CASE REPORT
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The olfactory bulb – gateway for SARS-Cov-2?

Olfaktorni bulbus – ulaz za SARS-Cov-2?

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Abstract

Introduction. Anosmia and ageusia are one of the most common and characteristic symptoms of severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection, with a frequency of almost 50% in patients in Western countries. Hypotheses proposing that the virus potentially affects the central nervous system (CNS) are on the rise. One hypothesis suggests that the virus enters via nasal mucosa and then enters the olfactory bulb via cribriform plate, with further dissemination to the CNS. **Case report.** A 34-year-old female patient experienced the loss of the sense of smell and taste about two months before testing positive for SARS-Cov-2. Coronavirus disease 2019 (COVID-19) presented with minor pneumonia and worsening anosmia and ageusia. After treatment, the patient recovered well, but anosmia and ageusia appeared again, varying in intensity, and since February 2021, they have become persistent. The case was evaluated by an otorhinolaryngologist, pulmonologist, and finally, a neurologist. In the meantime, the patient tested negative for SARS-Cov-2 and received two doses of the Sputnik V vaccine. Brain magnetic resonance imaging (MRI) was performed, and it clearly showed severe bilateral olfactory bulb atrophy. The patient has had anosmia and ageusia up to this day, and future MRI follow-up is planned. **Conclusion.** Loss of sense of smell and taste may be a predictor of further CNS dissemination of the virus and possible neurological complications (which is still a subject of consideration). The olfactory bulb could be a gateway to COVID-19 intrusion into the CNS, and its atrophy could be an indicator of the process. Further investigation on this topic is required, including a wide application of MRI, in order to come to definite conclusions.

Key words:
ageusia; anosmia; atrophy; covid-19; olfactory bulb; magnetic resonance imaging.

Apstrakt

Uvod. Gubitak čula mirisa i ukusa spadaju u najčešće i najtipičnije simptome infekcije izazvane virusom SARS-Cov-2 (*severe acute respiratory syndrome coronavirus 2)*, sa učestalošću od skoro 50% kod obolelih u zemljama Zapada. Javlja se sve više hipoteza o potencijalnim infekcijama centralnog nervnog sistema (CNS) tim virusom. Pretpostavlja se da virus ulazi u organizam preko nosne sluzokože, pa zatim putem *laminae cribrosae* ulazi u olfaktorni bulbus, sa daljom diseminacijom u CNS. **Prikaz bolesnika.** Bolesnica, stara 34 godine, žalila se na gubitak čula mirisa i ukusa oko dva meseca pre nego što je test pokazao da je bila pozitivna na SARS-Cov-2. Bolest koju izaziva SARS-Cov-2 (COVID-19) se ispoljila blagom pneumonijom i smanjenom osetljivosti čula mirisa i ukusa. Nakon lečenja, bolesnica se oporavila, ali su se gubitak čula mirisa i ukusa ponovo pojavili, sa varijacijama u intenzitetu, da bi od februara 2021. postali uporni. Bolesnica je praćena od strane otorinolaringologa, pulmologa i, na kraju, neurologa. U međuvremenu, test je pokazao da je bolesnica bila negativna na SARS-Cov-2, posle čega je primila dve doze vakcine Sputnik V. Urađena je magnetna rezonanca (MR) mozga, koja je jasno pokazala izraženu obostranu atrofiju olfaktornog bulbusa. Bolesnica do danas ima gubitak čula mirisa i ukusa i planirano je dalje praćenje MR-om. **Zaključak.** Gubitak čula mirisa i ukusa mogu biti prediktori dalje CNS diseminacije virusa i potencijalnih neuroloških komplikacija (što je još uvek predmet razmatranja). Olfaktorni bulbus bi mogao predstavljati mesto ulaska virusa u CNS, a atrofija bulbusa bi mogla biti indikator tog procesa. Za definitivne zaključke potrebna su dalja istraživanja na tu temu, uključujući i širu primenu snimanja MR-om.

