ORIGINAL ARTICLE

How COVID-19 brought smell disorders in the spotlight

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ABSTRACT

The rapid spread of the COVID-19 infection required prompt recognition and immediate isolation of patients. In the evolution of the disease various symptoms were indicated as suggestive of a SARS-CoV-2 infection, among them being also described anosmia and ageusia. In order to review how olfactory disorders are related to COVID-19 disease, we carried out an analysis by searching PubMed, Science Direct, Springer, and LILACS. The research was made using MeSH descriptors and the Boolean operator, "AND", for the terms "olfactory disorders" or "olfactory dysfunction" or "anosmia" or "neurologic manifestations" or "ENT symptoms" AND "COVID-19" or "SARS-CoV-2" or "coronavirus infections", with a filter on the publication date set for 01.01.2020 – 18.06.2021. A total of 956 articles were found in the databases, out of which 14 were included in the study. The statistics suggest that alterations of the chemosensory function are strongly correlated with COVID-19, although the exact pathophysiologic mechanism is not well established. Symptomatology suggestive of chemosensory dysfunction (smell primarily and then taste alterations) elevate the degree of suspicion of a SARS-CoV-2 infection and they commend prompt isolation and surveillance measurements.

KEYWORDS: COVID-19 infection, olfactory disorders, ENT manifestations, anosmia, hyposmia, SARS-CoV-2.

INTRODUCTION

According to the World Health Organization (WHO) statistics, as of 22 January 2020, there were over 172 million confirmed cases attributed to COVID-19 infection and the number is rising[1]. The main routes through which the SARS-CoV-2 infection can be transmitted is either by infectious aerosols expelled during coughing, talking or singing, or by direct contact with contaminated secretions (e.g., saliva). Gravity of symptoms can vary from mild to severe respiratory distress. Apart from the frequently reported symptoms such as fever, cough, malaise, dyspnea, cephalalgia, there are described a wide range of ENT-related symptoms, such as sore throat, rhinorrhea, olfactory dysfunction, taste alterations, xerostomia, otalgia, tinnitus, hearing loss, vertigo, facial palsy, vocal cord paralysis.

Initially, olfactory impairment was not presented as a symptom suggestive for SARS-CoV-2 infection, but after the rapid spread of the virus, especially in Europe, WHO recognized, in May 2020, anosmia/hyposmia as a symptom that could indicate the COVID-19 infection.

Olfactory disorders have been frequently reported even in patients otherwise asymptomatic and it came to be one of the main symptoms that raises the suspicion of a SARS-CoV-2 infection, having a prevalence that varies from 5.1% to 86.4% [2,3].

PRESUMED PATHOGENESIS OF OLFACTORY DYSFUNCTION

The olfactory epithelium is formed by three types of cells: receptor cells (the olfactory sensory neurons), supporting cells (sustentacular cells)

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and basal cells. The perception of smell starts when the volatile substances interact with the chemoreceptors located on the olfactory sensory neurons (OSNs). Each OSNs has at its apical end a knoblike extension that protrudes into the thick mucus layer that lines the olfactory epithelium[4].

OSNs are bipolar neurons involved in the transduction of olfaction and are considered unique because they have the ability to regenerate. Basal cells are considered stem cells for the olfactory epithelium and are able to regenerate the entire olfactory epithelium in 60-90 days[5]. OSNs are surrounded by sustentacular cells that provide support and are involved in the proper functioning of the neuronal metabolism[6,7].

For a cell to be susceptible to the SARS-CoV-2 invasion it needs to express on its surface the angiotensin-converting enzyme 2 (ACE2) receptors which work in conjunction with a transmembrane serine protease (TMPRSS2) to attach and include the virus inside the cell[8,9]. Recent studies using RNA-sequencing have shown that ACE2 receptors are expressed on the surface of sustentacular and Bowman gland's cells, but OSNs and olfactory bulb mitral cells lack the presence of the ACE2 receptor[7,8].

Multiple mechanisms have been proposed to be responsible for the appearance of olfactory impairment in COVID-19:

- Invasion and destruction of supporting cell of the olfactory epithelium (OE)[6,7].
- Invasion and destruction of vascular pericytes or immune-mediated microvascular injury of the olfactory mucosa or olfactory bulb[10].
- Inflammation of the olfactory bulb triggered by the SARS-CoV-2 infection[11-14].
- Invasion of the central nervous system (CNS) structures by neuronal retrograde pathway via olfactory epithelium and olfactory nerve pathway[15].
- Conductive anosmia due to nasal obstruction and rhinorrhea.

