($n = 185$) of patients from a London community and a secondary-care population tested positive for severe acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2) between March 1st and April 1st, 2020.

patients. Severe symptoms in hospitalized patients may initially overshadow the presence of anosmia, possibly explaining the delay in perceived onset. It is worth mentioning that, as of April 17th (end of the data collection period), 45 patients had ongoing COVID-19 symptoms and/or anosmia/hyposmia. This means the reported duration times are likely to be underrepresented.

All patients in this study were tested for SARS-CoV-2 due to clinical suspicion based on symptomatology. Therefore, by the nature of the selection process, it is unlikely that any COVID-19 patients with anosmia alone would have been tested. Over half of the symptomatic (but not tested) household contacts, however, reported anosmia, with a further six experiencing anosmia alone. Being close contacts of confirmed COVID-19 patients, it is likely the high prevalence of anosmia in this group is related to transmission of SARS-CoV-2. This shows consistency in prevalence of anosmia in an exposed (but not confirmed) population, but also that mild versions of the illness may present with anosmia alone. To obtain a true understanding of the clinical significance of anosmia in SARS-CoV-2, we need to prospectively investigate new-onset anosmia in the general population, potentially coupled with serological testing.

The strength of this study is that it provides an early insight into the chronological sequence of anosmia in COVID-19 and also the association between symptoms and household transmission. Since this analysis provides a snapshot of symptomatology in SARS-CoV-2-positive patients, it is not possible to draw population-wide conclusions. Recall bias of patients may also have influenced the clinically recorded data, especially of those hospitalized. Similarly, the absence of objective testing meant we were not able to clinically define the extent and severity of the anosmia and ageusia. Furthermore, physical examination was not possible in the community due to social distancing rules and the potential for onwards transmission. The use of a structured questionnaire, however, helped to ameliorate this possible reporting bias (Supplementary Material). It was not possible to estimate the number of

asymptomatic COVID-19 patients in our community population as asymptomatic patients may have been less likely to present to hospital, and may not have been eligible for community testing as per PHE diagnostic criteria. Several patients had ongoing anosmia, and further follow-up will be required to further discern the duration of these symptoms.

This analysis did not include patients under the age of 16, and it has been widely reported that children do not appear to present in the same way as adults but may still be asymptomatic. The symptomatology of COVID-19 in children needs to be examined.

More than half the patients with confirmed COVID-19 suffered anosmia and ageusia. This is significant when compared with the prevalence of anosmia and ageusia in other post-viral upper respiratory tract infections. These findings suggest that anosmia and ageusia be added to existing case definitions for COVID-19 and used to guide self-isolation procedures. This is critical in the absence of population-level testing.

The findings of this research highlight the need to investigate new-onset anosmia in the general population, particularly in those without other symptoms. A better understanding of the long-term outcomes of anosmia in COVID-19 patients is needed. Until a time when we have successful population-level vaccination coverage, these steps remain critical to managing the current and subsequent waves of this pandemic.

Author contributions

AP and EC developed the study design. AP, EC, DA, and AA were responsible for data collection. AP, EC and AA assisted with data interpretation. AP and EC performed the literature search and wrote the first draft of the paper. All authors have critically read and commented on draft versions of the manuscript and approved the final version.

Transparency declaration

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.05.026.

References

[1] Xydakis MS, Dehgani-Mobaraki P, Holbrook EH, Geisthoff UW, Bauer C, Hautefort C, et al. Smell and taste dysfunction in patients with COVID-19. Lancet Infect Dis 2020. https://doi.org/10.1016/S1473-3099(20)30293-0.

[2] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020. https://doi.org/10.1001/jamaneurol.2020.1127.

[3] Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa330.

[4] Hopkins C, Kumar N. Loss of sense of smell as marker of COVID-19 infection: joint statement from the. London: British Rhinological Society and ENT-UK; 2020.

[5] Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Oto-Rhino-Laryngology 2020;2. https://doi.org/10.1007/s00405-020-05965-1.

[6] Hummel T, Landis B, Huttenbrink K. Smell and taste disorders. GMS Curr Top Otorhinolaryngol Head Neck Surg 2011;10:Doc04. https://doi.org/10.1002/9781119952930.ch88.

[7] van Riel D, Verdijk R, Kuiken T. The olfactory nerve: a shortcut for influenza and other viral diseases into the central nervous system. J Pathol 2015;235: 277—87. https://doi.org/10.1002/path.4461.

[8] Welge-Lüssen A, Wolfensberger M. Olfactory disorders following upper respiratory tract infections. Adv Otorhinolaryngol 2006;63:125—32. https://doi.org/10.1159/000093758.

[9] Kaye R, Chang CWD, Kazahaya K, Brereton J, Denneny JC. COVID-19 anosmia reporting Tool: initial findings. Otolaryngol Neck Surg; 2020. https://doi.org/10.1177/0194599820922992.

[10] Public Health England. Guidance: COVID-19: investigation and initial clinical management of possible cases. 2020.

[11] Donovan JO, Tanveer S, Jones N, Hopkins C, Senior BA, Wise SK, et al. What is the evidence for anosmia (loss of smell) as a clinical feature of COVID-19? Cent Evidence-Based Med 2020.

[12] Menni C, Valdes AM, Freidin MB, Sudre CH, Nguyen LH, Drew DA, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. Nat Med 2020. https://doi.org/10.1038/s41591-020-0916-2.

[13] Deems DA, Doty RL, Settle RG, Moore-Gillon V, Shaman P, Mester AF, et al. Smell and taste disorders, a study of 750 patients from the university of Pennsylvania smell and taste center. Arch Otolaryngol Head Neck Surg 1991;117:519—28. https://doi.org/10.1001/archotol.1991.01870170065015.

[14] Hummel T, Heilmann S, Landis BN, Reden J, Frasnelli J, Small DM, et al. Perceptual differences between chemical stimuli presented through the ortho- or retronasal route. Flavour Fragr J 2006. https://doi.org/10.1002/ffj.1700.

[15] Doty RL. Sensory aging: chemical senses. Encycl Neurosci 2009. https://doi.org/10.1016/B978-008045046-9.00147-9.

LAMPIRAN 6 : Jurnal Studi Inklusi 6

RHINOLOGY

Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study

Jerome R. Lechien[1,2,3,4] · **Carlos M. Chiesa-Estomba**[1,5] · **Daniele R. De Siati**[1,6] · **Mihaela Horoi**[4] · **Serge D. Le Bon**[4] · **Alexandra Rodriguez**[4] · **Didier Dequanter**[4] · **Serge Blecic**[7] · **Fahd El Afia**[1,3] · **Lea Distinguin**[1,3] · **Younes Chekkoury-Idrissi**[1,3] · **Stéphane Hans**[3] · **Irene Lopez Delgado**[1,8] · **Christian Calvo-Henriquez**[1,9] · **Philippe Lavigne**[1,10] · **Chiara Falanga**[1,11] · **Maria Rosaria Barillari**[1,11] · **Giovanni Cammaroto**[1,12] · **Mohamad Khalife**[13] · **Pierre Leich**[14] · **Christel Souchay**[14] · **Camelia Rossi**[15] · **Fabrice Journe**[2] · **Julien Hsieh**[1,16] · **Myriam Edjlali**[17,18] · **Robert Carlier**[18] · **Laurence Ris**[19] · **Andrea Lovato**[20] · **Cosimo De Filippis**[20] · **Frederique Coppee**[21] · **Nicolas Fakhry**[1,22] · **Tareck Ayad**[1,10] · **Sven Saussez**[1,2,4,13]

Abstract

Objective To investigate the occurrence of olfactory and gustatory dysfunctions in patients with laboratory-confirmed COVID-19 infection.

Methods Patients with laboratory-confirmed COVID-19 infection were recruited from 12 European hospitals. The following epidemiological and clinical outcomes have been studied: age, sex, ethnicity, comorbidities, and general and otolaryngological symptoms. Patients completed olfactory and gustatory questionnaires based on the smell and taste component of the National Health and Nutrition Examination Survey, and the short version of the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS).

Results A total of 417 mild-to-moderate COVID-19 patients completed the study (263 females). The most prevalent general symptoms consisted of cough, myalgia, and loss of appetite. Face pain and nasal obstruction were the most disease-related otolaryngological symptoms. 85.6% and 88.0% of patients reported olfactory and gustatory dysfunctions, respectively. There was a significant association between both disorders ($p < 0.001$). Olfactory dysfunction (OD) appeared before the other symptoms in 11.8% of cases. The sQO-NS scores were significantly lower in patients with anosmia compared with normosmic or hyposmic individuals ($p = 0.001$). Among the 18.2% of patients without nasal obstruction or rhinorrhea, 79.7% were hyposmic or anosmic. The early olfactory recovery rate was 44.0%. Females were significantly more affected by olfactory and gustatory dysfunctions than males ($p = 0.001$).

Conclusion Olfactory and gustatory disorders are prevalent symptoms in European COVID-19 patients, who may not have nasal symptoms. The sudden anosmia or ageusia need to be recognized by the international scientific community as important symptoms of the COVID-19 infection.

Keywords Coronavirus · COVID · COVID-19 · SARS-CoV-2 · Anosmia · Smell · Hyposmia · Dysgeusia · Taste · Loss · Gustatory · Olfactory · Olfaction · Infection · ENT

Jerome R. Lechien and Carlos M. Chiesa-Estomba have equally contributed to this work and should be regarded as joint first authors.

Tareck Ayad and Sven Saussez have equally contributed to this work and should be regarded as joint senior authors.

Extended author information available on the last page of the article

Published online: 06 April 2020

Introduction

The coronavirus disease 2019 (COVID-19) is an ongoing viral pandemic that emerged from East Asia and quickly spread to the rest of the world [1]. This infection is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is so far responsible for more than 15,000 deaths worldwide [2]. Human-to-human transmission is characterized by a troubling exponential rate, which

Ⓩ Springer

gustatory function; and one question about the treatment of the COVID-19 infection. All patients were asked to complete the short version of the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS) [9]. The questionnaire has been translated into Spanish, Italian, and English by two native speaker otolaryngologists for each language.

Olfactory and gustatory outcomes

The occurrence of anosmia or hyposmia has been identified in the questionnaire. The impact of olfactory dysfunction on the quality of life (QoL) of patients has been assessed through the validated sQOD-NS (Appendix 1) [9]. This is a seven-item patient-reported outcome questionnaire including social, eating, annoyance, and anxiety questions. Each item is rated on a scale of 0–3, with higher scores reflecting better olfactory-specific QoL. The total score ranges from 0 (severe impact on QoL) to 21 (no impact on QoL) [9]. The rest of the olfactory and gustatory questions were based on the smell and taste component of the National Health and Nutrition Examination Survey [10]. This population survey was implemented by the Centers for Disease Control and Prevention to continuously monitor the health of adult citizens in the United States through a nationally representative sample of 5000 persons yearly [10]. The questions have been chosen to characterize the variation, timing, and associated symptoms of both olfactory and gustatory dysfunctions, and, therefore, they suggest a potential etiology. Note that we assessed the mean recovery time of olfaction through four defined propositions: 1–4 days; 5–8 days; 9–14 days; and > 15 days.

Referring to the studies that have demonstrated that the viral load was significantly decreased after 14 days [11], we assessed the short-term olfaction non-recovery rate on patients exhibiting double criteria: an onset of the infection > 14 days before the assessment and the lack of general symptoms at the time of the evaluation.

Statistical methods

Statistical Package for the Social Sciences for Windows (SPSS version 22,0; IBM Corp, Armonk, NY, USA) was used to perform the statistical analyses. The potential associations between epidemiological, clinical and olfactory and gustatory outcomes have been assessed through cross-tab generation between two variables (binary or categorical variables) and Chi-square test. Incomplete responses were excluded from analysis. The differences in sQOD-NS scores between patients regarding the olfactory dysfunction were made through the Kruskal–Wallis test. A level of $p < 0.05$ was used to determine statistical significance.