Ključne reči:
čulo ukusa, poremećaji; čulo mirisa, poremećaji; atrofija; covid-19; bulbus olfactorius; magnetska rezonanca, snimanje.

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Introduction

Anosmia and ageusia are one of the most common and characteristic symptoms of severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection, with the frequency of almost 50% in patients in Western countries [1, 2]. This symptom is not always present and cannot be the only diagnostic criteria for coronavirus disease 2019 (COVID-19). However, as the pandemic progresses, more and more hypotheses suggest that the virus potentially affects the central nervous system (CNS). The nasal mucosa is most commonly mentioned as the gateway for the virus intrusion into the brain. Angiotensin-converting enzyme-2 (ACE-2) and transmembrane serine protease-2 (TMPRSS2) receptors are considered essential for SARS-Cov-2 entrance into the host cells [3]. ACE-2 expression is highest in the pulmonary tissue, which explains pneumonia as the dominant manifestation, but it is also high in the nasal mucosa, as well as in some other tissues (liver, kidney, brain). It is presumed that the virus enters via nasal mucosa and then continues via cribriform plate to enter the olfactory bulb, with further dissemination to the CNS [4]. Of course, other hypotheses (like the hypercoagulable-vascular theory) are also considered, and those hypotheses do not exclude each other [5].

Case report

A 34-year-old female patient has been treated for anosmia and ageusia since July 2020. The loss of sense of taste and smell began suddenly and lasted for about a week. She did not have any other health issues. As the patient was aware that those symptoms are frequent in COVID-19, she went to a general practitioner and took a polymerase chain reaction (PCR) test on SARS-Cov-2, which was negative. One month later, she tested herself for SARS-Cov-2 antibodies; the test was also negative, and the patient concluded that her problems were due to allergic rhinitis, to which she inclined for the most of her life. Besides this, she suffered from hypothyreosis and had chronic problems with the cervical spine.

In September 2020, she had the same problems, which lasted only for several days, and she did not consult any doctor.

In the first half of November 2020, she felt minor itching in the throat. The next morning it was accompanied by uncomfortable pain in her hips, which she described as if it were spreading from the ovaries to the lower back. The next day, she felt the loss of sense of smell and taste again, and this time it was complete (previously, it was just partial loss). She took the PCR test again, and now, she tested positive for SARS-Cov-2. For the next five days, low back pain worsened, while throat itching disappeared. She felt disoriented and had memory difficulties. Anosmia and ageusia recovered slowly and became almost normal by the end of the month. She did not have a high fever, cough, or any other symptom. A chest X-ray was performed, which showed minor bilateral pneumonia. Amoxicillin/clavulanic acid was prescribed, and the patient felt better soon.

By the beginning of January 2021, she began to feel the loss of the sense of smell and taste again, and this time, it lasted for a whole month.

In March 2021, she got the Sputnik V vaccine and was revaccinated properly. Three weeks after the second dose of the vaccine, she began losing the sense of smell and taste again, and from that time on up to this day, she never recovered again.

The patient started to investigate her problem, starting with an otorhinolaryngologist. The doctor suspected allergic rhinitis and prescribed mometasone-furoate spray locally as well as a spray for moisturizing and repairing the nasal mucosa based on D-panthenol and vitamins E and A (Rinopanteina®, DMG IT, Italy), olfactory "training", and abundant nasal douching. Consultation with an endocrinologist and pulmonologist was requested.

The pulmonologist performed a control chest X-ray, which showed a complete reduction of the inflammatory process, with slight residual features in both lungs basally. He prescribed salbutamol (Ventolin® spray, GlaxoSmithKline).

In June 2021, the patient had a control examination with the otorhinolaryngologist. Nasal endoscopy, which showed a severe deviation of the nasal septum without any other pathological findings, was performed. The otorhinolaryngologist proposed the same therapy and 'training' and planned olfactometry in three months.

At the end of June 2021, magnetic resonance imaging (MRI) of the brain was performed. It revealed bilateral olfactory bulb atrophy, as well as slightly more voluminous extracerebral cerebrospinal fluid spaces for the average age.