Multiple conducted studies argue that the main mechanism responsible for the development of hypo- or anosmia is the damage produced to the supporting cells of the OE by direct invasion, which determines local inflammation and subsequent damage to the olfactory neurons. These theories rely on the fact that:

- ACE2 receptor is absent on the surface of olfactory neuron cells, but is expressed on the sustentacular cells, Bowman's gland and pericytes[8,16].
- Mean recovery period of 2 weeks is not compatible with the necessary interval for neuronal regeneration[11,12].
- Temporality of symptom presentation: before, simultaneous or after development of general symptoms (fever, cough, headache)[16,17].
- Neurotropism and neuroinvasion capabilities of SARS-CoV-2 allow the virus to be transported to the CNS through a retrograde pathway via the olfactory nerve[18].
- Anosmia is present most frequently without nasal obstruction or rhinorrhea[3,19].

EVOLUTION OF OLFACTORY MANIFESTATION IN THE COVID-19 PANDEMIC

A total of 956 articles were found in the PubMed, Science Direct, Springer, and LILACS databases, published between 01 January 2020 and 18 June 2021, using as search terms "olfactory disorders" or "olfactory dysfunction" or "anosmia" or "neurologic manifestations" or "ENT symptoms" AND "COVID-19" or "SARS-CoV-2" or "coronavirus infections". The research was made using MeSH descriptors and the Boolean operator "AND". We included only those articles that had available the full text written in English. In order to be eligible for this review, the articles had to be original studies that elaborate the relationship between COVID-19 infection and olfactory dysfunction, indicate the prevalence of smell disorders, their association with other symptoms and the confirmation of SARS-CoV-2 infection by the RT-PCR test.

After excluding duplicates, articles which did not fulfil the inclusion criteria, from the total of 956 articles, only 14 were included in our review (Table 1).

The first study to acknowledge the development of smell disorders in the context of SARS-CoV-2 infection was made by Mao et al. in March 2020, when the presence of olfactory dysfunction was described in 5.1% of patients[2]. After the rapid spread of the virus throughout the world, gradually more studies started to present anosmia as a frequent symptom developed in the SARS-CoV-2 infection, pointing to a prevalence of up to 86.4%[3]. The low rate of anosmia in the study of Mao et al. might be due to the fact that patients admitted in the hospital at the beginning of the pandemic had mainly moderate to severe forms of the disease, making it challenging to assess anosmia in life-threatening scenarios.

Disruption of the olfactory transmission after viral infections is known as post-viral anosmia, and it is a process well-known and described for various viruses (influenza, rhinoviruses, coronaviruses). In most viral infections, anosmia has a conductive origin, being associated with nasal obstruction and rhinitis resulting in a temporary anosmia and leaving an intact olfactory epithelium,

Table 1. Prevalence of olfactory impairment in patients with a positive RT-PCR test for COVID-19.

Author(s)	Country	Study type	No. of patients included in the study	Prevalence of smell disorders	Olfaction testing method	Published in
Mao et al.[2]	China	Retrospective, observational case series	214	11 (5.1%)	Anamnestic evaluation	03.2020
Vaira et al.[20]	Italy	Retrospective, observational case series	72	53 (73.6%)	Anamnestic evaluation Butanol threshold assessment Odour identification test using common odours	04.2020
Hopkins et al.[3]	UK	Observational	382	330(86.4%)	Anamnestic evaluation (self-reported questionnaire)	05.2020
D'Ascanio et al.[21]	Italy	Case-control study	68	40 (59%)	Anamnestic evaluation (questionnaire)	07.2020
Giacomelli et al.[22]	Italy	Cross-sectional survey	59	20 (33.9%)	Anamnestic evaluation (questionnaire)	07.2020
Leichen et al.[23]	France Italy Spain Belgium Swiss	Observational	1420	997(70.2%)	Anamnestic evaluation (questionnaire)	07.2020
Yan et al.[24]	USA	Cross-sectional study	1480	40 (68%)	Anamnestic evaluation (questionnaire)	07.2020
Lechien et al.[19]	France Spain Belgium	Observational	417	357 (85.6%)	Anamnestic evaluation (questionnaire)	08.2020
Klopfenstein et al.[25]	France	Retrospective study	70	37 (53%)	Anamnestic evaluation	08.2020
Samaranayakea et al.[26]	UAE	Observational	149	124 (83%)	Anamnestic evaluation (questionnaire)	10.2020
Freni et al.[27]	Italy	Prospective study	50	46 (92%)	Anamnestic evaluation (questionnaire)	10.2020
Sakalli et al.[17]	Turkey	Observational	172	88 (51.2%)	Anamnestic evaluation (questionnaire)	12.2020
Mendonca et al.[24]	Brazil	Observational	261	173(66.28%)	Anamnestic evaluation (questionnaire)	12.2020
Ninchritz-Becerra et al.[28]	Spain	Prospective study	1043	826 (79.2%)	Anamnestic evaluation (questionnaire)	12.2020