Results

A total of 417 patients completed the study. The mean age of patients was 36.9 ± 11.4 years (range 19–77). There were 263 females and 154 males. The following ethnicities composed the cohort: European (93.3%), South American (2.7%), Sub-Saharan African (2.2%), Black African (1.4%), Asian (0.2%), and North American (0.2%) (Table 1). The most prevalent comorbidities of patients were allergic rhinitis, asthma, high blood pressure, and hypothyroidism (Fig. 1). The mean time between the onset of the infection and the evaluation was 9.2 ± 6.2 days. At the time of the study, 34.5% of patients were in the acute phase of the infection, whereas the rest of the patients did not yet have general symptoms.

Clinical outcomes

The general symptoms of patients during the infection are described in Fig. 2. Cough, myalgia, loss of appetite, diarrhea, fever, headache, and asthenia were the most prevalent symptoms, accounting for more than 45% of patients. The otolaryngological symptoms most related to the infection are reported in Table 2.

Olfactory outcomes

A total of 357 patients (85.6%) had olfactory dysfunction related to the infection. Among them, 284 (79.6%) patients were anosmic and 73 (20.4%) were hyposmic. Phantosmia and parosmia concerned 12.6% and 32.4% of patients during the disease course, respectively. The olfactory dysfunction appeared before (11.8%), after (65.4%) or at the same time as the appearance of general or ENT symptoms (22.8%). Note that 9.4% of patients did not remember the time of onset of olfactory dysfunction and, therefore, were not considered for the percentage evaluation.

Considering the 247 patients with a clinically resolved infection (absence of general and ENT symptoms), the olfactory dysfunction persisted after the resolution of other symptoms in 63.0% of cases. The mean time between the onset of the disease and the assessment of this group of patients was 9.77 ± 5.68 days.

The short-term olfaction recovery rate, which was assessed in 59 clinically cured patients, was 44.0%. The different recovery times of the olfactory function of patients who reported a recovery of the olfactory function are available in Fig. 3. In total, 72.6% of these patients recovered olfactory function within the first 8 days following the resolution of the disease. Among the patients who reported anosmia, then, excluding hyposmic patients, the olfactory

**Table 1** Demographic and epidemiological characteristics of patients

Characteristics	Mean ± SD	Range
Age (years old)	36.9 ± 11.4	19–77
Characteristics	Number	Percentages
Gender		
Male	154	36.9
Female	263	63.1
Ethnicity		
European	389	93.3
Asian	1	0.2
Black African	6	1.4
Sub-Saharan African	9	2.2
North American	1	0.2
South American	11	2.6
Oceanian	0	0.0
Addictions		
Non-smoker	361	86.6
Mild smoker (1–10 cigarettes daily)	40	9.6
Moderate smoker (11–20 cigarettes daily)	16	3.8
Heavy smoker (> 20 cigarettes daily)	0	0.0
Allergic patients	85	20.4

SD standard deviation
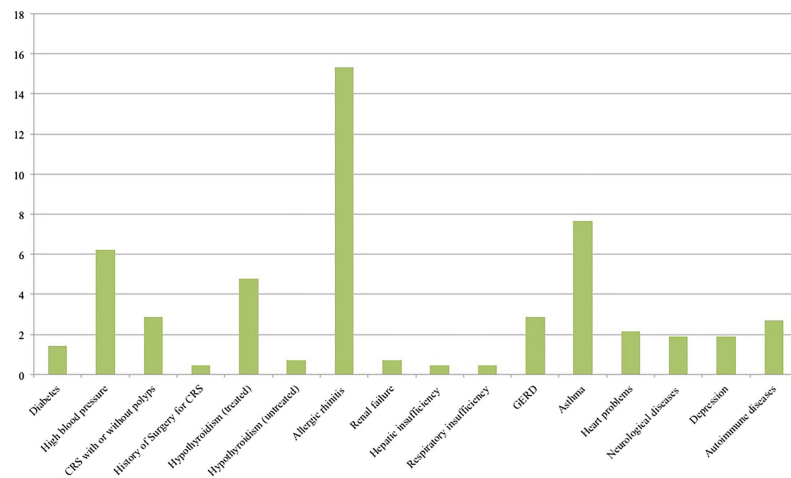
Fig. 1 Comorbidities of COVID-19 patients. The ordinate axis consists of percentages of patients with comorbidities in the cohort. Respiratory insufficiency consists of COPD, emphysema, fibrosis, or other chronic disease associated with a respiratory insufficiency. Neu-rological diseases include Parkinson disease, myasthenia, multiple sclerosis, and all degenerative diseases. *COPD* chronic obstructive pulmonary disease, *CRS* chronic rhinosinusitis, *GERD* gastroesopha-geal reflux disease
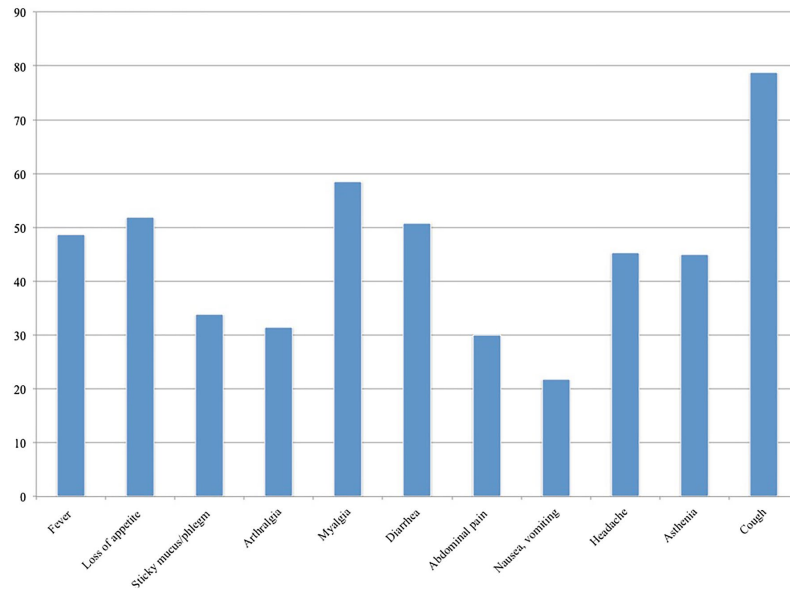
Fig. 2 General symptoms associated with COVID-19 infection. The ordinate axis consists of percentages of patients with such symptoms associated with the infection

Table 2 Otolaryngological complaints associated with COVID-19 Infection

	Not related		Somewhat related		Highly related
	(0)	(1)	(2)	(3)	(4)
Nasal obstruction	131 (31.49)	91 (21.88)	77 (18.51)	67 (16.11)	50 (12.02)
Rhinorrhea	154 (37.11)	122 (29.40)	81 (19.52)	40 (9.64)	18 (4.34)
Postnasal drip	203 (48.80)	97 (23.32)	61 (14.66)	26 (6.25)	29 (6.97)
Sore throat	192 (46.15)	96 (23.08)	57 (13.70)	38 (9.13)	33 (7.93)
Face pain/heaviness	198 (47.60)	66 (15.87)	59 (14.18)	39 (9.38)	54 (12.98)
Ear pain	310 (74.52)	45 (10.82)	32 (7.69)	16 (3.85)	13 (3.13)
Dysphagia	24 (22.64)	40 (37.74)	24 (22.64)	11 (10.38)	7 (6.60)
Dyspnea	218 (52.40)	83 (19.95)	61 (14.66)	35 (8.41)	19 (4.57)

Percentages are in brackets. Patients had to rate each of the following symptoms in terms of their relationship with your COVID-19 infection (scale: 0–4, where 0 = not related, 4 = highly related)

function recovered throughout the 8 first days following the resolution of the disease in 67.8% of cases (Fig. 3).

In the present study, 76 patients did not suffer from nasal obstruction or rhinorrhea (18.2%). Among them, 20.3% did not report olfactory dysfunction, whereas 66.2% and 13.5% suffered from anosmia and hyposmia, respectively.

The impact of olfactory dysfunction on patient QoL is reported in Table 3. Anosmic patients at the time of the evaluation had a significant lower sQOD-NS score compared with hyposmic and normosmic individuals ($p = 0.001$; Kruskal–Wallis).

Gustatory outcomes

A total of 342 patients (88.8%) reported gustatory disorders, which was characterized by impairment of the following four

Fig. 3 Pattern of recovery
time for patients with olfac-
tory dysfunction. The ordinate
axis consists of percentages
of patients. The patients with
hyposmia or anosmia had the
following recovery times **a**
1–4 days (33.0%), 5–8 days
(39.6%), 9–14 days (24.2%),
and more than 15 days (3.3%).
The patients with anosmia had
the following recovery times
b 1–4 days (20.3%), 5–8 days
(47.5%), 9–14 days (28.8%),
and more than 15 days (3.4%)
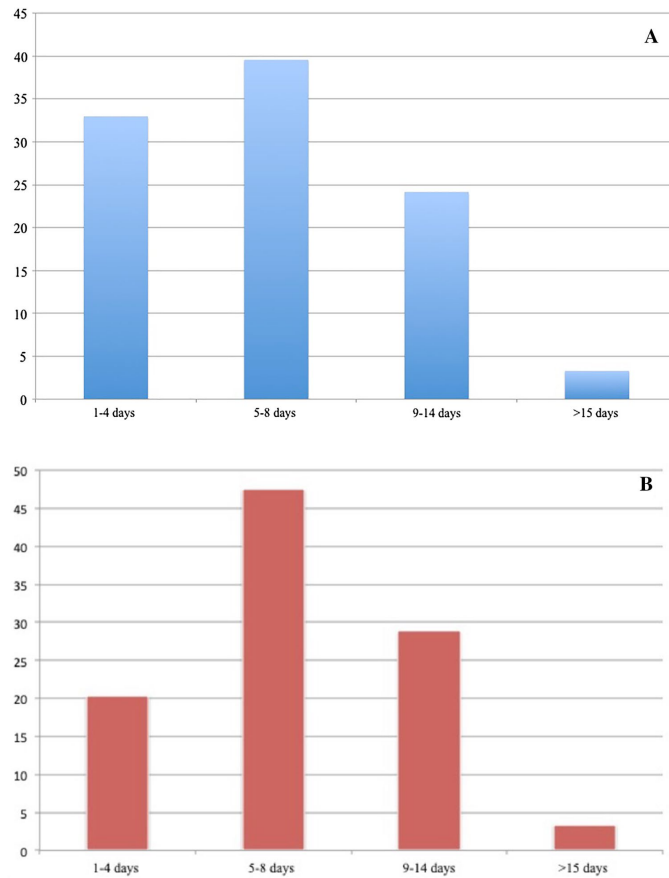
taste modalities: salty, sweet, bitter, and sour. Note that 32
patients did not remember if they had gustatory dysfunction
and, therefore, they were not considered for the assessment
of the gustatory disorder prevalence. The gustatory dysfunc-
tion consisted of reduced/discontinued or distorted ability to
taste flavors in 78.9% and 21.1% of patients, respectively.

Among the 43 patients without gustatory dysfunction, 19
(44.2%) have no olfactory dysfunction, whereas 16 (37.2%)
and 4 (9.3%) patients had anosmia or hyposmia.

The olfactory and gustatory disorders were constant and
unchanged over the days in 72.8% of patients, whereas they
fluctuated in 23.4% of patients. Among the patients who

reported gustatory and olfactory disorders, 3.8% revealed
that these disorders occurred during their rhinorrhea or nasal
obstruction episodes.

Among the cured patients who had residual olfactory
and/or gustatory dysfunction, 53.9% had isolated olfactory
dysfunction, 22.5% had isolated gustatory dysfunction, and
23.6% had both olfactory and gustatory dysfunctions.

Olfactory and gustatory outcome associations

There was no significant association between comorbidities
and the development of olfactory or gustatory dysfunctions.