A neurologist was consulted for the first time, and together with a neuroradiologist, a joint analysis of the MRI findings was done, together with additional measurements.

The measurement of the volume of the olfactory bulbs was performed with the standard methodology (Duprez TP and Rombaux P) [6], using T2 weighted fast spin-echo sequence (T2W FSE) in coronal view with 2 mm thick slices, which is optimal for displaying the anatomy of the olfactory bulb and the surrounding regions and allows volumetric evaluation. This sequence is added to the standard view of endocranium, which has to be performed in order to exclude potential traumatic or other lesions of the brain, which were excluded in our patient.

Performed measurements revealed a reduced volume of olfactory bulbs (about 18 mm^3 on the right side, and 20 mm^3 on the left side) (Figure 1); the depth of the olfactory sulcus on the right side was slightly above the limit value, and on the left side it was reduced (8.34 mm on the right side, 7.60 mm on the left side) (Figure 2). Olfactory bulb volume below 40 mm^3 and depth of olfactory sulcus $\leq$ 8 mm is considered reduced in the referent literature**.**

At this moment, the patient still shows no improvement regarding the sense of smell and taste. She is COVID-19 negative and has no other symptoms. Symptomatic therapy of vitamin B was added, and a control MRI is planned.

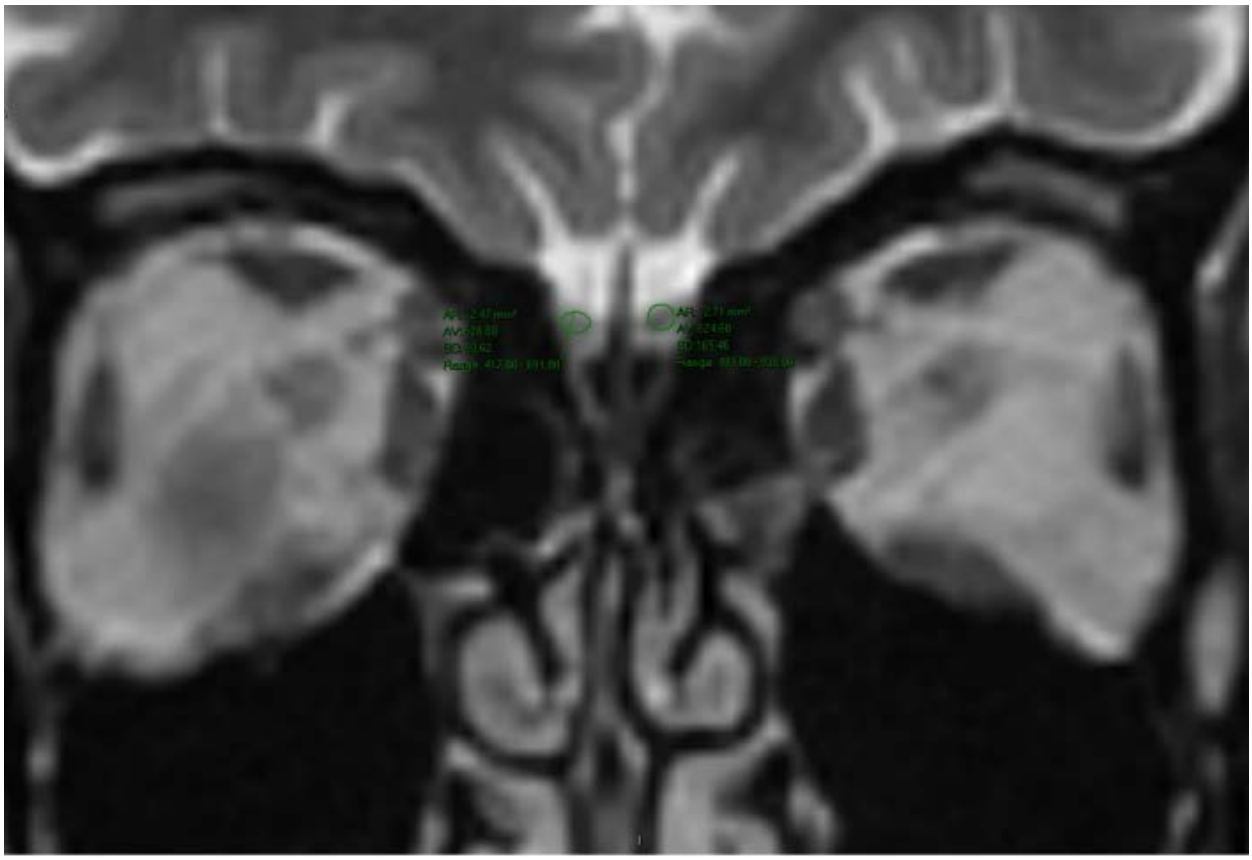


Fig. 1 ─ Coronal T2W thin-sliced tomogram with measurement of the volume of the olfactory bulb which shows signs of volume reduction.