distinguishing COVID-19 infection from other viral causes of anosmia. Another difference between other viral infections that determine the occurrence of anosmia is the significantly higher prevalence of anosmia in COVID-19 infection, having up to 86.4% prevalence[3].

Regarding the novel coronavirus, there are studies which state that olfactory disorders can exist even without nasal obstruction or rhinitis. Freni et al.[27] reported that only 4% of patients presented rhinitis, while in Klopfenstein et al.[25] study only 22% of patients with anosmia claimed

Table 2. Anosmia's time of onset in comparison with general symptoms debut.

Study	Anosmia as first symptom	Simultaneous with other symptoms	Anosmia as the last symptom
Hopkins et al.[3]	14.9%	39.3%	45.8%
Freni et al.[27]	40%	43%	7%
Sakalli et al.[17]	21.5%	52.2%	26.1%

to have concomitant nasal obstruction. The research conducted by Sakalli et al. revealed loss of smell without nasal obstruction or rhinorrhea in 51.1% of patients[17].

The average period of anosmia is about 7-8 days. Klopfenstein et al. found that only 1 out of 37 patients with anosmia had persistent symptomatology after 28 days[25], while Sakalli et al. mentioned that 19 patients showed no improvement after 20 days[17].

Luigi Angelo Vaira et al. conducted a study, on 72 patients, that had as the main goal to objectively assess smell and taste disorder in the context of COVID-19 infection[20]. He reported 14 patients (14.4%) only with smell disorder, 30 patients (41.7%) with olfactory and taste disorders. In his study, one can observe the difference between anamnestic evaluation of anosmia (34 patients reported anosmia and 8 patients reported hyposmia) and the evaluation through olfactometry (2 patients were confirmed through n-butanol test with anosmia and 58 with hyposmia of different degree: 22 mild, 33 moderate and 3 severe). Taking this into consideration, we can argue that a reduction in smell perception will be described by patients as complete loss of smell, but using a standardized test to determine the olfactory threshold, various degrees of olfactory impairment can be revealed. The study concluded that chemosensory disorders are symptoms that develop early in the evolution of COVID-19 infection, being reported within the first five days of the clinical onset. For 13 patients (18.1%) smell and taste dysfunction constituted the first symptom of disease. Evaluation at 20 days revealed that 66% of cases reported spontaneous recovery of chemosensory function. However, by objectively evaluating patients, 80% of them still maintained various degree of hyposmia or dysgeusia.

Another important aspect of smell disorders related to COVID-19 is the time of onset. Reviewing the literature, one can find that hypo- or anosmia can be a primarily or a last symptom of this disease (Table 2). Hopkins et al. reported that 14.9% of cases had developed anosmia before other symptoms suggestive of COVID-19, 39.3% simultaneous with other associated COVID-19 symptoms and 45.8% after the debut of other symptoms[3]. Francesco Freni et al. conducted a study in which he included 50 patients COVID-19 positive and reported that 40% of patients developed olfactory dysfunction before other symptoms related to SARS-CoV-2 infection, 43% concomitant with other symptoms and in 7% of the patients smell disorders were the final related symptoms[27]. Sakalli et al. mentioned the occurrence of anosmia before, simultaneous and after other symptoms suggestive of SARS-COV 2 infection in 21.5% of cases, 52.2%, and 26.1% respectively[17].

Other studies stated that patients with olfactory impairment due to COVID-19 infection might present hyposmia or anosmia as the only symptom that could rise the suspicion of a SARS-COV-2 infection[3]. At the time of the survey, Hopkins et al. found that 14.9% of the evaluated patients had no other concurrent symptoms apart from smell disorders during the COVID-19 infection[3].

Lechien et al. described anosmia as the principal symptom in 11.9% of cases and 79.7% of patients with anosmia had no accusation of nasal obstruction or nasal discharge[19].

THE RELATIONSHIP BETWEEN OLFACTORY AND GUSTATORY DYSFUNCTION

Olfactory disorder has been frequently described in association with gustatory dysfunction.

