REVIEW ARTICLE

Olfactory and Gustatory Dysfunction in Patients with COVID-19

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Abstract

Introduction: Infection with the new coronavirus [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] was first registered in December 2019 in China and then later spread rapidly to the rest of the world. On 31st December 2019, the World Health Organization on 11th March 2020 declared a pandemic with this virus. In Bosnia and Herzegovina, the first infected person was registered on 5th March 2020 in Banja Luka.

Aim: To present some aspects of the olfactory and gustatory dysfunction in patients with the coronavirus disease of 2019 (COVID-19).

Methods: The article has an analytical character and review of the literature.

Results and Discussion: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a high similarity with SARS-CoV-1 and uses the same receptors to enter the human body [angiotensin-converting enzyme 2 (ACE2)].[2] COVID-19 is a respiratory infection that is primarily transmitted *via* respiratory droplets. In the first year of the pandemic, the SARS-CoV-2 coronavirus has mutated several times, resulting in genetically different variants. The variants are named by using letters of the Greek alphabet. The Alpha variant (Wuhan, China), Beta variant (first outbreak in South Africa), the Gamma variant (first outbreak in Brazil), and the Delta variants (first outbreak in India and Omicron variant) have caused an increase in cases worldwide. Typical symptoms of COVID-19 infection can be very moderate to very severe, with severe respiratory symptoms and fatal outcomes. COVID-19 is primarily a disease of the respiratory system, but SARS-CoV-2 also penetrates the central nervous system (CNS) and apparently could be responsible for fatal outcomes in some cases. The entry of the virus into the brain can lead to different neurological and psychiatric manifestations, including headache, loss of smell (anosmia) and the loss of taste (ageusia), encephalopathy, encephalitis, paresthesia, myalgia, Guillain-Barre syndrome, and cerebrovascular diseases.

Conclusion: The coronavirus disease of 2019 (COVID-19) is primarily a disease of the respiratory system, but SARS-CoV-2 also penetrates the CNS, leading to serious neurological disorders, and apparently, it is also responsible for mortality. The frequency of anosmia and ageusia in patients with COVID-19 varies widely, from 10 to 65%, being the primary symptom in about 12% of patients. Most of the analyzed subjects reported olfactory recovery. However, anosmia and ageusia can last several months or even longer. For now, the etiopathogenesis of anosmia and ageusia in SARS-CoV-2 infection is still unknown. Nasal or systemic corticosteroids were recommended in the acute phase as well as olfactory training (sniffing the smell of rose, lemon, and cloves) in the acute and chronic phases, and many other drugs as potential therapeutics.

Keywords: COVID-19, Etiopathogenesis, Gustatory dysfunction, Olfactory dysfunction, Treatment.

Sažetak

Uvod: Infekcija novim korona virusom (SARS-CoV-2) prvi put je registrirana u prosincu 2019. u Kini, a potom se brzo proširila na ostatak svijeta. 31. prosinca 2019. Svjetska zdravstvena organizacija (WHO) 11. ožujka 2020. proglasila je pandemiju s ovim virusom. U Bosni i Hercegovini prva zaražena zaražena osoba registrirana je 5.3.2020.godine u Banja Luci.

Cilj: Predstaviti neke od aspekata olfaktorne i gustatorne disfunkcije u bolesnika s COVID-19.

Metode: Članak ima analitički karakter i pregled literature.