Table 3 Short version of questionnaire of olfactory disorders-negative statements of patient

Short version QOD-NS items	Anosmia	Hyposmia	No LS
Changes in my sense of smell isolate me socially	1.68 ± 0.91*	2.34 ± 0.75	2.53 ± 0.65
The problems with my sense of smell have a negative impact on my daily social activities	1.37 ± 0.93*	2.11 ± 0.84	2.56 ± 0.69
The problems with my sense of smell make me more irritable	1.46 ± 0.92*	2.21 ± 0.82	2.64 ± 0.59
Because of the problems with my sense of smell, I eat out less	1.30 ± 1.09*	2.12 ± 0.99	2.31 ± 1.04
Because of the problems with my sense of smell, I eat less than before (loss of appetite)	1.00 ± 0.88*	1.59 ± 0.97	2.36 ± 0.90
Because of the problems with my sense of smell, I have to make more effort to relax	1.67 ± 0.88*	2.91 ± 0.79	2.61 ± 0.60
I'm afraid I'll never be able to get used to the problems with my sense of smell.	0.73 ± 0.86*	1.90 ± 1.06	2.06 ± 1.19
Short version QOD-NOS total score	9.15 ± 4.60*	14.44 ± 4.59	13.60 ± 8.17

sQOD-NS is a seven-item patient-reported outcome questionnaire including social, eating, annoyance, and anxiety questions. Each item is rated on a scale of 0–3, with higher scores reflecting better olfactory-specific QOL. The total score ranges from 0 (severe impact on QoL) to 21 (no impact on QoL) [9]. The item and total scores of sQOD-NS significantly differ between patients with anosmia at the time of the assessment, and those with hyposmia or without olfactory dysfunction (*$p = 0.001$)

LS loss of smell, *sQOD-NS* Short version of Questionnaire of Olfactory Disorders-Negative Statements

Olfactory dysfunction was not significantly associated with rhinorrhea or nasal obstruction. There was a significant positive association between olfactory and gustatory dysfunctions ($p < 0.001$). The statistical analysis identified a significant association between the fever and the anosmia ($p = 0.014$). The females would be proportionally more affected by hyposmia or anosmia compared with males ($p < 0.001$). Similar results were found for gustatory dysfunction ($p = 0.001$, Mann–Whitney U test).

Treatments of COVID-19 patients

The following general treatments have been considered for patients with the COVID-19 infection: paracetamol (62.4%); non-steroidal anti-inflammatory drugs (9.8%); nasal saline irrigations (9.6%); Chloroquine (7.9%); mucolytics (5.0%); and oral corticosteroids (1.4%, with concomitant antibiotics) (Fig. 4). The treatments that have been most used for olfactory dysfunction were nasal saline irrigations (16.7%); nasal corticosteroids (8.1%), oral corticosteroids (2.5%), and others (2.5%, e.g., vitamins, non-corticoid decongestants, and trace elements) (Fig. 4). Gustatory dysfunction was treated in 1.4% of patients: four patients received treatment, consisting of L-carnitine or trace elements and vitamins. Telemedicine has been used in 42.6% of patients for prescribing the treatment.

Discussion

Over the past few weeks, an increasing number of otolaryngologists reported sudden anosmia or hyposmia as concurrent symptoms of COVID-19 infection. In these patients, the diagnosis of COVID-19 could be missed, because these symptoms were not known to be specific. As a result, the patients were not isolated and the spread of the virus
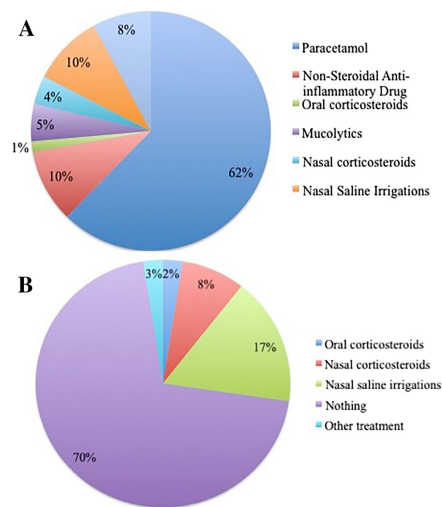
Fig. 4 Therapeutic strategies for COVID-19 infection (**a**) and olfactory dysfunction (**b**)

continued. In this context, the COVID-19 Task Force of the YO-IFOS has conducted this study to investigate the prevalence and the short-term evolution of both olfactory and gustatory disorders.

Based on the National Health and Nutrition Examination Survey questions, our results support that olfactory and gustatory dysfunctions are both prevalent in patients with mild-to-moderate COVID-19 infection. Thus, 85.6% of patients reported olfactory dysfunction; 79.6% of them

🖄 Springer

having anosmia. Interestingly, many profiles of patients have been identified. First, our data showed that 79.7% of patients without nasal obstruction or rhinorrhea reported hyposmia or anosmia, supporting the role of otolaryngologists as the first-line physicians for some COVID-19 patients. Second, the olfactory dysfunction may appear before, during, or after the general symptoms, with the occurrence of fever being associated with the olfactory dysfunction. There have been few studies on the occurrence of olfactory and gustatory dysfunctions in Asia, since only one study reported hyposmia as a symptom of the COVID-19 infection [12]. In the study of Mao et al., patients with peripheral nervous system symptoms attributed to COVID-19 infection, the most common the most common complaints were hypogeusia (5.6%) and hyposmia (5.1%) [12]. According to the data of the present study, the prevalence of olfactory and gustatory dysfunction is substantially higher in European COVID-19 patients. In addition to the high prevalence, physicians must keep in mind that olfactory disorder may appear before the rest of the complaints in 11.8% of cases, yielding the symptoms important for the early detection of the disease.

One of the most important questions from the otolaryngologists concerned the recovery of olfactory and gustatory functions. Although our results are still preliminary, it seems that, at least, 25.5% of patients recovered both olfactory and gustatory functions throughout the 2 weeks after the resolution of general symptoms. Considering the time to get a significant reduction of the viral load [10], we have estimated that 56% of patients have persistent olfactory dysfunction over the days following the resolution of the COVID-19 general clinical manifestations. In the same vein, some patients seemed to recover olfaction, but not taste, and vice versa. Naturally, there are short-term observations and it is reasonable to think that a large number of these patients will recover the olfactory or gustatory functions over the weeks following the disease resolution. To summarize, the present study clearly supports the recent declarations of many physicians from South Korea, Iran, Germany, Italy, Spain, France, Belgium, UK, and US that olfactory and gustatory functions may be impaired in COVID-19 patients.

The pathophysiological mechanisms leading to the olfactory and gustatory dysfunctions in the COVID-19 infection are still unknown. Coronavirus has already been identified as a family of viruses that may be associated with anosmia [6]. In 2007, Suzuki et al. demonstrated that coronavirus may be detected in the nasal discharge of patients with olfactory dysfunction. Moreover, they observed that some patients with normal acoustic rhinometry did not recover their olfaction, suggesting that nasal inflammation and related obstruction were not the only etiological factors underlying the olfactory dysfunction in viral infection.

The ability of human coronavirus to invade the olfactory bulb and, therefore, the central nervous system, is most likely a future research path for improving the knowledge about the clinical presentation of patients. From a biomolecular standpoint, viruses could infect peripheral neurons, using the cell machinery of active transport to access the central nervous system [13]. Thus, for the SARS-CoV receptor (human angiotensin-converting enzyme 2), it has been demonstrated on transgenic mice that SARS-CoV may enter the brain through the olfactory bulb, leading to rapid transneuronal spread [14]. Interestingly, authors demonstrated that the virus antigen was first detected 60–66 h post-infection and was most abundant in the olfactory bulb. Regions of the cortex (*piriform* and *infralimbic cortices*), basal ganglia (*ventral pallidum* and *lateral preoptic* regions), and midbrain (*dorsal raphe*) were also strongly infected after the virus had spread [14]; these regions are connected with the olfactory bulb. The rapid spread of SARS-CoV in the brain was also associated with significant neuronal death. In humans, autopsy samples from eight patients with SARS revealed the presence of SARS-CoV in brain samples by immunohistochemistry, electron microscopy, and real-time RT-PCR [15]. It is currently suspected that the neuroinvasive potential of SARS-CoV2 plays a key role in the respiratory failure of COVID-19 patients [16]. Medical imaging and neuropathology will certainly play an important rule to detect abnormalities in olfactory bulb, cranial nerves, and brain of COVID-19 patients.

The otolaryngological symptoms in our European cohort were particularly prevalent compared with the Asian cohorts. In their clinical series of 99 patients, Chen et al. reported four patients with rhinorrhea (4%) [17]. Then, Guan et al. reported a prevalence of nasal obstruction in 5% of patients in a cohort of 1099 patients [18]. The lack of otolaryngological complaints in Asian papers, e.g., nasal obstruction, rhinorrhea, and olfactory and gustatory dysfunctions, raises many questions. Either they did not assess the ENT complaints, or the Chinese patients had a few ENT complaints. The second hypothesis may be likely regarding previous studies. Benvenuto et al. have recently compared the complete genomes of 15 virus sequences from patients treated in different regions of China with other coronaviruses [19]. Interestingly, they observed mutations of surface proteins (spike-S-protein and nucleocapsid-N-protein), conferring stability to the viral particle. Such mutations could be clinically relevant, because the viral spike protein is responsible for virus entry into the cell, whereas the N-protein plays a pivotal role in the virus transcription and assembly efficiency. Previously, Chan et al. determined five virus sequences from patients traveling in Wuhan at the end of December 2019. This study reported identities, but less than 68%, with the SARS-related coronaviruses in specific domains. Particularly, the external subdomain region of receptor-binding domain of the S-protein only presents 39% identity, and Chan et al. propose that it might affect

the choice of human receptor and, therefore, the biological behaviour of this virus [20]. The affinity of some viruses for some tissues and individuals constitutes another area to investigate and explain the potential clinical differences between patients from different world regions. Recent studies suggested that the angiotensin converting enzyme 2 (ACE2), which is the receptor of SARS-CoV-2, could be specific to certain populations. Li et al. demonstrated that some ACE2 variants could reduce the association between human ACE2 and SARS-CoV S-protein [21]. In other words, the expression level of ACE2 in different tissues might be critical for the susceptibility, symptoms, and outcomes of COVID-19 infection [21]. Moreover, the comparison of the 15 expression quantitative trait loci (eQTLs) variants of the ACE2 gene suggested that there will be a lot of ACE2 polymorphisms and ACE2 expression levels between Asian and European populations [22]. According to these studies, it is conceivable that the diversity of ACE2 expression pattern in Asian and European populations could be an important track that needs further investigation.

Moreover, regarding our results, future studies have to explore the potential gender differences in the development of anosmia. The highest susceptibility of females to develop olfactory and gustatory dysfunctions would be related to the gender-related differences in the inflammatory reaction process [23].

The present study has several limitations. First, our patients did not benefit from specific examinations for olfactory and gustatory functions, including psychophysical tests or electrophysiological methods [24, 25]. The use of objective approaches makes sense for investigating both gustatory and olfactory functions in COVID-19 patients, and to avoid the confusion related to the retro-olfaction. These approaches would provide many responses for patients who may recover olfaction, but not taste, and vice versa. Second, our patient sample consisted of young and mild-to-moderate COVID-19 patients with little comorbidities. They may be not representative of the infected population. However, it seems ethically difficult to investigate olfaction and gustatory function in patients in life-threatening condition, such as patients in intensive-care units. Note that in this study, the majority of included patients were identified from hospital laboratory results. However, many infected physicians completed the study, and, therefore, it remains possible that many infected physicians participated to the study, because they suffered from olfactory dysfunction, although the authors have been particularly vigilant to this potential bias. Third, the lack of consistent follow-up of our patients limits us from inquiring into the recovery time of olfactory and gustatory functions, and, therefore, the rate of permanent anosmia or ageusia. Fourth, it seems difficult to identify the potential negative impact of nasal and oral corticosteroids on the clinical course of the disease; these treatments are usually used for anosmia or in common nasal complaints. In the absence of such data, the precautionary principle may prevail and, according to the guidelines of the French Society of Otolaryngology, patients must avoid corticosteroids for the treatment of the COVID-19 infection. All of these weaknesses should be considered in future studies to investigate and characterize the olfactory and gustatory functions in COVID-19 patients.