Francesco Freni reported that in his study all patients that reported anosmia or hyposmia had concomitant taste impairment[27].

Although frequently associated, taste and smell disorders are not always concomitant. In a cohort study performed in 2020, Samaranayake et al. described the association of anosmia and dysgeusia in relationship to the severity of the C0VID-19 as follows: in mild cases they were associated in 9% of the patients, in moderate cases only 6% of the patients presented both symptoms, while in severe COVID-19 patients the tandem anosmia-dysgeusia was the most predominant feature found (81% of patients)[26]. Klopfenstein et al. reported that 31 out of 34 patients with dysgeusia also had some degree of olfactory disorder[25]. Giacomelli et al. conducted a cross-sectional survey on 59 hospitalized patients and 18.6% reported olfactory and gustatory dysfunction (2 patients, 3.4%, with dysgeusia and hyposmia; 2 patients, 3.4%, with dysgeusia and anosmia; 2 patients, 3.4%, ageusia and hyposmia; 5 patients, 8.5%, ageusia and anosmia)[22].

OLFACTORY IMPAIRMENT IN RELATIONSHIP WITH THE SEVERITY OF SARS-CoV-2 INFECTION

Studies conducted from the beginning of the pandemic that analysed the relationship of hypo-, anosmia with the clinical presentation of COVID-19 point out that olfactory dysfunction is more frequently associated with mild or moderate clinical cases.

Klopfenstein et al. mentioned that pulmonary parenchyma injuries are noted less often in patients with anosmia, and that these patients need to be hospitalized less often and have reduced need of oxygen therapy[25]. At the same time, Samaranayake et al. observed that, out of entire cohort, patients with mild cases reported more frequently anosmia (87%) versus the severe cases (8%)[26].

Considering that the mechanism of cellular invasion in the olfactory epithelium is through ACE2 receptors and the fact that higher expression of ACE2 receptors is associated with a more severe course of disease might be reasons why anosmia and dysgeusia are more frequently reported in severe COVID-19 disease[29].

Although there are numerous studies which imply that anosmia might be a good prognosis factor[17,30], we must keep in mind that in face of an acute respiratory distress syndrome, anosmia merely goes unreported. This observation is due to the lack of studies that objectively measure the olfactory function in patients with various degree of disease severity.

OLFACTORY DISORDERS AND ASSOCIATED COMORBIDITIES

It is by now a recognized fact that patients with comorbidities are prone to developing a severe form of COVID-19, and a few studies were made trying to determine the link between comorbidities and olfactory dysfunction[29,30].

In a recent cohort study conducted on 5868 patients in the multicenter international HOPE Registry, smell and gustatory dysfunctions were present more frequent in patients under 65-year-old, in the presence of hypertension, diabetes mellitus, dyslipidemia, renal impairment, heart and lung neoplasm and neurological disease. Olfactory and gustatory dysfunction was also associated with 5-fold lower risk of death, being considered a protective factor[30].

In a study published in the American Journal of Rhinology & Allergy, Sehanobish and colleagues came to the conclusion that anosmia and dysgeusia are more frequently found in younger patients[31], having in general fewer comorbidities and a better prognosis of the COVID-19 infection.

Klopfenstein et al. conducted a study with 114 patients, and they pointed that those patients with anosmia are younger and have a Charlson comorbidity index inferior to those that did not report anosmia and who were more frequently diabetic, hypertensive or with other pulmonary or cardiovascular disease. He mentions that the only affliction that he found more frequent in patients with anosmia was asthma, association also observed by Freni et al.[25,27].

CONCLUSIONS

The leading mechanism involved in the development of anosmia is through damage of the olfactory epithelium, affecting mainly non-neuronal cells. Nonetheless, neuronal cells can also be involved, worsening the olfactory function[32].

Due to the fact that chemosensory impairment is frequently associated with the COVID-19 infection, and the association of anosmia with dysgeusia has been shown to have a positive predictive value, it is recommended that the patients who report these symptoms should be promptly isolated[33]. Despite the high rate of occurrence of anosmia in SARS-CoV-2 infection, symptomatology alone does not replace RT-PCR testing, being mandatory to confirm the infection.

Patients with anosmia are frequently younger, are less frequent hypertensive or diabetic, have lower Charlson comorbidity index and they need

hospitalization less often.

The peculiarity of anosmia in COVID-19 is given by the fact that its prevalence is much higher and the duration of symptoms is longer, unlike other viral infections, with a lower rate of complete recovery of olfactory function.