Rezultati i rasprava: SARS-CoV-2 ima veliku sličnost sa SARS-CoV-1 i koristi iste receptore za ulazak u ljudsko tijelo (angiotenzin-konvertirajući enzim 2/ACE2).[2] COVID-19 je respiratorna infekcija koja se primarno prenosi kapljičnim putem. U prvoj godini pandemije, SARS-CoV-2 koronavirus je mutirao nekoliko puta što je rezultiralo genetski različitim varijantama. Varijante su imenovane slovima grčkog alfabeta. Alpha varijanta (Wuhan, Kina), Beta varijante (prva epidemija u Južnoj Africi), Gamma varijante (prva epidemija u Brazilu), Delta varijante (prva epidemija u Indiji i Omicron varijanta) uzrokovale su povećanje broja slučajeva širom svijeta. Tipični simptomi infekcije COVID-19 mogu biti vrlo umjereni do vrlo teški, s teškim respiratornim simptomima i smrtnim ishodom. COVID-19 je primarno bolest dišnog sustava, ali SARS-CoV-2 prodire i u središnji živčani sustav (SŽS), te bi izgleda mogao biti odgovoran za smrtni ishod u nekim slučajevima. Ulazak virusa u mozak može dovesti do različitih neuroloških i psihijatrijskih manifestacija, uključujući glavobolju, gubitak njuha (anozmija) i gubitak okusa (ageuzija), encefalopatiju, encefalitis, paresteziju, mijalgiju, Guillain-Barreov sindrom, cerebrovaskularne bolesti.

Zaključak: COVID-19 je prvenstveno bolest dišnog sustava, ali SARS-CoV-2, prodire i u CNS, dovodeći do ozbiljnih neuroloških poremećaja, a očito je odgovoran i za smrtnost. Učestalost anosmije i ageuzije u bolesnika s COVID-19 varira uvelike, od 10 do 65%, a primarni su simptom u oko 12% bolesnika. Većina analiziranih subjekata izvijestila je o olfaktornom oporavku. Međutim, anosmija i ageuzija mogu trajati nekoliko mjeseci ili čak i duže. Za sada je etiopatogeneza ansomije i ageuzije kod SARS-CoV-2 infekcije još nepoznata. Preporučeni su nazalni ili sistemski kortikosteroidi u akutnoj fazi, olfaktorni trening (njušenje mirisa ruže, limuna i klinčića) u akutnoj i kroničnoj fazi te mnogi drugi lijekovi kao potencijalni terapeutici.

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Introduction

So far, seven types of coronaviruses have been identified, two of which, called SARS-CoV and one called Middle East respiratory syndrome coronavirus (MERS-CoV), caused large epidemics with a significant percentage of severe clinical pictures and fatal outcomes, while the remaining four caused mild symptoms of upper respiratory tract infection. Apparently, SARS-CoV-2, like other similar viruses, is of animal origin, but it is not yet clear which animal is the primary source and how the virus was transmitted to humans. SARS-CoV-2, which leads to COVID-19, is genetically distinct from SARS-CoV-1 and MERS-CoV, which were previously the cause of two epidemics in the world.[1,2]

The coronavirus disease of 2019 (COVID-19) is a respiratory infection that is primarily transmitted *via* respiratory droplets, and the primary route of transmission is close contact with a person who has the virus, especially during coughing, sneezing, and different medical interventions in the respiratory tract.[3] SARS-CoV-2 has a high level of sequential similarities to SARS-CoV-1 and uses the same receptors when it enters the human body (ACE2).[4] COVID-19 is a respiratory infection that is primarily transmitted *via* respiratory droplets. In the first year of the pandemic, the SARS-CoV-2 coronavirus has mutated several times, resulting in genetically different variants. The variants are named by using letters of the Greek alphabet. The Alpha variant (Wuhan, China), Beta variant (first outbreak in South Africa), the Gamma variant (first outbreak in Brazil), the Delta variant (first outbreak in India, and the Omicron variant) have caused an increase in cases worldwide.[1,4,5]

Typical symptoms of COVID-19 infection can be very moderate to very severe, with severe respiratory symptoms (bilateral severe pneumonia) and fatal outcomes. COVID-19 is primarily a disease of the respiratory system, but SARS-CoV-2 also penetrates the CNS and apparently could be responsible for fatal outcomes in some cases.[4–8]

Experiments on animals have demonstrated that SARS-CoV probably enters the brain *via* the olfactory bulb (OB) and then spreads to other specific parts of the brain, such as the thalamus and brainstem, through the olfactory nerves. Furthermore, there is evidence that coronaviruses attack peripheral nerve endings and reach the CNS *via* nerve synapses.[6] The entry of the virus into the brain can lead to different neurological and psychiatric manifestations, including headache, loss of smell (anosmia) and the loss of taste (ageusia), encephalopathy, encephalitis, paresthesia, myalgia, Guillain-Barre syndrome, and cerebrovascular diseases.[1,6,9]