Conclusion

Since the disease is new and the virus is most likely associated with different mutations and clinical patterns, as of yet, there remain more questions than answers. This study is the first to identify both olfactory and gustatory dysfunctions as significant symptoms in the clinical presentation of the European COVID-19 infection. Based on our results, it seems that infected patients may just present olfactory and gustatory dysfunctions without other significant complaints. The sudden anosmia or ageusia need to be recognized by the international scientific community as important symptoms of the COVID-19 infection. Future epidemiological, clinical, and basic science studies must elucidate the mechanisms underlying the development of these symptoms in such a specific world population.

Compliance with ethical standards

References

1. Guan WJ, Ni ZY, Hu Y et al (2020) Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. https://doi.org/10.1056/NEJMoa2002032

2. Ramanathan K, Antognini D, Combes A, Paden M, Zakhary B, Ogino M, MacLaren G, Brodie D, Shekar K (2020) Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. Lancet Respir Med. https://doi.org/10.1016/s2213-2600(20)30121-1

3. Wu YC, Chen CS, Chan YJ (2020) Overview of the novel coronavirus (2019-nCoV): the pathogen of severe specific contagious pneumonia (SSCP). J Chin Med Assoc. https://doi.org/10.1097/JCMA.0000000000000270

4. Young BE, Ong SWX, Kalimuddin S et al (2020) Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA. https://doi.org/10.1001/jama.2020.3204

5. Wan S, Xiang Y, Fang W, Zheng Y et al (2020) Clinical features and treatment of COVID-19 patients in Northeast Chongqing. J Med Virol. https://doi.org/10.1002/jmv.25783

6. Suzuki M, Saito K, Min WP, Vladau C, Toida K, Itoh H, Murakami S (2007) Identification of viruses in patients with postviral olfactory dysfunction. Laryngoscope 117(2):272–277

7. van Riel D, Verdijk R, Kuiken T (2015) The olfactory nerve: a shortcut for influenza and other viral diseases into the central nervous system. J Pathol 235(2):277–287. https://doi.org/10.1002/path.4461

8. Ayad T, Stephenson K, Smit D et al (2018) Young Otolaryngologists of International Federation of Oto-rhino-laryngological Societies (YO-IFOS) committees. Eur Ann Otorhinolaryngol Head Neck Dis 135(5S):S61–S65. https://doi.org/10.1016/j.anorl.2018.08.004

9. Mattos JL, Edwards C, Schlosser RJ, Hyer M, Mace JC, Smith TL, Soler ZM (2019) A brief version of the questionnaire of olfactory disorders in patients with chronic rhinosinusitis. Int Forum Allergy Rhinol 9(10):1144–1150. https://doi.org/10.1002/alr.22392

10. Bhattacharyya N, Kepnes LJ (2015) Contemporary assessment of the prevalence of smell and taste problems in adults. Laryngoscope 125(5):1102–1106. https://doi.org/10.1002/lary.24999

11. Zou L, Ruan F, Huang M et al (2020) SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med 382(12):1177–1179. https://doi.org/10.1056/NEJMc2001737

12. Mao L, Wang M, Chen S et al (2020) Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. MedRXiv. https://doi.org/10.1101/2020.02.22.20026500

13. Koyuncu OO, Hogue IB, Enquist LW (2013) Virus infections in the nervous system. Cell Host Microbe 13(4):379–393. https://doi.org/10.1016/j.chom.2013.03.010

14. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S (2008) Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol 82(15):7264–7275. https://doi.org/10.1128/JVI.00737-08

15. Gu J, Gong E, Zhang B et al (2005) Multiple organ infection and the pathogenesis of SARS. J Exp Med 202(3):415–424

16. Li YC, Bai WZ, Hashikawa T (2020) The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol. https://doi.org/10.1002/jmv.25728

17. Chen N, Zhou M, Dong X et al (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395(10223):507–513. https://doi.org/10.1016/S0140-6736(20)30211-7

18. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J et al (2020) Clinical characteristics of 2019 novel coronavirus infection in China. Medrxiv

19. Benvenuto D, Giovanetti M, Ciccozzi A, Spoto S, Angeletti S, Ciccozzi M (2020) The 2019-new coronavirus epidemic: evidence for virus evolution. J Med Virol 92(4):455–459

20. Chan JF, Yuan S, Kok KH et al (2020) A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 395(10223):514–523. https://doi.org/10.1016/S0140-6736(20)30154-9

21. Li W, Zhang C, Sui J, Kuhn JH et al (2005) Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. EMBO J 24(8):1634–1643

22. Cao Y, Li L, Feng Z, Wan S, Huang P, Sun X, Wen F, Huang X, Ning G, Wang W (2020) Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell Discov 6:11. https://doi.org/10.1038/s41421-020-0147-1

23. Lefèvre N, Corazza F, Valsamis J, Delbaere A, De Maertelaer V, Duchateau J, Casimir G (2019) The number of X chromosomes influences inflammatory cytokine production following toll-like receptor stimulation. Front Immunol 10:1052. https://doi.org/10.3389/fimmu.2019.01052

24. Hummel T, Whitcroft KL, Andrews P et al (2017) Position paper on olfactory dysfunction. Rhinol Suppl 54(26):1–30

25. Gudziol H, Guntinas-Lichius O (2019) Electrophysiologic assessment of olfactory and gustatory function. Handb Clin Neurol 164:247–262. https://doi.org/10.1016/B978-0-444-63855-7.00016-2

Affiliations

Jerome R. Lechien[1,2,3,4] · Carlos M. Chiesa-Estomba[1,5] · Daniele R. De Siati[1,6] · Mihaela Horoi[4] ·
Serge D. Le Bon[4] · Alexandra Rodriguez[4] · Didier Dequanter[4] · Serge Blecic[7] · Fahd El Afia[1,3] · Lea Distinguin[1,3] ·
Younes Chekkoury-Idrissi[1,3] · Stéphane Hans[3] · Irene Lopez Delgado[1,8] · Christian Calvo-Henriquez[1,9] ·
Philippe Lavigne[1,10] · Chiara Falanga[1,11] · Maria Rosaria Barillari[1,11] · Giovanni Cammaroto[1,12] · Mohamad Khalife[13] ·
Pierre Leich[14] · Christel Souchay[14] · Camelia Rossi[15] · Fabrice Journe[2] · Julien Hsieh[1,16] · Myriam Edjlali[17,18] ·
Robert Carlier[18] · Laurence Ris[19] · Andrea Lovato[20] · Cosimo De Filippis[20] · Frederique Coppee[21] · Nicolas Fakhry[1,22] ·
Tareck Ayad[1,10] · Sven Saussez[1,2,4,13]

✉ Jerome R. Lechien
Jerome.Lechien@umons.ac.be

1 COVID-19 Task Force of the Young-Otolaryngologists of the International Federations of Oto-rhino-laryngological Societies (YO-IFOS), Paris, France

2 Department of Human Anatomy and Experimental Oncology, Faculty of Medicine, UMONS Research Institute for Health Sciences and Technology, University of Mons (UMons), Mons, Belgium

3 Department of Otorhinolaryngology and Head and Neck Surgery, Foch Hospital, School of Medicine, UFR Simone

LAMPIRAN 7 : Jurnal Studi Inklusi 7

Smell dysfunction: a biomarker for COVID-19

Shima T. Moein, MD, PhD[1], Seyed MohammadReza Hashemian, MD, FCCM[2], Babak Mansourafshar, MD[2], Ali Khorram-Tousi, MD[1], Payam Tabarsi, MD[3] and Richard L. Doty, PhD, FAAN[4]

Background: Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), is responsible for the largest pandemic since the 1918 influenza A virus subtype H1N1 influenza outbreak. The symptoms presently recognized by the World Health Organization are cough, fever, tiredness, and difficulty breathing. Patient-reported smell and taste loss has been associated with COVID-19 infection, yet no empirical olfactory testing on a cohort of COVID-19 patients has been performed.

Methods: The University of Pennsylvania Smell Identification Test (UPSIT), a well-validated 40-odorant test, was administered to 60 confirmed COVID-19 inpatients and 60 age- and sex-matched controls to assess the magnitude and frequency of their olfactory dysfunction. A mixed effects analysis of variance determined whether meaningful differences in test scores existed between the 2 groups and if the test scores were differentially influenced by sex.

Results: Fifty-nine (98%) of the 60 patients exhibited some smell dysfunction (mean [95% CI] UPSIT score: 20.98 [19.47, 22.48]; controls: 34.10 [33.31, 34.88]; $p < 0.0001$). Thirty-

five of the 60 patients (58%) were either anosmic (15/60; 25%) or severely microsmic (20/60; 33%); 16 exhibited moderate microsmia (16/60; 27%), 8 mild microsmia (8/60; 13%), and 1 normosmia (1/60; 2%). Deficits were evident for all 40 UPSIT odorants. No meaningful relationships between the test scores and sex, disease severity, or comorbidities were found.

Conclusion: Quantitative smell testing demonstrates that decreased smell function, but not always anosmia, is a major marker for SARS-CoV-2 infection and suggests the possibility that smell testing may help, in some cases, to identify COVID-19 patients in need of early treatment or quarantine. © 2020 ARS-AAOA, LLC.

Key Words:
chronic rhinosinusitis; olfactory disorders; olfaction; olfactory test; UPSIT; COVID-19; biomarker

How to Cite this Article:
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;10:944–950.

[1]School of Biological Sciences, Institute for Research in Fundamental Sciences, Tehran, Iran; [2]Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran; [3]Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran; [4]Smell & Taste Center, Department of Otorhinolaryngology-Head and Neck Surgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Correspondence to: Richard L. Doty, PhD, FAAN, Smell & Taste Center, Department of Otorhinolaryngology–Head and Neck, Surgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; e-mail: doty@pennmedicine.upenn.edu

Recently there have been numerous reports in the media that anosmia occurs in persons who have contracted coronavirus disease 2019 (COVID-19) by exposure to the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) virus. These include 1 published single case report,[1] and self-report surveys from Germany,[2] Great Britain,[3] Iran,[4] Italy,[5] and the United States,[6] with smell loss reports ranging from 34% to 68% of COVID-19–positive patients. Otorhinolaryngology authorities have warned that loss of smell and taste, in combination with other symptoms, appears to be a strong predictor of COVID-19 infection.[7,8]

To date, validated quantitative olfactory testing has not been performed in a cohort of COVID-19 patients to

53

verify or determine the true magnitude of their deficits and whether less-than-total loss occurs in some patients. Moreover, the proportion of COVID-19 patients exhibiting true olfactory disturbances is unknown. Most studies suggest that, in general, a significant number of persons with smell loss are unaware of their deficit until formal testing[9] and that self-reports of both smell and taste abilities correlate poorly with the results of quantitative smell and taste tests.[10,11]

In this case-control study, we administered the Persian version of the 40-item University of Pennsylvania Smell Identification Test (UPSIT)[12] to 60 confirmed COVID-19 patients and 60 age- and sex-matched controls to assess the presence, magnitude, and frequency of their olfactory dysfunction. We determined whether the smell loss was related to the sex of the subjects and inquired, for those patients who were aware of their dysfunction before testing, when they first noticed their chemosensory disorder.

Patients and methods

Subjects

The age, sex, comorbidities, smoking status, and complaints of chemosensory dysfunction of the 120 study participants are presented in Table 1. The 60 SARS-COV-2–positive subjects had been admitted with the symptoms of COVID-19 to the Masih Daneshvari Hospital, Tehran, Iran, between March 21, 2020, and March 23, 2020, or March 31, 2020, and April 5, 2020. At the time of the olfactory testing, all were inpatients in the recovery period of the disease and were ready to be discharged within 4 days. The study was explained in detail to 68 such patents, of which 8 declined to participate (ie, the participation rate was 88%).

The control subjects were from a database of 141 subjects collected in Iran for an earlier study. They were tested in the olfactory laboratory of the Institute for Research in Fundamental Sciences, Tehran, Iran, and comprised a convenience sample obtained from e-mail lists, flyers, and word of mouth. None had influenza or common cold symptoms at the time of testing. The recruitment period for this database (August 8, 2019, to February 13, 2020) preceded the first reported confirmed cases of COVID-19 in Iran (February 19, 2020). A control subject was individually matched as closely as possible to each COVID-19 patient. Exact age matches were possible for 34 subjects, 1-year differences for 22 subjects, and 2-year differences for 4 subjects. In cases where >1 match was possible, the first match in the database sequence was used.