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REFERENCES

1. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. [Internet]. Available from: https://covid19.who.int/. Accessed June 18, 2021.
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;77(6):683-90. DOI: 10.1001/jamaneurol.2020.1127.
3. Hopkins C, Surda P, Whitehead E, Kumar BN. Early recovery following new onset anosmia during the COVID-19 pandemic - an observational cohort study. J Otolaryngol - Head Neck Surg. 2020;49(1):26. DOI: 10.1186/s40463-020-00423-8.
4. Purves D, Augustine GJ, Fitzpatrick D, et al., editors. Neuroscience. 2nd edition. Sunderland (MA): Sinauer Associates; 2001. The Olfactory Epithelium and Olfactory Receptor Neurons. Available from: https://www.ncbi.nlm.nih.gov/books/NBK10896/.
5. Graziadei PPC, Karlan MS, Graziadei GA, Bernstein JJ. Neurogenesis of sensory neurons in the primate olfactory system after section of the fila olfactoria. Brain Res. 1980;186(2):289-300. DOI: 10.1016/0006-8993(80)90976-2.
6. Gupta K, Mohanty SK, Mittal A, Kalra S, Kumar S, Mishra T, et al. The cellular basis of loss of smell in 2019-nCoV-infected individuals. Brief Bioinform. 2021;22(2):873-81. DOI: 10.1093/bib/bbaa168.
7. Brann DH, Tsukahara T, Weinreb C, Lipovsek M, Van den Berge K, Gong B, 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. DOI: 10.1126/sciadv.abc5801.
8. Chen M, Shen W, Rowan NR, Kulaga H, Hillel A, Ramanathan M, et al. Elevated ACE2 expression in the olfactory neuroepithelium: implications for anosmia and upper respiratory SARS-CoV-2 entry and replication. Eur Respir J. 2020;56:2001948. DOI:10.1183/13993003.01948-2020.
9. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-80.e8. DOI:10.1016/j.cell.2020.02.052.
10. Lee MH, Perl DP, Nair G, Li W, Maric D, Murray H, et al. Microvascular injury in the brains of patients with Covid-19. N Engl J Med. 2021;384(5):481-3. DOI: 10.1056/NEJMc2033369.
11. Eshraghi AA, Mirsaeidi M, Davies C, Telischi FF, Chaudhari N, Mittal R. Potential mechanisms for COVID-19 induced anosmia and dysgeusia. Front Physiol. 2020;11:1039. DOI: 10.3389/fphys.2020.01039.
12. Bryche B, St Albin A, Murri S, Lacôte S, Pulido C, Ar Gouilh M, et al. Massive transient damage of the olfactory epithelium associated with infection of sustentacular cells by SARS-CoV-2 in golden Syrian hamsters. Brain Behav Immun. 2020;89:579-86. DOI: 10.1016/j.bbi.2020.06.032.
13. Eliezer M, Hamel AL, Houdart E, Herman P, Housset J, Jourdaine C, et al. Loss of smell in COVID-19: MRI data reveals a transient edema of the olfactory clefts. Neurology. 2020;95(23):e3145-52. DOI: 10.1212/WNL.0000000000010806.
14. Kandemirli SG, Altundag A, Yildirim D, Tekcan Sanli DE, Saatci O. Olfactory bulb MRI and paranasal sinus CT findings in persistent COVID-19 anosmia. Acad Radiol. 2021;28(1):28-35. DOI: 10.1016/j.acra.2020.10.006.
15. 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):7264-75. DOI: 10.1128/JVI.00737-08.
16. Bilinska K, Jakubowska P, Von Bartheld CS, Butowt R. Expression of the SARS-CoV-2 entry proteins, ACE2 and TMPRSS2, in cells of the olfactory epithelium: identification of cell types and trends with age. ACS Chem Neurosci. 2020;11(11):1555-62. DOI: 10.1021/acschemneuro.0c00210.
17. Sakalli E, Temirbekov D, Bayri E, Alis EE, Erdurak SC, Bayraktaroglu M. Ear nose throat-related symptoms with a focus on loss of smell and/or taste in COVID-19 patients. Am J Otolaryngol. 2020;41(6):102622. DOI: 10.1016/j.amjoto.2020.102622.
18. Yachou Y, El Idrissi A, Belapasov V, Benali SA. Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: understanding the neurological manifestations in COVID-19 patients. Neurol Sci. 2020;41(10):2657-69. DOI:10.1007/s10072-020-04575-3.
19. 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 Otorhinolaryngol. 2020;277(8):2251-61. DOI: 101007/s00405-020-05965-1.
20. Vaira LA, Hopkins C, Salzano G, Petrocelli M, Melis A, Cucurullo M, et al. Olfactory and gustatory function impairment in COVID-19 patients: Italian objective multicenter-study. Head Neck. 2020;42(7):1560-9. DOI: 10.1002/hed.26269.
21. D'Ascanio L, Pandolfini M, Cingolani C, Latini G, Gradoni P, Capalbo M, et al. Olfactory dysfunction in COVID-19 patients: prevalence and prognosis for recovering sense of smell. Otolaryngol Head Neck Surg. 2021;164(1):82-6. DOI: 10.1177/0194599820943530.
22. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. Clin Infect Dis. 2020;71(15):889-90. DOI: 10.1093/cid/ciaa330.
23. Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. J Intern Med. 2020;288(3):335-44. DOI: 10.1111/joim.13089.
24. Mendonça CV, Neto JAM, Suzuki FA, Orth MS, Neto HM, Nacif SR. Olfactory dysfunction in COVID-19: a marker of good prognosis? Braz J Otorhinolaryngol. 2021;S1808-8694(20)30240-8. DOI: 10.1016/j.bjorl.2020.12.002. [Epub ahead of print].
25. Klopfenstein T, Zahra H, Kadiane-Oussou NJ, Lepiller Q, Royer PY, Toko L, et al. New loss of smell and taste: Uncommon symptoms in COVID-19 patients on Nord Franche-Comte cluster, France. Int J Infect Dis. 2020;100:117-22. DOI: 10.1016/j.ijid.2020.08.012.
26. Samaranayake LP, Fakhruddin KS, Mohammad OE, Panduwawala C, Bandara N, Ngo HC. Attributes of dysgeusia and anosmia of coronavirus disease 2019 (COVID-19) in hospitalized patients.