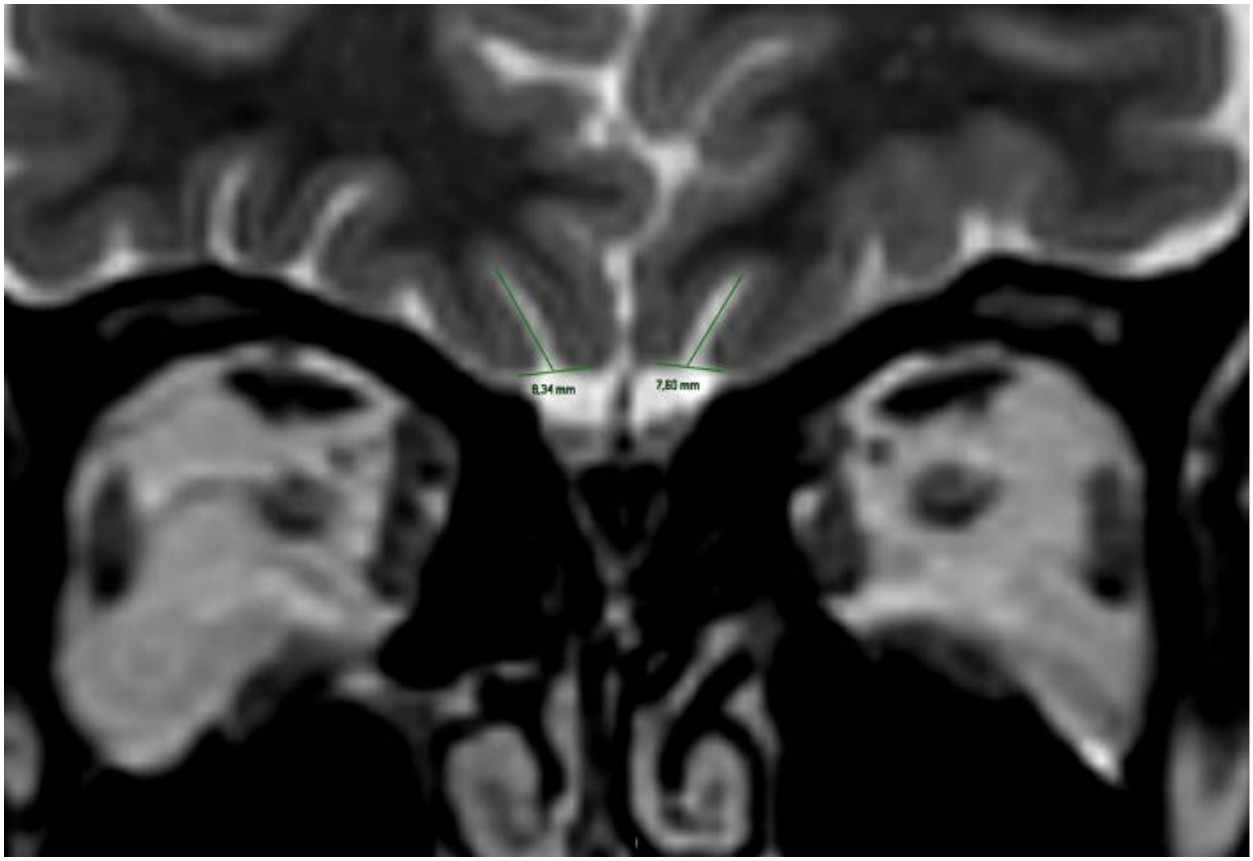


Fig. 2 ─ Coronal T2W thin-sliced tomogram with measurement of the depth of the olfactory sulcus which is reduced.

Discussion

From the beginning of the COVID-19 pandemic in November/December 2019, many controversies and dilemmas were caused over the origin of the virus, its influence on different organs, and means of transmission [7]. Loss (or weakness) of the sense of smell and taste was one of the first and most characteristic symptoms noticed in COVID-19. The whole situation around the COVID-19 pandemic included a variety of extraordinary measures aimed at preserving social and economic order and saving human lives. In these circumstances, planned, randomized, multicentric studies with pre-planned diagnostics still lack. Along with it, many hypotheses evolved as we obtained more and more knowledge about SARS-Cov-2.

Neurological manifestations of COVID-19 are becoming an increasingly interesting aspect of this new disease. Data on this are still very far from being systemized, and studies from different parts of the world show very different results [8]. What we do know is that the two main means of affecting the brain are either via the direct impact of the virus, which causes neurodegenerative processes (mainly atrophy), or through the brain's vascular system with pro-thrombotic state and consequent infarctions.

Nasal mucosa, olfactory bulb, and frontal lobe, in general, had been considered the gateway for SARS-Cov-2 to the brain from the beginning. Anosmia and ageusia, as very common initial symptoms, are supposed to be the result of the effect of the virus on these structures. Some studies mention damage to the nasal mucosa as a primary lesion, but that does not explain ageusia. Most other studies point to the olfactory bulb as the primary target that causes anosmia and ageusia and try to explain the mechanisms of the virus entering the brain. Almost all studies indicate the importance of expression of ACE-2 in particular tissues as indicators of organotropism of the virus [9, 10]. Expression of ACE-2 is particularly high in brain tissue. SARS-CoV-2 uses its spike protein to bind with ACE-2, and this link is formed with the aid of TMPRSS2. TMPRSS2 is a protease present on the surface of the target