Informed written consent was obtained from each patient and control, and the study protocol was approved by the local ethics committee and the Iranian Ministry of Health (license number IR.SBMU.NRITLD.REC.1399.013). All testing was performed with the highest regard for examiner safety with appropriate personal protective equipment.

TABLE 1. Patient and control subject demographics[*]

Parameter	COVID-19 patients	Controls	p (Fisher exact probability test)
Sample size, n	60	60	
Age (years), mean ± SD	46.55 ± 12.17	46.55 ± 12.07	
Gender (male/female), n	40/20	40/20	
Smoker (current/never), n	2/58	11/49	**0.016**
Taste/smell complaints, n	21	0	**0.001**
Comorbidities, n			
Asthma	3	0	0.244
Atherosclerosis	0	2	0.496
Autoimmune disease	4[a]	0	0.119
Carcinoma	2[b]	0	0.496
Congenital melanocytic nevi	1	0	1.000
Diabetes	8[c]	0	**0.007**
Hemophilia	0	1	1.000
Hepatic failure	0	1	1.000
Hyperlipidemia	1	1	1.000
Hypertension	6[c]	5	1.000
Hypothyroidism	4[c]	2	0.679
Migraine	0	1	1.000
Osteoporosis	0	1	1.000
Sinusitis	2	0	0.496

*Significant p differences indicated in bold.
[a]Autoimmune disease included Behcet's disease in combination with Crohn's disease (n = 1), multiple sclerosis (n = 2), and rheumatoid arthritis (n = 1).
[b]Prostate and cervical cancers.
[c]Although, in rare cases, changes in dosage and medications may have occurred during the course of inpatient treatments, most patients remained on their preadmission medications.
COVID-19 = coronavirus disease 2019; SD = standard deviation.

Diagnosis and clinical severity classification of COVID-19 patients

COVID-19 diagnosis was based on the COVID-19 detection protocol of Masih Daneshvari Hospital. All of the patients underwent 16-slice chest computed tomography (CT) imaging (Scope Power Siemens CT Scan, Munich, Germany) and had positive chest CT findings.[13] Subsequently, the diagnosis of COVID-19 disease was confirmed by quantitative detection of SARS-CoV-2 RNA using the real-time reverse-transcription polymerase chain reaction (rRT-PCR) in respiratory specimens.[14] The RT-PCR assays were performed using Sansure Biotech's 2019-nCoV 30-Minute Nucleic Acid Reagent Kits (Sansure Biotech, Inc., Development Zone, Changsha, China). The respiratory specimens were

54

collected from the patients' nasopharyngeal wash/aspirate or nasal aspirate.

COVID-19 clinical severity was classified as mild, moderate, or severe according to the Massachusetts General Hospital COVID-19 treatment guidance algorithm.[15] Mild clinical COVID-19 presentation was defined as having oxygen saturation (SpO$_2$) >90% along with or without risk factors. Moderate clinical COVID-19 presentation was considered for patients who had at least 1 epidemiological risk factor along with a risk factor in vital signs or laboratory findings at the admission point of time. Patients in the intensive care unit (ICU) or with progressive disease were classified as having severe clinical presentation of COVID-19. Epidemiological risk factors included age >55 years or preexisting pulmonary disease, chronic kidney disease, diabetes with glycated hemoglobin (A1c) >7.6%, history of hypertension or cardiovascular disease or transplant, or immunosuppression or human immunodeficiency virus (HIV). Risk factors of vital signs comprised respiratory rate >24 breaths/minute, heart rate >125 beats/minute, and SpO$_2$ <90% on ambient air. In laboratory findings, fibrin degradation product D-dimer >1000 ng/mL, creatine phosphokinase (CPK) more than twice the upper limit of normal, C-reactive protein (CRP) >100 mg/L, lactate dehydrogenase (LDH) >245 U/L, elevated troponin, admission absolute lymphocyte count <0.8, and ferritin >300 μg/L. For COVID-19 patients with mild disease with SpO$_2$ >90%, supportive care was provided and hydroxychloroquine administration was started (200 mg twice per day [BID] $\times$ 2 doses, then 100 mg BID for 5 days). For the patients with moderate to severe COVID-19 presentations, lopinavir/ritonavir 200/50 mg BID for up to 10 days) was prescribed. In patients with progressive COVID-19 disease admitted to the ICU, intravenous immunoglobulin (IVIG) at standard dose of 0.5 g/kg/day daily for 5 days was administered.[16]

Olfactory testing

A modified and validated Persian version of the UPSIT was administered in this study (Sensonics International, Haddon Heights, NJ). The UPSIT is a well-validated and reliable (test-retest $r = 0.94$) test that employs microencapsulated "scratch and sniff" odorants.[11,12,17,18] It provides an index of absolute dysfunction (ie, anosmia, severe microsmia, moderate microsmia, mild microsmia, normosmia, malingering), as well as relative dysfunction based upon age- and gender-adjusted normative percentile ranks. The total number of odorant stimuli out of 40 that is correctly identified serves as the test measure. Scores on this test correlate well with other types of olfactory tests, including threshold tests.[19] Although the UPSIT is designed to be self-administered, to be certain that the COVID-19 patients correctly performed the test during the limited clinical time window, the testing was assisted by a trained examiner.
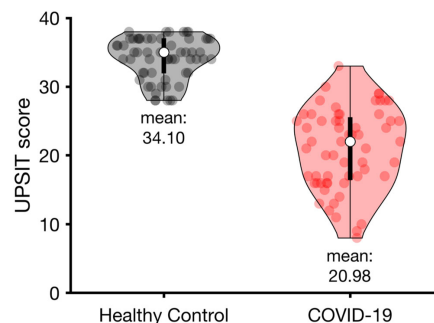
FIGURE 1. UPSIT scores of the COVID-19 patients compared to those of healthy controls. The distribution of the participants' scores in each group is depicted in violin plot. The white circles indicate the median of the score for each group. COVID-19 = coronavirus disease 2019; UPSIT = University of Pennsylvania Smell Identification Test.

Statistical analyses

Statistical analyses were performed using either SYSTAT 13 (Systat Software, Inc., San Jose, CA)[20] or MATLAB 2019b (The MathWorks, Inc., Natick, MA). A subject group by gender mixed factor analysis of variance (ANOVA) was used to determine whether the UPSIT scores differed significantly between the patient and control groups and whether gender influenced the test scores. Standard ANOVAs were used to compare other means. Differences in frequencies were assessed using the Fisher's exact probability test.

Results

The COVID-19 patients' non-mutually exclusive presenting symptoms were fever (n = 46, 77%), cough (n = 35, 58%), shortness of breath (n = 31, 52%), headache (n = 22, 37%), myalgia (n = 5, 8%), sweating (n = 2, 3%), shivering (n = 2, 3%), anorexia (n = 2, 3%), stomachache (n = 1, 2%), and tinnitus (n = 1, 2%). The mean (95% CI) time between the onset of symptoms and the olfactory testsing was 12.76 (11.47, 14.06) days.

The UPSIT testing revealed that, relative to controls and published normative data, the COVID-19 patients exhibited marked olfactory dysfunction. Thus, as illustrated in Figure 1, the mean (95% confidence interval [CI]) UPSIT score for the COVID-19 patients was 20.98 (19.47, 22.48), reflecting severe microsmia,[21] whereas the mean UPSIT score (95% CI) for the age- and sex-matched controls fell within the normal range (34.10 [33.31, 34.88]; ANOVA group main effect F [1,58] = 232.99, $p < 0.0001$, $\eta^2 = 0.80$). The COVID-19 deficit was not specific to any 1 UPSIT odorant, being evident for all 40 stimuli (Fig. 2).

Importantly, all but 1 of the 60 patients with COVID-19 had some degree of measured olfactory dysfunction (98%). Thirty-five of the 60 patients (58%) were either anosmic
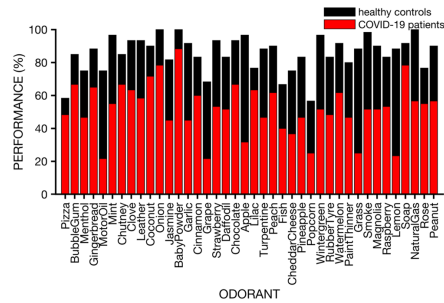
FIGURE 2. Performance on individual UPSIT odorants for the COVID-19 patients and matched healthy controls. Note that dysfunction was evident for all 40 UPSIT odorants. Performance for each group is calculated as the percent of individuals having correctly identified the odorant. COVID-19 = coronavirus disease 2019; UPSIT = University of Pennsylvania Smell Identification Test.

TABLE 2. Classification of olfactory function of the UPSIT scores of COVID-19 patients and matched controls

UPSIT function category	COVID-19 patients n (%)	Controls n (%)	UPSIT score range
Normosmia	1 (2)	49 (82)	31–40
Mild microsmia	8 (13)	11 (18)	28–30
Moderate microsmia	16 (27)	0	24–27
Severe microsmia	20 (33)	0	17–23
Anosmia	15 (25)	0	6–16
Probable malingering	0	0	0–5

COVID-19 = coronavirus disease 2019; UPSIT = University of Pennsylvania Smell Identification Test.

(15/60; 25%) or severely microsmic (20/60; 33%); 16/60 (27%) exhibited moderate microsmia, 8/60 (13%) mild microsmia, and 1/60 (2%) normosmia according to Persian-adjusted UPSIT norms (Table 2).[21] This contrasts markedly from the controls, of which 49 of 60 (82%) were normal with the remaining 11 of 60 (18%) having only mild borderline dysfunction. Relative to the normal controls, the 11 controls with mild borderline dysfunction tended to be disproportionately men (10/11 [91%] vs 30/49 [61%]; $p = 0.08$) of older age (respective mean ages [95% CIs] = 51.18 [42.63, 59.73] and 45.51 [42.11, 48.90]; $p = 0.18$). Even though there was a tendency for women, overall, to outperform men on the UPSIT (respective mean [95% CI] UPSIT scores: 22.55 [20.13, 24.97] and 20.20 [18.27, 22.13]; F [1,58] = 3.82, $p = 0.055$, $\eta^2 = 0.06$), this was unrelated to COVID-19 (sex by group interaction F [1,58] = 0.396, $p = 0.53$).

Thirty-five percent (21/60) of the COVID-19 patients reported a loss in either smell or taste function, with 12% (7/60) reporting smell loss only, 7% (4/60) taste loss only,

TABLE 3. Relationship between COVID-19 clinical disease severity and mean (95% CI) scores on the UPSIT

COVID-19 disease severity	n (%)	UPSIT score mean (95%CI)
Mild	25 (42)	22.04 (20.11–24.72)
Moderate	29 (48)	19.69 (17.24–21.99)
Severe	6 (10)	22.83 (17.65–25.77)

CI = confidence interval; COVID-19 = coronavirus disease 2019; UPSIT = University of Pennsylvania Smell Identification Test.

and 17% (10/60) both taste and smell loss. There was no significant difference between UPSIT scores of patients who were aware or unaware of their chemosensory loss ($p = 0.28$). All 21 reported that the onset of the olfactory dysfunction occurred at the same time or immediately after the onset of their other COVID-19 symptoms. None reported recognizing any smell or taste deficits prior to their other COVID-19 symptoms, namely fever, cough, or shortness of breath. In the healthy control group, none of the participants reported any smell or taste problems.

As shown in Table 1, significantly fewer smokers were present in the COVID-19 group than in the control group (2/60 vs 11/60; $p = 0.016$). Eight patients with diabetes were present in the COVID-19 group, unlike the control group (8/60 vs 0/60; $p = 0.007$). However, the respective mean (95% CI) UPSIT scores for COVID-19 patients with and without diabetes did not differ (21.38 [18.18, 24.56] vs 20.92 [19.32, 22.62], respectively; F [2,57] = 1.43, $p = 0.24$, $\eta^2 = 0.05$). No association of UPSIT scores with disease severity, as per the Massachusetts General Hospital COVID-19 treatment guidance algorithm, was apparent (Table 3; F [2,57] = 1.45, $p = 0.24$, $\eta^2 = 0.05$).