Oral Dis. 2020. DOI: 10.1111/odi.13713. [Epub ahead of print].

27. Freni F, Meduri A, Gazia F, Nicastro V, Galletti C, Aragona P, et al. Symptomatology in head and neck district in coronavirus disease (COVID-19): A possible neuroinvasive action of SARS-CoV-2. Am J Otolaryngol. 2020;41(5):102612. DOI: 10.1016/j.amjoto.2020.102612.
28. Ninchritz-Becerra E, Soriano-Reixach MM, Mayo-Yánez M, Calvo-Henríquez C, Martínez-Ruiz de Apodaca P, et al. Subjective evaluation of smell and taste dysfunction in patients with mild COVID-19 in Spain. Med Clin (Engl Ed). 2021;156(2):61-4. DOI: 10.1016/j.medcle.2020.08.004.
29. Pinto BGG, Oliveira AER, Singh Y, Jimenez L, Gonçalves ANA, Ogava RLT, et al. ACE2 expression is increased in the lungs of patients with comorbidities associated with severe COVID-19. J Infect Dis. 2020;222(4):556-63. DOI: 10.1093/infdis/jiaa332.
30. Porta-Etessam, J, Núñez-Gil IJ, González García N, Fernandez-Perez C, Viana-Llamas MC, Eid CM, et al. COVID-19 anosmia and gustatory symptoms as a prognosis factor: a subanalysis of the HOPE COVID-19 (Health Outcome Predictive Evaluation for COVID-19) registry. Infection. 2021;49(4):677-84. DOI: 10.1007/s15010-021-01587-9.
31. Sehanobish E, Barbi M, Fong V, Kravitz M, Tejera DS, Asad M, et al. COVID-19-induced anosmia and ageusia are associated with younger age and lower blood eosinophil counts. Am J Rhinol Allergy. 2021;194589242110048. DOI: 10.1177/19458924211004800. [Epub ahead of print].
32. Lima MHLC, Cavalcante ALB, Leão SC. Pathophysiological relationship between COVID-19 and olfactory dysfunction: A systematic review. Braz J Otorhinolaryngol. 2021;S1808-8694(21)00073-2. DOI: 10.1016/j.bjorl.2021.04.001. [Epub ahead of print].
33. Zayet, S, Klopfenstein T, Mercier J, Kadiane-Oussou NJ, Wah LLC, Royer PY, et al. Contribution of anosmia and dysgeusia for diagnostic of COVID-19 in outpatients. Infection. 2020;1-5. DOI: 10.1007/s15010-020-01442-3. [Epub ahead of print].