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COVID-19 and Olfactory and Gustatory Dysfunction

Olfactory dysfunction associated with a viral infection of the upper respiratory tract is not only related to infection with the SARS-CoV-2 virus. It has long been known that postviral olfactory dysfunction (PVOD) is the main cause of clinically significant loss of smell and that it accounts for about 40% of the total incidence of olfactory dysfunction.[10,11]

Smell disorders encompass a wide range of disorders of the sense of smell and can be classified in different ways. Quantitatively, there is a difference between hyposmia (reduced ability to detect smells) and anosmia (complete inability). Qualitative changes in the sense of smell are called dysosmia. They are divided into parosmia (altered perception of smell when an olfactory stimulus is present) and phantosmia (perception of smell without the presence of an actual stimulus). Smell disorders are often accompanied by impaired taste impairment, such as ageusia or dysgeusia, and it is believed that the main component of the sense of taste is the olfactory dysfunction itself, which prevents

the development of the subjective sense of taste.[11,12] Viral infections of the upper respiratory tract are accompanied by olfactory dysfunction in 17–36% of respondents in specialist consultations.[11,13] Therefore, smell dysfunction in the course of upper respiratory tract infections is considered a widespread symptom. The intensity and duration of PVOD are highly variable depending on the speed of regeneration of the neuroepithelium.[11]

The intensity and duration of this dysfunction, termed PVOD, are highly variable depending on the capacity and rate of regeneration of the neuroepithelium.[11] PVOD is more common in women and people over 50 years of age. It can last from 1 week to 1 or 2 years. If PVOD lasts longer and if the severity is greater, the recovery of olfactory function is very limited.[11–17] A third of patients notice symptoms of recovery after a few months and usually make a full recovery after 13 months.[15,16]

At the beginning of the pandemic, the acute loss of smell and taste was not considered an important symptom of COVID-19, although olfactory dysfunction after SARS-CoV-2 infection was also previously recorded in SARS from 2002.[18,19]

The first report that mentions anosmia and ageusia, and the first about neurological symptoms in general, in patients with COVID-19, is a report from Wuhan by Mao et al.,[20] who stated that in the 214 patients they analyzed, 5.1% had hyposmia, and 5.6% hypogeusia. Following the initial reports on smell and taste disturbances in patients with COVID-19, the American Academy of Otolaryngology-Head and Neck Surgery, British Association of Otorhinolaryngology (ENT UK), and the British Rhinological Society independently published guidance that includes hyposmia and dysgeusia as screening symptoms for further testing for COVID-19.[21]

There is a large number of papers on different frequencies of disorders of the sense of smell and taste in different countries of the world. According to a survey from Doha, Qatar, within a primary care health center, this is 24.82% (141 respondents). The largest number of patients were aged >30 years (73.76%). All subjects had normalization of anosmia or ageusia with an average duration of the disorder of 6.89 days.[22] A multicenter study conducted in several countries in Europe was published on 6th April 2020. Patients with laboratory-confirmed COVID-19 infection were recruited from 12 European hospitals. A total of 417 mild-to-moderate COVID-19 patients completed the study (263 females/154 males), and 85.6% of patients reported olfactory and 88.0% gustatory dysfunctions. There was a significant association between both disorders ($p < 0.001$). Olfactory dysfunction appeared before the other symptoms in 11.8% of cases. The early olfactory recovery rate was 44.0%. Females were significantly more affected by olfactory and gustatory dysfunctions than males ($p = 0.001$).[23]