Discussion

This study quantitatively evaluated olfaction in a sizable cohort of patients diagnosed with the SARS-CoV-2 virus infection. By employing a well-validated 40-item smell test, COVID-19 patients were able to be classified into distinct categories of olfactory dysfunction, with 35 of 60 (58%) exhibiting either anosmia or severe microsmia. In the present study, only 35% of the patients were aware of their olfactory deficit before testing, a percentage near to that of 34% reported in an interview with COVID-19 inpatients in Italy,[5] but lower than those reported in 2 online surveys (59%[3] and 68%[6]). This difference between self-report rate and quantified smell assessment conceivably reflects a disproportionate sampling of hospital admitted cases and/or the well-documented underestimation of self-reported smell and taste dysfunction present for the general population[9,10] and for such diseases as Alzheimer's disease (AD)[11] and Parkinson's disease (PD).[22,23] In general, smell loss is most noticeable when marked loss, such as anosmia, is present.[11,22] It should be pointed out that

56

the present study's sample resembles the demographic and clinical characteristics of COVID-19 patients reported in a compilation of 43 studies involving 3600 patients,[24] implying it is likely representative of COVID-19 patients in general.

The basis for the smell loss due to SARS-CoV-2 is not entirely clear, although it is well established that viruses and other xenobiotics can damage the olfactory neuroepithelium. Indeed, acute viral upper respiratory viral infections that damage this epithelium are the major cause of chronic olfactory dysfunction and numerous viruses are known to enter the brain through cellular and pericellular transport via this epithelium.[25] In North America, the peak period of non-influenza–related smell loss, including that possibly due to coronaviruses, occurs during the months of April, May, and June, whereas influenza-related smell loss peaks in December, January, and February.[26] Currently, the prevalence of COVID-19 in North America seems to follow a similar function to that observed for olfactory deficits due to other viruses, including other coronaviruses. What seems unique, however, is that nearly everyone who contacts COVID-19 appears to exhibit measurable loss of smell seemingly independent of severe nasal congestion or inflammation.

Although SARS-CoV-2 has the ability to enter epithelial cells by directly binding to the angiotensin converting enzyme 2 (ACE2) protein on the cell surface,[27] olfactory receptor cells do not express ACE2, as well as another gene involved in SARS-CoV-2 entry (TMPRSS2), unlike epithelial sustentacular and stem cells.[28] Thus, damage to the olfactory receptors may be mediated indirectly through SARS-CoV-2 uptake into other cells critical for sustaining the olfactory receptor cell population. For example, olfactory ensheathing glial cells that surround the olfactory receptor cell axons and form the olfactory fila are 1 candidate by which ACE2-independent virus transfer can occur into olfactory receptor neurons by way of exosomes. A possible scenario suggests that at this point olfactory receptor neurons may initiate a rapid immune response in the host with the manifestation of olfactory dysfunction.[29] That being said, the olfactory neuroepithelium has considerable propensity for regeneration if the stem cell layer is not markedly damaged[30-32] – regeneration that is likely related to spontaneous improvement in olfactory function over time.[33]

It is of interest that significantly fewer smokers were found in our COVID-19 cohort than in the control cohort. Our findings correspond with studies that report current smokers as rare as 1.4% and 1.3% in Chinese[34] and U.S.[35] COVID-19 patient populations, respectively. A recent study reported that smoking upregulated the expression of ACE-2 in the airways, potentially predisposing individuals to increased risk of coronavirus infection but, paradoxically, protecting the host against acute lung injury.[36] Interestingly, nonsmokers appear to be much more susceptible than smokers to olfactory dysfunction from industrial exposures to acrylate and methacrylate[37] and

smoking appears to protect, to some degree, against the olfactory loss of PD.[38] Future research is needed to determine to what degree the reported low frequency of smokers in COVID-19 populations is impacted by selection bias (eg, more smokers may have died before reaching the hospital) and reverse causation (ie, cessation of smoking in patients with severe symptoms prior to entering the hospital, thereby being counted as nonsmokers). The latter is unlikely in our study, however, because each patient was specifically asked whether they currently smoked or had smoked in the past.

The complaint of taste loss by a small number of our COVID-19 patients most likely reflects, to a significant degree, damage to the olfactory system, rather than damage to the taste buds or taste afferents, per se. Thus, the vast majority of individuals who clinically present with complaints of taste loss actually exhibit smell dysfunction, including those with a viral etiology.[39] Taste bud–mediated sensations are largely limited to the basic taste qualities of sweet, sour, bitter, salty, and umami. With the exception of such sensations, all "tastes" are flavor sensations from olfactory receptor stimulation by volatiles entering from the nasopharynx during deglutition.[40] This tendency for many persons with smell loss to misconstrue their problem as taste loss[39] must be considered in studies relying only on self-report. Future research employing quantitative taste tests is clearly needed to definitively establish whether SARS-CoV-2 also can damage taste afferents or, in rare cases, more central taste-related brain regions.

More men than women were present in our sample, in accord with the reported demographic and clinical characteristics of COVID-19 patients.[24] However, the magnitude of olfactory dysfunction, as measured by the UPSIT, was essentially the same in both sexes. This implies that there is little or no protection from being a female in terms of the degree to which SARS-CoV-2 damages the olfactory system, in accord with some other studies of postviral olfactory deficits.[41] If this observation is confirmed with larger samples, it would appear that the olfactory dysfunction of COVID-19 differs from that of AD and PD, where women significantly outperform men.[11,22,38]

It is important to note that the COVID-19–positive patients evaluated in this study had severe enough symptoms to be admitted to the hospital. It is unknown whether less severe cases also exhibit the same degree of smell dysfunction as documented in this study, although within our hospitalized cohort no relationship was evident between the olfactory test scores and disease severity. This is similar to what is seen in the smell loss of PD, where no clear association is present between the magnitude of the classic motor signs and the amount of olfactory dysfunction.[22]

Even though the COVID-19 patients in this study were undergoing drug treatments for their disease, it is unlikely that the involved drugs were a meaningful cause of their olfactory dysfunction. Despite the fact that a significant number of medications are reported to have taste side effects,[42] alterations in smell function are relatively rare and have

not been associated with hydroxychloroquine, lopinavir-ritonavir, or IVIG. Because the same degree of smell function was evident among patients with COVID-19 taking each of these medications, it is improbable that any one medication would have produced the smell deficits observed in this study.

Although RT-PCR was by far the frontline response to the SARS-CoV-2 outbreak, the accuracy and conditions under which the results of RT-PCR were achieved must be kept in context, because a false-negative rate of at least 15% has been reported.[43-45] The present findings, along with the wealth of anecdotal data, suggest that quantitative testing of the sense of smell might serve as a rapid and inexpensive alternative diagnostic means to screen for COVID-19 in large numbers of individuals. Indeed, the sensitivity and specificity of olfactory tests for COVID-19–positive patients under the age of 65 years would seem to be quite strong, because age-related changes in smell function occur mainly after the age of 65 years.[17]

The present study has both strengths and weaknesses. Among its strengths are (1) the use of a sensitive test of olfactory function that allows for determining different degrees of olfactory function, (2) testing of well-validated COVID-19 patients whose clinical severity was well documented, and (3) the use of controls matched closely to those of the patients on the basis of age and sex who were sampled outside of the period in which COVID-19 was first identified in Iran. Its major limitation is the sampling of the study population at only 1 point in time relative to the onset of COVID-19 symptoms. Future studies are needed to establish (1) the exact time of onset of smell symptoms, (2) whether the olfactory dysfunction is transient, long-lasting, or permanent, (3) whether such symptoms are evident in those who fail to develop other COVID-19 symptoms, and (4) whether the deficits follow seasonal patterns such as those noted for other virus-related cases

of smell dysfunction.[26] Information as to permanency is of considerable significance, because loss of the ability to smell significantly impacts quality of life, the flavor of foods, and beverages, and safety from spoiled food, fire, and leaking natural gas. Importantly, smell loss can be a harbinger of a number of neurological diseases, most notably AD and PD—diseases which, in some cases, have been associated with a number of viruses.[46,47] Although the reasons are poorly understood, older persons with smell loss are 3 times more likely to die over the course of an ensuring half-decade than older persons with a normal sense of smell.[48,49]

Conclusion

The present study provides a quantitative assessment of the olfactory function of a cohort of patients with COVID-19. Its findings strongly suggest that some degree of loss of smell function is present in nearly all COVID-19 patients near the end of their acute recovery period. However, anosmia, per se, was present in only about one-quarter of COVID-19 positive patients in our sample, with about one-third evidencing severe microsmia. In light of the current findings and pandemic environment, and the widespread anecdotal evidence of smell dysfunction in COVID-19, it does not seem unreasonable that testing the olfaction of persons who may be at risk or have subtle COVID-19 signs, such as low-grade fevers, may aid in identifying COVID-19 patients who are in need of early treatment or quarantine. 🙵

Acknowledgments

References

1. Eliezer M, Hautefort C, Hamel AL, et al. Sudden and complete olfactory loss function as a possible symptom of COVID-19. *JAMA Otolaryngol Head Neck Surg*. (in press). Epub 08 April 2020. https://doi.org/10.1001/jamaoto.2020.0832.

2. Luers JC, Klussmann JP, Guntinas-Lichius O. [The Covid-19 pandemic and otolaryngology: what it comes down to?]. *Laryngorhinootologie*. 2020;99(5):287–291. https://doi.org/10.1055/a-1095-2344. German.

3. Menni C, Valdes A, Freydin MB, et al. Loss of smell and taste in combination with other symptoms is a strong predictor of COVID-19 infection. *medRxiv*. 2020.04.05.20048421. Epub 07 April 2020. https://doi.org/10.1101/2020.04.05.20048421.

4. Bagheri SHR, Asghari AM, Farhadi M, et al. Coincidence of COVID-19 epidemic and olfactory dysfunction outbreak. *medRxiv*. 2020.03.23.20041889. Epub 27 March 2020. https://doi.org/10.1101/2020.03.23.20041889.

5. Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clin Infect Dis*. (in press). Epub 26 March 2020. https://doi.org/10.1093/cid/ciaa330.

6. Yan CH, Faraji M, Prajapati DP, Boone CE. Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms. *Int Forum Allergy Rhinol*. (in press). Epub 12 April 2020. https://doi.org/10.1002/alr.22579.

7. American Academy of Otolaryngology–Head and Neck Surgery Foundation. *ENT Health. Hyposmia and anosmia*. Alexandria, VA: American Academy of Otolaryngology–Head and Neck Surgery Foundation; 2020. https://www.enthealth.org/conditions/hyposmia-and-anosmia/. Accessed May 14, 2020.

8. Hopkins C, Kumar N. *Loss of sense of smell as marker of COVID-19 infection 2020*. London, UK: ENT UK, The Royal College of Surgeons of England; 2020. https://www.entuk.org/loss-sense-smell-marker-covid-19-infection-0. Accessed May 14, 2020.

9. Wehling E, Nordin S, Espeseth T, Reinvang I, Lundervold AJ. Unawareness of olfactory dysfunction and its association with cognitive functioning in middle aged and old adults. *Arch Clin Neuropsychol*. 2011;26:260-269.

10. Soter A, Kim J, Jackman A, Tourbier I, Kaul A, Doty RL. Accuracy of self-report in detecting taste dysfunction. *Laryngoscope*. 2008;118:611-617.

11. Doty RL, Reyes PF, Gregor T. Presence of both odor identification and detection deficits in Alzheimer's disease. *Brain Resh Bull* 1987;18:597-600.

12. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. *Physiol Behav*. 1984;32:489-502.

13. Chung M, Bernheim A, Mei X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). *Radiology*. 2020;295:202-207.

14. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med*. 2020;382:1177-1179.