cell, which plays an important role in the virus entry pathway as it cleaves a specific point of the spike protein, thus allowing a connection between the C-terminal domain (CTD) of pico protein and ACE-2. Recent studies have shown that another transmembrane protease, TMPRSS4, is able to perform the same function as TMPRSS2, hence being an alternative protease for SARS-CoV-2. In addition to transmembrane proteases, there is also the intracellular protease known as cathepsin-L, which can also be responsible for the entry of the virus [10].

Many authors tried to determine exactly which part of the olfactory system is attacked by the virus and understand the potential further invasion of the nervous system [10]. Furthermore, a question was raised about the pathophysiologic origin of the anosmia and subsequent mechanism of recovery. Gupta et al. [9] researched the significance of ACE-2 and TMPRSS2 expression towards particular types of olfactory mucosa cells. The results showed that sustentacular cells (SUS), olfactory stem cells (OSC), and Bowman's gland cells (BGS) are particularly sensitive to binding with spike protein of the virus and that they are most probably responsible for anosmia. The study of De Melo et al. [11], performed on hamsters, is in accordance with these conclusions. It is known that some viruses can penetrate the olfactory bulb in such a manner and later disseminate in the brain, but whether SARS-Cov-2 has the same mechanism is still debated. Butowt and von Bartheld [12] propose the following four possible mechanisms of anosmia: local nasal obstruction due to congestion, destruction of olfactory receptor neurons, infiltration of the olfactory bulb, and damage of supportive cells, which they consider the most probable explanation (although our case shows otherwise). These authors also point out a much higher prevalence of anosmia in patients from the Western hemisphere compared to East Asian patients, for which we still have no valid explanation. Bilinska et al. [13] consider that the transfer of the virus from SUS cells to olfactory neurons cannot yet be proven, but, as it is known, the olfactory receptor neurons are enwrapped with SUS cells, and that kind of transfer is possible via exosomes, which was proven for the herpes virus.