According to a study conducted in South Korea, which was based on a telephone interview of 3,191 patients, it was determined that 15.3% of patients had acute anosmia or ageusia in the early stages of the disease, and 15.7% were present in those who were asymptomatic (and positive for the SARS-CoV-2 virus) or with a moderate clinical picture of the disease. The frequency was significantly higher in women ($p = 0.01$) and younger people ($p < 0.001$). Most patients recovered within three weeks (median 7 days for both symptoms). In a meta-analysis performed in August 2020, which included publications (24 in total) published until 31.5.2020 in the databases MEDLINE, EMBASE, and MedRxiv, a total of 8438 patients from 13 countries, there were 41% (from 28.5 to 53.9%) with olfactory dysfunction, and 38.2% with gustatory dysfunction (from 24 to 53.6%). Older age was associated with a lower prevalence of both olfactory and gustatory dysfunction.[24]

In one study from India, out of 167 patients (tertiary care hospital), 105 patients had an altered sense of smell (62.87%), and 98 had an altered sense of taste (58.68%). The majority of patients in our study were less than 29 years of age (61/167), attributing to 36.53%. After 14 days, there was a 74% improvement in the sense of smell when compared to smell during the disease period. There was a 45.26% decrease in the sense of taste during the disease among all the patients when compared to before the disease. After 14 days, there was a 63.21% improvement in the sense of taste when compared to taste during the disease period.[25] According to one study from Turkey (155 subjects from a "pandemic hospital" were included in the period from 25.3. to 25.4. 2020, age 18–72 years, average 36.3 ± 8.1 years), 35.4% of the subjects had anosmia and 16.1% ageusia. There were 58.7% women and 42.2% men.[26] In another study from Turkey that included 101 subjects (54 men and 47 women), 71 had anosmia and/or ageusia, 55 had both disorders, and 11 had only anosmia). So, here the frequency is more frequent than in the previous announcement.[27]

In a meta-analysis published in October 2021, the prevalence of post-COVID-19 symptoms in patients recovered from COVID-19 was analyzed using MEDLINE, CINAHL, PubMed, EMBASE, and Web of Science databases, as well as medRxiv and bioRxiv preprint servers up to 15th March 2021. From 15,577 studies identified, 29 peer-reviewed studies and four preprints met inclusion criteria (15,244 hospitalized and 9,011 nonhospitalized patients). The results showed that 63.2, 71.9, and 45.9% of the sample exhibited ≥1 post-COVID-19 symptom at 30, 60, or ≥90 days after onset/hospitalization. Fatigue and dyspnea were the most prevalent symptoms, with a pooled prevalence ranging from 35 to 60%, and anosmia was present in 10–20%, ageusia in 15–20% of analyzed patients.[28]

It is known that children usually have milder respiratory symptoms than adults or are often asymptomatic, and the loss of the sense of smell and taste is not rare. According to one systematic review that included publications from the period from 1st December 2019 to 30th April 2021, only nine articles were singled out, with a total of 316 cases with confirmed COVID-19, of which 156 had olfactory dysfunction. Most of the analyzed subjects reported olfactory recovery. By reviewing the literature, it can be concluded that the rate of olfactory dysfunction is 49% among children and adolescents

suffering from COVID-19. Furthermore, the persistence of olfactory dysfunction was reported in 7.1% of patients.[29] In one study from Italy, it was demonstrated that about 30% of children affected by COVID-19 presented with taste and smell disorders. Anosmia seems to be more frequent than ageusia, and both occur mainly during the first phase of the disease. About 5% of children would continue to complain of the persistence of these symptoms even after healing.[30]

Thus, reports on the frequency of anosmia and ageusia in patients in patients with COVID-19 vary widely, and most often, it is about high percentages (about 60% and more) being the primary symptom in about 12% of patients.[24,31]

Etiopathogenesis of Anosmia and Ageusia

The olfactory system is very complex and is organized from different structural and functional cellular components. Briefly, odorants must reach the olfactory epithelium and bind to odorant-binding proteins. Then, after activating the olfactory receptor neurons (ORNs), they transmit the signal to the OB. The sum of these signals is then further transmitted to higher cortical and central areas, where olfactory processing becomes even more complex. A viral attack on any of these structures can potentially lead to olfactory dysfunction. Magnetic resonance imaging in patients with SARS-CoV-2-associated anosmia shows normal OB volume.[23]