15. Massachusetts General Hospital. *Massachusetts General Hospital COVID-19 Treatment Guidance*. Boston, MA: Massachusetts General Hospital; 2020. https://www.massgeneral.org/assets/MGH/pdf/news/coronavirus/covid-19_domID_treatmentGuide.pdf. Accessed May 14, 2020.

16. Jamaati H DF, Tabarsi P, Marjani M, Saffaei A, Hashemian SM. A fourteen-day experience with coronavirus disease 2019 (COVID-19) induced acute respiratory distress syndrome (ARDS): an Iranian treatment protocol. *Iran J Pharm Res* 2020;19(1):31–36.

17. Doty RL, Shaman P, Applebaum SL, Giberson R, Siksorski L, Rosenberg L. Smell identification ability: changes with age. *Science* 1984; 226: 1441-1443.

18. Doty RL, Frye RE, Agrawal U. Internal consistency reliability of the fractionated and whole university of Pennsylvania smell identification test. *Percept Psychophys* 1989;45(5): 381-384.

19. Doty RL, Wylie C, Potter M, Beston R, Cope B, Majam K. Clinical validation of the olfactory detection threshold module of the Snap & Sniff(R) olfactory test system. *Int Forum Allergy Rhinol* 2019;9(9): 986-992.

20. Wilkinson L. *SYSTAT: The System for Statistics*. Evanston, IL: SYSTAT, Inc.; 1990.

58

21. Doty RL. *The Smell Identification Test™ Administration Manual*. 3rd ed. Haddon Heights, NJ: Sensonics, Inc.; 1995.

22. Doty RL, Deems DA, Stellar S. Olfactory dysfunction in parkinsonism: a general deficit unrelated to neurologic signs, disease stage, or disease duration. *Neurology*. 1988;38:1237-1244.

23. Doty RL, Perl DP, Steele JC, et al. Odor identification deficit of the parkinsonism-dementia complex of Guam: equivalence to that of Alzheimer's and idiopathic Parkinson's disease. *Neurology*. 1991;41(5 Suppl 2):77-80.

24. Fu L, Wang B, Yuan T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. *J Infect*. 2020;80:656-665.

25. Doty RL. The olfactory vector hypothesis of neurodegenerative disease: is it viable? *Ann Neurol*. 2008;63:7-15.

26. Potter MR, Chen JH, Lobban N-S, Doty RL. Olfactory dysfunction from acute upper respiratory infections: relationship to season of onset. *Int Forum Allergy Rhinol*. 2020;10(6):706–712. https://doi.org/10.1002/alr.22551.

27. Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. *Biochem Biophys Res Commun*. 2020;526:135-140.

28. Brann DH, Tsukahara T, Weinreb C, et al. Non-neural expression of SARS-ClV-2 entry genes in the olfactory epithelium suggests mechanisms underlying anosmia in COVD-19 patients. *bioRxiv* 2020.03.25.009084. Epub 09 April 2020. https://doi.org/10.1101/2020.03.25.009084.

29. Butowt R, Bilinska K. SARS-CoV-2: olfaction, brain infection, and the urgent need for clinical samples allowing earlier virus detection. *ACS Chem Neurosci*. 2020;11:1200-1203.

30. Chang SY, Glezer I. The balance between efficient anti-inflammatory treatment and neuronal regeneration in the olfactory epithelium. *Neural Regen Res*. 2018;13:1711-1714.

31. Choi R, Goldstein BJ. Olfactory epithelium: cells, clinical disorders, and insights from an adult stem cell niche. *Laryngoscope Investig Otolaryngol*. 2018;3:35-42.

32. Joiner AM, Green WW, McIntyre JC, Allen BL, Schwob JE, Martens JR. Primary cilia on horizontal basal cells regulate regeneration of the olfactory epithelium. *J Neurosci*. 2015;35:13761-13672.

33. London B, Nabet B, Fisher AR, White B, Sammel MD, Doty RL. Predictors of prognosis in patients with olfactory disturbance. *Ann Neurol*. 2008;63:159-166.

34. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*. (in press). Epub 19 February 2020. https://doi.org/10.1111/all.14238.

35. CDC COVID-19 Response Team. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019 - United States, February 12-March 28, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:382-386.

36. Leung JM, Yang CX, Tam A, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. *Eur Respir J*. 2020;55:2000688.

37. Schwartz BS, Doty RL, Monroe C, Frye R, Barker S. Olfactory function in chemical workers exposed to acrylate and methacrylate vapors. *Am J Public Health*. 1989;79:613-618.

38. Sharer JD, Leon-Sarmiento FE, Morley JF, Weintraub D, Doty RL. Olfactory dysfunction in Parkinson's disease: positive effect of cigarette smoking. *Mov Disord*. 2015;30:859-862.

39. Deems DA, Doty RL, Settle RG, et al. Smell and taste disorders, a study of 750 patients from the University of Pennsylvania Smell and Taste Center. *Arch Otolaryngol Head Neck Surg*. 1991;117:519-528.

40. Burdach KJ, Doty RL. The effects of mouth movements, swallowing, and spitting on retronasal odor perception. *Physiol Behav*. 1987;41:353-356.

41. Tian J, Wei YX, Li L, Sun ZF, Wang BQ. [Analysis of clinical characteristics of 141 patients with postviral olfactory dysfunction]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2017;31:749-752. Chinese.

42. Schiffman SS. Influence of medications on taste and smell. *World J Otorhinolaryngol Head Neck Surg* 2018;4:84-91.

43. Li D, Wang D, Dong J, et al. False-negative results of real-time reverse-transcriptase polymerase chain reaction for severe acute respiratory syndrome coronavirus 2: role of deep-learning-based CT diagnosis and insights from two cases. *Korean J Radiol*. 2020;21: 505-508.

44. Ai J-W, Zhang H-C, Xu T, et al. Optimizing diagnostic strategy for novel coronavirus pneumonia, a multi-center study in Eastern China. *medRxiv*. 2020.02.13.20022673. Epub 17 February 2020. https://doi.org/10.1101/2020.02.13.20022673.

45. Liang Y, Liang J, Zhou Q, et al. Prevalence and clinical features of 2019 novel coronavirus disease (COVID-19) in the Fever Clinic of a teaching hospital in Beijing: a single-center, retrospective study. *medRxiv*. 2020.02.25.20027763. Epub 28 February 2020. https://doi.org/10.1101/2020.02.25.20027763.

46. Balin BJ, Hudson AP. Herpes viruses and Alzheimer's disease: new evidence in the debate. *Lancet Neurol*. 2018;17:839-841.

47. Olsen LK, Cairns AG, Aden J, et al. Viral mimetic priming enhances alpha-synuclein-induced degeneration: implications for Parkinson's disease. *Brain Behav Immun*. 2019;80:525-535.

48. Pinto JM, Wroblewski KE, Kern DW, Schumm LP, McClintock MK. Olfactory dysfunction predicts 5-year mortality in older adults. *PLoS One*. 2014;9:e107541.

49. Devanand DP, Lee S, Manly J, et al. Olfactory deficits predict cognitive decline and Alzheimer dementia in an urban community. *Ann Neurol*. 2015;84:182-189.

59

LAMPIRAN 8 : Jurnal Studi Inklusi 8

Contents lists available at ScienceDirect

Médecine et maladies infectieuses

ELSEVIER

Short communication

Features of anosmia in COVID-19

T. Klopfenstein [a,*], N.J. Kadiane-Oussou [a], L. Toko [a], P.-Y. Royer [a], Q. Lepiller [b], V. Gendrin [a], S. Zayet [a]

[a] Infectious Diseases Department, Nord Franche-Comté Hospital, 90400 Trévenans, France
[b] Virology Department, Centre-Hospitalier Universitaire de Besançon, 25000 Besançon, France

ARTICLE INFO

ABSTRACT

Background. – Medical publications about anosmia with COVID-19 are scarce. We aimed to describe the prevalence and features of anosmia in COVID-19 patients.
Methods. – We retrospectively included COVID-19 patients with anosmia between March 1st and March 17th, 2020. We used SARS-CoV-2 real time PCR in respiratory samples to confirm the cases.
Results. – Fifty-four of 114 patients (47%) with confirmed COVID-19 reported anosmia. Mean age of the 54 patients was 47 ($\pm$ 16) years; 67% were females and 37% were hospitalised. The median Charlson comorbidity index was 0.70 ($\pm$ 1.6 [0–7]). Forty-six patients (85%) had dysgeusia and 28% presented with pneumonia. Anosmia began 4.4 ($\pm$ 1.9 [1–8]) days after infection onset. The mean duration of anosmia was 8.9 ($\pm$ 6.3 [1–21]) days and 98% of patients recovered within 28 days.
Conclusions. – Anosmia was present in half of our European COVID-19 patients and was often associated with dysgeusia.

© 2020 Elsevier Masson SAS. All rights reserved.

1. Introduction

Clinical description from coronavirus disease 2019 (COVID-19) outbreak in China reveals that most patients (81%) present with influenza-like illness (ILI) or mild pneumonia, and 19% of cases experience severe or critical pneumonia [1]. Fever, cough, fatigue, and myalgia are usually the main symptoms. The expression of COVID-19 ILI seems non-specific; no specific symptom can lead to suspecting a case without any notion of exposure [2–7]. A major French cluster of COVID-19 began on March 1st, 2020 in the city of Mulhouse, France (less than 30 miles from our hospital). After clinical examination of the first patients, we noticed that many cases reported anosmia. The description of anosmia and other ENT symptoms is scarce with COVID-19. For instance, a recent review on COVID-19 by ENT specialists on March 26 emphasised that ENT symptoms were uncommon with COVID-19 as nasal congestion and rhinorrhea were observed in less than 5% of cases. However, they noticed that there were few reports of anosmia and dysgeusia with no real description of symptoms [8]. Recently, in April, descriptions of cases of anosmia in a multicentric cohort have been

associated with COVID-19 [9–11]. We aimed to describe the prevalence and features of anosmia in COVID-19 patients.

2. Method

We conducted a retrospective observational study in the NFC (*Nord Franche-Comté*) hospital. Between March 1st and March 17th, 2020, we enrolled all adult patients ($\geq$ 18 years) with confirmed COVID-19 who were examined at the infectious disease consultation or hospitalised in the hospital and who reported anosmia. Pregnant women, children (< 18 years), and patients with dementia (who cannot report functional symptoms) were excluded. We stopped the study follow-up on March 24th, 2020.

Diagnosis was confirmed by real-time PCR (RT-PCR) on respiratory samples, mainly nasopharyngeal swabs, sputum, bronchial aspirates, or bronchoalveolar lavage fluids. Viral RNA was extracted using the NucleoSpin® RNA Virus kit (Macherey-Nagel) according to the manufacturer's instructions, and amplified by RT-PCR protocols developed by *Charité* (E gene) [12] and the *Institut Pasteur* (RdRp gene) [13] on LightCycler 480 (*Roche*). Quantified positive controls were kindly provided by the French National Reference Centre for Respiratory Viruses, *Institut Pasteur*, Paris.

Our national guidelines recommended home follow-up for non-hospitalised patients [14]. Non-hospitalised and discharged patients were called seven days ($\pm$ 7 days) after the first symptoms and every week until recovery to monitor clinical outcome.

* Corresponding author at: Department of Infectious Diseases, Nord Franche-Comté Hospital, 90400 Trévenans, France.
E-mail addresses: timothee.klopfenstein@hnfc.fr (T. Klopfenstein), souhail.zayet@gmail.com (S. Zayet).

Data required for the study was collected from the medical files of patients: age, sex, comorbidities, features of anosmia (date of apparition since symptom onset, duration of anosmia), other symptoms, physical signs, and outcome. Usual descriptive statistics were used. Categorical variables were expressed as numbers, percentages, or mean. Continuous variables were expressed as mean with standard deviation (SD).

We aimed to describe the prevalence and characteristics of anosmia in patients with confirmed COVID-19.