Many studies tried to find out morphological evidence of the direct effect of SARS-Cov-2 on the brain. However, neuroimaging of the brain, especially the olfactory region, is not regularly performed on patients with anosmia and ageusia; hence we can usually find case reports and series of cases rather than studies. Chiu et al.[14] reported a patient with a loss of sense of smell and taste as an initial symptom of COVID-19. They performed an MRI of the brain, which showed olfactory bulb atrophy. Coincidentally, the patient had already measured the olfactory bulb due to diagnosed prolactinoma. Therefore, baseline dimensions of the bulb were already known. The duration of anosmia in this patient was two months. In their paper, Shor et al. [15] focused on olfactory bulb atrophy primarily from a radiological perspective and dealt with possible misinterpretation of MRI findings. On the contrary, Galougahi et al. [16] present us a case of a patient with clear unilateral anosmia during COVID-19 infection that showed no abnormalities of the olfactory bulb on MRI. The case report and analysis of Liang et al. [17] gives us data of a patient with COVID-19 and anosmia which lasted long after the patient was PCR tested negative several times, and emphasizes that MRI olfactometry should be performed minimum one month after the symptom onset if we want to document any changes on MRI. According to them, olfactory bulb atrophy is almost always asymmetric, and we should not check only for anatomical changes but also for functional decrease. Las Casas Lima et al. [18] give us a systematic review of numerous papers presenting morphological changes in the olfactory bulb connected to COVID-19 anosmia and ageusia. They also emphasize the importance of ACE-2 and TMPRSS 2 receptors in the olfactory epithelium cells. Their main hypothesis is that anosmia is caused due to damage to non-neuronal cells, which then affects the normal olfactory metabolism. MRI studies display the connection between a

decrease of the neuronal epithelium and the olfactory bulb atrophy. Damage to other cells, which are not neuronal, explains why the average recuperation lasts several weeks. This damage can be worsened by an enhanced immune response, leading to additional damage to neuronal and stem cells, inciting long-lasting or permanent loss of sense of smell. Tsivgoulis et al. [19] conducted a study on 8 patients who survived COVID-19 infection and had a persistent loss of sense of smell and taste for longer than 40 days. All of them presented with olfactory bulb atrophy (mild to moderate) but also thickness and edema of the nasal mucosa. Xydakis et al. [20], in their review article, tried to comprehend all the knowledge we have obtained on COVID-19 until now. The replication of the virus in neurons and glia have not been proven. Neurotropic characteristics of SARS-CoV-2 are not understood completely. However, malfunctioning of the olfactory tract can be understood as a focal neurological deficit in patients with COVID-19. Collected information indicates inflammation in the olfactory epithelium, olfactory bulb, or both. The mechanisms of olfactory dysfunction are hard to understand because of the dissimilarity of clinical features. That kind of dissimilarity indicates that SARS-CoV-2 infection can cause impairment of the olfactory function at various levels and by the means of different pathophysiological mechanisms which do not exclude each other. The factors which affect different kinds of recovery are unknown. Multiple hypotheses are trying to explain olfactory bulb dysfunction. One of them considers the sterile immune reaction triggered by active replication of the virus, where the virus plays the initial triggering but secondary role. There are many other conditions responsible for the invasion of the olfactory bulb cells by the virus**.** One of those conditions – the neurotropism of the virus – can be emphasized.