For now, it is more or less possible to only speculate on the mechanism of anosmia in patients with SARS-CoV-2 infection, and we may have some understanding of pathogenesis from other viral infections, including coronaviruses. Anosmia can be broadly divided into conductive and sensorineural loss of smell. Conductive loss occurs when we have impaired airflow through the nose, and this disorder is usually reversible after the nasal obstruction stops.[10]

There are several possible mechanisms that could be behind SARS-CoV-2 anosmia that can lead to anosmia in isolation or in combination with other symptoms. According to one theory, the virus binds to ACE receptors in the nasal epithelium and causes degeneration of the nasal mucosa and then inflammation and damage to the nerve receptors responsible for the smell. Another hypothesis, currently the most widely accepted, suggests a direct effect of the virus on the CNS.[32,33]

In one comprehensive paper, which is a systematic review focused on explaining the pathophysiology of viral olfactory dysfunction and which included seven human studies and 38 animal studies, published in September 2020, it is concluded that the pathophysiological mechanism of olfactory dysfunction in COVID-19 is virus-dependent and very complex. The clinical manifestations of olfactory disorders can be explained by a combination of direct damage to ORNs, damage to olfactory neuronal regeneration and the inflammatory response, cytokine action, and greater damage to the cortex.[34] On the other hand, long-term or permanent impairment of smell after the end of viral infection and cellular regeneration very likely involves additional mechanisms in the olfactory system.

It is possible that the simultaneous presence of olfactory dysfunction negatively affects the ability to perceive taste in patients with COVID-19 due to the close connection between olfactory and gustatory functions. However, various pathways have also been suggested, including direct damage to taste buds and salivary glands, binding to sialic acid receptors, and inflammation.[35] Furthermore, it has been suggested that ACE2 inhibitors inactivate the G protein-coupled proteins and sodium-ion channels located in the taste receptors. Similarly, it is possible that SARS-CoV-2-induced down-regulation of ACE2 and the consequent impairment of the renin-angiotensin-aldosterone system may be associated with taste dysfunction in patients with COVID-19.[36]

Possibility of Treatment

The treatment strategy of POVD, based on the natural clinical course of the disorder, can be aimed at the acute phase, and on the other hand, at the chronic phase. Probably the best form of intervention is to prevent the initial entry of the virus, which could be relevant to COVID-19. For a virus that causes inflammation, topical or systemic corticosteroids may prove beneficial in the acute phase of PVOD.[10]

The presence of olfactory dysfunction, in addition to cell damage, also includes damage to synaptic plasticity. Related to this hypothesis, it has previously been shown that influenza A can cause long-lasting changes in synaptic plasticity in the hippocampus even after virus clearance, possibly through cytokines, activated microglia, and altered gene expression.[34,37] It is similar in the case of respiratory syncytial virus infection, where damage to synaptic plasticity was found, which leads such people to cognitive impairment. The characteristic of neurotropic viruses to damage synaptic plasticity has also been demonstrated in diseases caused by the Borna virus, which leads to impaired recycling of synaptic vesicles.[38,39]

Nasal corticosteroids are recommended, for treatment, although a randomized controlled study did not demonstrate statistically significant evidence that they are better than olfactory training. Namely, in the study, the first group of patients was treated with a corticosteroid nasal spray (mometasone fluorate) for 3 weeks, and the second had only olfactory training (sniffing the scent of rose, lemon, and clove for 20 seconds twice a day for 3 weeks). Both groups had 50 patients each. In the first group, 62% of respondents, at the end of the third week, had a complete recovery of the sense of smell, and in the second group, 52%. Differences between groups were not statistically significant. Furthermore, a statistically significant recovery of the sense of smell was found in both groups at the end of the third week of treatment.[40,41] Why olfactory training is an effective therapy for PVOD can be explained by the fact that the main characteristic of synaptic plasticity is its ability to learn and modify.[42–44]

There are several drugs that are considered potential therapeutics.[35] According to Khani et al.,[35] the summary of

Table 1: Categorization of the proposed medications for COVID-19 smell and taste loss