3. Results

Fifty-four of 114 patients (47%) with confirmed COVID-19 reported anosmia and were included in this study. Among these 54 patients, the mean age was 47 ($\pm$16) years and 36 (67%) were females. The median Charlson comorbidity index was 0.70 ($\pm$1.6 [0–7]). The most frequent comorbidities were asthma (13%, n=7), arterial hypertension (13%, n=7), and cardiovascular disease (11%, n=6). Other comorbidities were less frequent (Table 1) and no patient had chronic obstructive pulmonary disease (COPD).

Among the 54 patients, the mean duration of anosmia was 8.9 ($\pm$6.3 [1–21]) days. Duration was $\geq$ 7 days for 55% (24/44) and $\geq$ 14 days for 20% (9/44) (Fig. 1); one patient (1/44) had not recovered at the end of the follow-up (after 28 days). Anosmia was never the first or second symptom to develop, but it was the third symptom in 38% (22/52) of cases. Anosmia developed 4.4 ($\pm$1.9 [1–8]) days after infection onset.

As for the other ENT symptoms, anosmia was associated with dysgeusia in 85% of cases (n=46). Thirty-one patients had rhinorrhea (57%) and only 16 patients (30%) had nasal obstruction. Epistaxis, tinnitus, and hearing loss were uncommon (< 15%).

As for other symptoms, seven symptoms were present in more than half of patients: fatigue (93%, n=50), cough (87%, n=47), headache (82%, n=44), fever (74%, n=40), myalgia (74%, n=40), arthralgia (72%, n=39), and diarrhea (52%, n=28). Other symptoms were less present (Table 1).

Fifteen (28%) patients received a clinical diagnosis of pneumonia with COVID-19. Their oxygen saturation was at 94.6% [$\pm$4.6] at admission. More than a third of our patients (37%, n=20) were hospitalised, including five patients (9%) in the intensive care unit (ICU). Four patients (7%) had oxygen saturation < 90% at admission, 11 patients (20%) needed oxygen therapy during hospitalisation, and two patients (4%) died.

4. Discussion

A multicentric European study published on April 6 conducted by Lechien et al. reported 357 patients with olfactory dysfunction related to COVID-19 [11]. We mostly used this publication to discuss our results, as it is the only publication with a large cohort of patients with COVID-19-related olfactory dysfunction.

The mean age of our population was 47 ($\pm$16) years, and 67% were females. The prevalence of asthma in our study was $\geq$ 10% and we did not have any COPD patient, which is uncommon in patients with COVID-19. Patients with anosmia seemed to be younger with a predominance of females, they had fewer comorbidities with a lower Charlson comorbidity index (< 1), and more often presented with asthma in comparison with the population usually described with COVID-19; the same population characteristics were described by Lechien et al.

Until recently, ENT symptoms had not been reported with COVID-19, except for nasal congestion and rhinorrhea [2–8]. However, 54 (47%) of our 114 COVID-19 patients reported anosmia. Lechien et al. reported anosmia in 86% (n=357/417) of their patients. This higher frequency may be explained by their

Table 1
Comorbidities, symptoms, and outcome of the 54 patients with anosmia.
Comorbidités, symptômes et devenir des 54 patients anosmiques.

Characteristics	Number (%)
Medical history	
Age (Y): mean (SD)	47 ($\pm$16)
Sex	
Female	36 (67%)
Male	18 (33%)
Current smoking	6 (11%)
Comorbidities	
Arterial hypertension	7 (13%)
Cardiovascular disease[a]	6 (11%)
Diabetes	2 (4%)
Asthma	7 (13%)
COPD[b]	0 (6%)
Malignancy	2 (4%)
Immunosupression[c]	1 (4%)
Charlson comorbidity index: mean (SD)	0.70 ($\pm$1.6, [0–7])
ENT symptoms	
Rhinorrhea	31 (57%)
Nasal obstruction	16 (30%)
Epistaxis	6 (11%)
Dysgeusia	46 (85%)
Tinnitus	6 (11%)
Hearing loss	4 (7%)
Other symptoms	
Fever measured > 38 °C	40 (74%)
Feeling of fever	12 (22%)
Highest temperature (T°C): mean (SD)	38.6 ($\pm$0.8)
Fatigue	50 (93%)
Myalgia	40 (74%)
Arthralgia	39 (72%)
Sore throat	23 (43%)
Headaches	44 (82%)
Conjunctival hyperemia	2 (4%)
Tearing	4 (7%)
Dry eyes	2 (4%)
Blurred vision	4 (7%)
Sneezing	18 (33%)
Cough	47 (87%)
Sputum production	12 (22%)
Hemoptysis	3 (6%)
Dyspnea	21 (39%)
Respiratory rate > 22/min	10 (19%)
Sat O_2 at admission (%)	94.6 ($\pm$4.6)
Auscultation with crackling sounds	15 (28%)
Nausea	19 (35%)
Vomiting	3 (6%)
Diarrhea	28 (52%)
Abdominal pain	15 (28%)
Outcome	
Hospitalisation	20 (37%)
Hospitalisation in the intensive care unit	5 (9%)
Oxygen therapy	11 (20%)
Death	2 (4%)

[a] Defined by: cardiac failure, cardiac arrhythmia, coronary heart disease, stroke, peripheral arterial obstructive disease, and thromboembolic disease.
[b] Chronic obstructive pulmonary disease.
[c] Defined by: transplantation, cirrhosis, long-term steroid therapy, and immunomodulator treatments.

population profiles, which were ambulatory cases that consulted at ENT consultations (patients with a mean age of 37 [$\pm$11.4] years without cardiovascular comorbidities) and for whom it is probably easier to relate functional symptoms than patients with oxygen therapy or critical patients. Anosmia was therefore a frequent symptom in COVID-19 patients in our French study and in this European study. However, few descriptions of ENT symptoms are available, especially in Asian studies. These differences between Asia and Europe should be discussed. We made several assumptions. First, the theoretical possibility of a mutation of SARS-CoV-2 viral genome associated with a clinical impact, but not yet
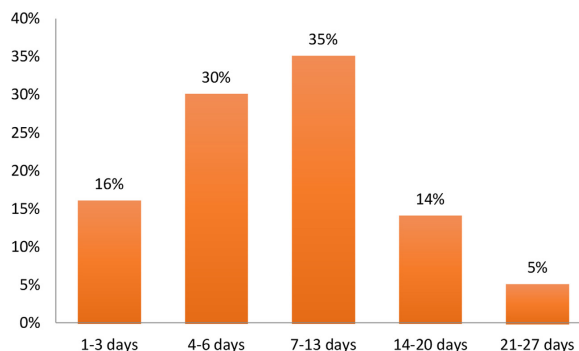
Fig. 1. Recovery time for patients with anosmia (*n* = 43 patients, 10 patients did not remember duration until recovery and one patient did not recover after 28 days).
Durée de l'anosmie (n=43, 10 patients ne se rappelaient pas de la durée et 1 patient était toujours anosmique à J28).

described. On the other hand, it is difficult to precisely report ENT symptoms of critical patients. These symptoms may seem of less importance when considering the potential severity of the disease [15]. Finally, Lechien et al. discussed the affinity of SARS-CoV-2 for tissues and individual possible genetic features. Their main argument was that the angiotensin-converting enzyme 2 (as receptor of SARS-CoV-2) can be specific to an ethnic group.

Anosmia was associated with dysgeusia in 85% of cases and in more than half of cases with rhinorrhea (57%). However, 70% of our patients with anosmia did not present with nasal obstruction. This leads to suspecting another pathogenesis for anosmia than mechanical nasal obstruction. In addition, anosmia during viral rhinitis with nasal obstruction usually resolves within three days [16], while we observed a mean duration of anosmia of nine days. The concept of anosmia after viral infection is known as post-infectious/post-viral olfactory loss (POL). Different kind of viruses can induce POL, including coronaviruses such as HCoV-229E [17]. However, medical literature data indicates that the duration of POL can be long: a study of 63 patients with POL reported that after one year 80% of patients had subjective recovery [18]. In our study, only one patient did not recover at the end of the study follow-up (after a follow-up of 28 days); 80% of our patients recovered within 14 days. Compared with POL, the outcome of COVID-19-related acute anosmia most frequently seems favourable in the short term.

Our patients had the same other symptoms (other than ENT symptoms) as those reported in other studies [2–7]. However, just like Lechien et al., we observed that diarrhea was reported in more than 50% of patients. Except for one study (occurrence of 33%), the occurrence of diarrhea is < 20% in the medical literature [19]. The frequency of diarrhea seems to be high in patients with anosmia.

One of our study limitations was the limited number of patients. However, our study is, to our knowledge, the main monocentric cohort of confirmed COVID-19 patients with anosmia in France and in the medical literature. Our results are similar to those published by the recent multicentric European study performed by Lechien et al.

5. Conclusion

COVID-19-related anosmia is a new description in the medical literature. Half of the patients with COVID-19 present with anosmia. Anosmia is associated with dysgeusia in more than 80% of cases. The outcome seems favourable in less than 28 days. This notion needs to be communicated to the medical community.

Contribution of authors

SZ and JNKO collected the epidemiological and clinical data. TK and SZ drafted the article. LT, PYR, QL, and VG reviewed the final version of the article.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Centre for Disease Control and Prevention. JAMA 2020 [cited 2020 Mar 23; available from: https://jamanetwork.com/journals/jama/fullarticle/2762130].
[2] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalised patients with 2019 novel Coronavirus-infected pneumonia in Wuhan, China. JAMA 2020.
[3] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
[4] Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis, 2020 [Internet]. [cited 2020 Mar 22]; Available from: https://academic.oup.com/cid/advancearticle/doi/10.1093/cid/ciaa272/5807944.
[5] Wu J, Liu J, Zhao X, Liu C, Wang W, Wang D, et al. Clinical Characteristics of Imported Cases of COVID-19 in Jiangsu Province: A Multicenter Descriptive Study. Clin Infect Dis, 2020 [Internet]. [cited 2020 Mar 22]; Available from: https://academic.oup.com/cid/advancearticle/doi/10.1093/cid/ciaa199/5766408.
[6] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of 2019 novel coronavirus infection in China. medRxiv 2020 [2020.02.06.20020974].
[7] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13.
[8] Vukkadala N, Qian ZJ, Holsinger FC, Patel ZM, Rosenthal E. COVID-19 and the otolaryngologist – preliminary evidence-based review. Laryngoscope 2020.
[9] Gane SB, Kelly C, Hopkins C. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome? Rhinology 2020.
[10] Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and ageusia: common findings in COVID-19 patients. Laryngoscope 2020.
[11] Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicentre European study. Eur Arch OtoRhinoLaryngol 2020.

[12] Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DKW, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill 2020;25.

[13] Bernard Stoecklin S, Rolland P, Silue Y, Mailles A, Campese C, Simondon A, et al. First cases of coronavirus disease 2019 (COVID-19) in France: surveillance, investigations and control measures, January 2020. Euro Surveill 2020;25.

[14] DICOM.Lisa C. COVID-19 : prise en charge en ambulatoire [Internet]. Ministère des Solidarités et de la Santé; 2020 [cited 2020 Mar 23; available from: http://solidarites-sante.gouv.fr/soins-et-maladies/maladies/maladies-infect ieuses/coronavirus/covid-19-informations-aux-professionnels-de-sante/artic le/covid-19-prise-en-charge-en-ambulatoire].

[15] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020 [cited 2020 Mar 22; available from: https://www. thelancet.com/journals/lanres/article/PIIS2213-2600(20)30079-5/Abstract].

[16] Akerlund A, Bende M, Murphy C. Olfactory threshold and nasal mucosal changes in experimentally induced common cold. Acta Otolaryngol 1995;115: 88–92.

[17] Suzuki M, Saito K, Min W-P, Vladau C, Toida K, Itoh H, et al. Identification of viruses in patients with post-viral olfactory dysfunction. Laryngoscope 2007;117:272–7.

[18] Lee DY, Lee WH, Wee JH, Kim J-W. Prognosis of post-viral olfactory loss: follow-up study for longer than one year. Am J Rhinol Allergy 2014;28:419–22.

[19] Li X-Y, Dai W-J, Wu S-N, Yang X-Z, Wang H-G. The occurrence of diarrhea in COVID-19 patients. Clin Res Hepatol Gastroenterol 2020.