Future efforts on this topic are needed, with broader use of structural and functional olfactory system MRI, which should be done during the acute phase of COVID-19. They could contribute to a better understanding of this problem [20]. The recovery of the sense of smell occurs mostly during the first 4–6 months. Renaud et al. [21] studied the dynamics of recovery of the sense in patients with COVID-19 (half of the patients were assessed by olfactometry, and half by their subjective assessment). The recovery went gradually, and after one year, 96.1% of the patients recovered their sense of smell completely. There is evidence that the olfactory bulb and olfactory tract could be the focus of some neurodegenerative diseases. Thomann et al. [22] investigated olfactory bulb volumes in patients with mild cognitive disorder and patients with probable Alzheimer's disease (AD), along with healthy people as a control group. The olfactory bulb atrophy was most prominent in patients with AD, with also a significant reduction of medial temporal lobe gray matter density. This study implies that the atrophy of these two regions could be connected and could constitute predictor markers of AD. It is widely accepted that the so-called non-motor symptoms of Parkinson's disease (PD) can precede the presentation of the disease itself. The common symptom of PD which precedes motor symptoms is anosmia. Post-mortem studies showed a high prevalence of olfactory bulb atrophy in such patients but also in other neural structures responsible for the functioning of the sense of smell (anterior olfactory nucleus, piriform cortex, amygdaloid cortex, entorhinal complex, and the hippocampus [23]). A meta-analysis of Wattendorf et al. [24] points out the significance of MRI detection of olfactory bulb atrophy as an early symptom of PD.

Regarding the impact of vaccination on anosmia, Lechien et al. [25] point out that such complications are rare and are occasionally recorded after AstraZeneca's and Pfizer-BioNTech's vaccines. They explain such complications either by post-vaccinal inflammatory reaction of the olfactory neuroepithelium or by an immune reaction to the asymptomatic presence of the virus in the neuroepithelium after the vaccination (the prevalence of asymptomatic carriers of the virus ranges from 17.9% to 51%). The absence of nasal congestion makes the former hypothesis unlikely, whilst repeated negative nasal swabs question the latter, hence further investigations are needed. Farsalinos et al. [26] propose a hypothesis according to which the spike protein, expressed locally after vaccination, interacts with alpha-7 nicotinic acetylcholine receptors (nAChRs) in macrophages. Cholinergic pathway disorder triggers cytokine production, which could be transferred via neural pathways to distant regions. Such an inflammatory reflex produces neural signals, which are transferred via vagal nerve to the brain stem, and further to distant tissues by efferent neural pathways. The existence of such neuroimmune interaction may explain the inflammatory response in distant neural regions, as is the olfactory epithelium.

Persistent anosmia can severely damage the quality of life in patients recovering from COVID-19. Although we cannot still efficiently cure anosmia, the neural plasticity of the olfactory system offers treatment options in terms of stimulating the sense of smell. In their article, Sorokowska et al. [27] state that the regenerative capabilities of olfactory pathways vary from changes in membrane excitability and change in synaptic efficiency to neurogenesis and apoptosis. Studies that dealt with this olfactory training show promising results. On their model on mice, Liu et al. [28] prove that primarily sensory populations of neurons and their projections can retain plasticity in the adult age, which offers the basis for the mechanisms of learning and olfactory 'training'. Finally, Zhang et al. [29] present the protocol for future study, which will deal with the efficiency and safety of the olfactory 'training' for the patients with COVID-19 anosmia.

Although anosmia and ageusia began before the patient tested positive for COVID-19, the most probable cause is the virus, as real-time (RT) PCR testing of SARS-Cov-2 has only moderate sensitivity [30]. The impairment is severe and long-lasting, and the prognosis is uncertain. The prevalence of this kind of COVID-19 consequences is also uncertain, as MRI is rarely routinely done in COVID-19 patients. Possible pathological findings on patients' brains are practically nonexistent, as an autopsy on COVID-19 patients in Serbia is practically prohibited.

Conclusion

Loss of sense of smell and taste is a very common symptom of COVID-19. It may be a predictor of further CNS dissemination of the virus and possible neurological complications (which is still a subject of consideration). The olfactory bulb could be a gateway to COVID-19 intrusion into CNS, and its atrophy could be an indicator of the process. Further investigation on this topic is required, including the wide application of MRI, in order to come to definite conclusions.

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