Medication	*Mechanism of action*	*Outcomes (study design)*	*Class of recommendation/ Level of evidence*	*References*
Pentoxifylline	Phosphodiesterase (PDE) inhibitor	Promising results in smell loss (postmarketing surveillance study), No beneficial effects in patients with posttraumatic anosmia (case series)	IIb/B-NR	45,46
Caffeine	PDE inhibitor, adenosine receptors antagonist	Direct correlation between coffee consumption and smell scores in patients with Parkinson's disease (retrospective cohort), 65 mg of caffeine showed no beneficial effects in patients with hyposmia related to upper respiratory tract infection or sinus node dysfunction [randomized controlled clinical trials (RCT)]	IIb/B-R	47,48
Theophylline	PDE inhibitor	Improved the smell and taste dysfunction caused by various diseases (two non-RCT)	IIb/B-NR	49,50
Intranasal insulin	Neuroprotective	Beneficial effects in olfactory dysfunction caused by infection (non-RCT), COVID-19 (non-RCT), and other diseases (RCT)	IIa/B-R	51–53
Statins	Neuroprotective, anti-inflammatory	Improved anosmia in mice models (two animal studies)	IIb/C-EO	54,55
Minocycline	Neuroprotective	Inhibit apoptosis of olfactory sensory neurons (OSNs) in rat models (histological analysis)	IIb/C-EO	56
Zinc	Trace element, growth factor	Reports of anosmia with intranasal zinc gluconate, No beneficial effects of zinc sulfate in chemotherapy-induced taste and smell loss (RCT)	III/B-R	57,58
Intranasal vitamin A	Anti-neurodegenerative	Beneficial effects in postinfectious smell dysfunction (retrospective cohort study)	IIb/C-LD	59
Omega-3	Neuroprotective	Beneficial effects in olfactory loss caused by tumors (RCT)	IIb/B-R	60
Intranasal mometasone	Anti-inflammatory	No beneficial effects in COVID-19 smell loss (RCT)	III/B-R	40
Intranasal fluticasone	Anti-inflammatory	Beneficial effects in COVID-19 smell loss (non-RCT)	IIa/B-NR	61
Oral triamcinolone paste	Anti-inflammatory	Beneficial effects in COVID-19 dysgeusia (non-RCT)	IIa/B-NR	61
Melatonin	Neuroprotective, anti-inflammatory	Inhibit apoptosis of OSNs in rat models (animal study)	IIb/C-EO	62

A, high-quality randomized clinical trials; B-NR, moderate-quality non-randomized clinical trial; B-R, moderate-quality randomized clinical trial; C-EO, expert opinion; C-LD, limited data; I, strong; Iia, moderate; Iib, weak; III, moderately no benefit or strongly harmful

the promising agents against COVID-19-related smell and/or taste loss is shown in Table 1.

Given the large scale of the COVID-19 pandemic and the high transmissibility of the SARS-CoV-2 virus, evidence that already exists of this virus' association with the CNS (including disorders of smell and taste), there is concern among experts about the potential long-term effects of SARS-CoV-2 virus infection on the CNS. Namely, it is considered that patients

who survive COVID-19 are at high risk for the further development of neurological diseases, especially Alzheimer's disease. Namely, it seems that in the survivors of COVID-19, in the following period, the systemic inflammatory process or the inflammatory process of the brain could trigger mechanisms that could lead to an increase in the frequency of neurological and neurodegenerative disorders.[9,63]

Conclusion

The coronavirus disease of 2019 (COVID-19) is primarily a disease of the respiratory system, but the SARS-CoV-2 virus, which causes the disease, also penetrates the CNS in a number of patients and leads to serious neurological disorders. The frequency of anosmia and ageusia in patients in patients with COVID-19 vary widely, and most often, it is about high percentages (about 60% and more) being the primary symptom in about 12% of patients. For now, it is more or less possible to only speculate on the mechanism of olfactory and gustatory dysfunction in patients with SARS-CoV-2 infection. Nasal or systemic corticosteroids were recommended in the acute phase as well as olfactory training (sniffing the smell of rose, lemon, and cloves) in the acute and chronic phases, and many other drugs as potential therapeutics.

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