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REVIEW ARTICLE

Anosmia and Ageusia in Sars-Cov-2 Infection

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ABSTRACT

Background: Corona infection is primarily a respiratory disease, but the SARS-CoV-2 virus also penetrates other organs, causing various symptoms, including olfactory and gustatory dysfunction, which is why we can consider COVID-19 as a multisystem disease.

Aim: To present review of some aspects of the olfactory and gustatory dysfunction in SARS-CoV- infection.

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). COVID-19 is primarily a disease of the respiratory system, but SARS-CoV-2 also penetrates the other organs including central nervous system (CNS). Patients with SARS-CoV-2 infection can experience a range of clinical manifestations, from no symptoms to critical illness. The entry of the virus into the brain can lead to different neurological and psychiatric manifestations, including loss of smell (anosmia) and the loss of taste (ageusia). 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. For now, the etiopathogenesis of anosmia and ageusia in SARS-CoV-2 infection is still unknown. Most of the analyzed subjects reported olfactory recovery. However, anosmia and ageusia can last several months or even longer. While most patients are expected to recover their sense of smell or taste within the first three months, a major subpopulation of patients might develop long lasting dysfunction. Although a substantial proportion of patients with Covid-19 might develop long lasting of diferent level of ansomia and ageusia it is uncertain what proportion of patients develop persistent dysfunction. Anosmia/ageusia can be as an important risk factor for fog, anxiety, and depression that may show a prolonged and/or delayed impact. However, we do not yet know what long-term effects these disorders may have on the central nervous system and mental health in general.

Conclusion: The COVID-19 is primarily a disease of the respiratory system, but SARS-CoV-2 also penetrates other organs (multisystem disease), causing various symptoms, including olfactory and gustatory dysfunction. The frequency of anosmia and ageusia in patients with COVID-19 is common but according to different papaers 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. We do not yet know what long-term consequences these disorders may have on the central nervous system and mental health in general.

Keywords: COVID-19, Etiopathogenesis, Ansomia, Ageusia, Long-term consequences.

Introduction

Infection with the new coronavirus (severe acute respiratory syndrome coronavirus 2 /SARS-CoV-2) or COVID-19 was first registered in December 2019 in China and then later spread rapidly to the rest of the world. In Bosnia and Herzegovina, the first infected person was registered on 5th March 2020 in Banja Luka¹. Corona infection is primarily a respiratory disease, but the SARS-CoV-2 virus also penetrates other organs, causing various symptoms, including olfactory and gustatory dysfunction, which is why we can consider COVID-19 as a multisystem disease.

In general, adults with SARS-CoV-2 infection can be grouped into the several categories: *asymptomatic or presymptomatic infection; mild illness; moderate illness; severe illness; critical illness*. Mild illness can include different symptoms: fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell, but do not have shortness of breath, dyspnea, or abnormal chest imaging².

Aim of this paper is to present review of some aspects of the olfactory and gustatory dysfunction in SARS-CoV-2 infection.

COVID-19 and anosmia and ageusia

Olfactory dysfunction (OD) associated with a viral infection of the upper respiratory tract is not only related to infection with the SARS-CoV-2. Namely, different viral infections, sinus diseases, and head trauma, as well as Parkinson disease could also cause OD³, but, SARS-CoV-2 has been found to cause a more severe form of hyposmia compared to other seasonal cold viruses⁴. 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 OD, and is more common in women and in age over 50 years^{5,6-7}.

According to Cowart et al⁸ approximately two thirds of the patients who present to specialized chemosensory clinical centers complain of taste loss, but the vast majority of tested patients display olfactory rather than gustatory dysfunction as the basis for their "taste" complaint.

The duration of PVOD are quite variable (from one week to one or two years) and intensity depending on the speed of regeneration of the neuroepithelium^{6,9-10}. Usually, a one third of patients begin recovery after a few months and achieves a full recovery after 13 months. However, if severity of PVOD is greater and if lasts longer, the recovery of olfactory function is very modest (9-10). Although olfactory dysfunction after corona virus infection was previously recorded in SARS pandemic in 2002., at the very beginning of the COVID-19 pandemic, the acute loss of smell and taste was not considered an important symptom of SARS-CoV-2 infection¹¹⁻¹³. However, soon after the first mentions of anosmia among the symptoms of COVID-19, acute loss of smell and taste were recognized as key diagnostic symptoms reported by approximately 60% of infected individuals¹⁴⁻¹⁸. Furthermore, OD is also one of the most common neurological complications reported among patients with COVID-19¹⁹⁻²⁰.

Symptoms of olfactory and gustatory dysfunction, respectively include anosmia (complete lack of olfactory sense), hyposmia (reduced olfactory sense), parosmia (distorted olfactory sense), and phantosmia (sensing odors that don't exist).

The first report that mentions anosmia and ageusia in patients with COVID-19, is a report by Mao et al²¹ which they determined that in the 214 patients they analyzed, 5.6% had hypogeusia, and 5.1% hyposmia.

The most common clinical course of olfactory dysfunction is with an acute onset of hyposmia or anosmia, respectively. Recovery from this disorder usually occurs a few days to a week after the onset^{13,16}. However, more than of 20% (up to 60) of patients, report persistently diminished smell at 6 months and 1 year²²⁻²³, with 40% of them experiencing qualitative changes in the sense of smell in a disorder known as parosmia^{16,24-25}.

Epidemiology

A large number of studies have been published on the different frequency of these disorders in people with corona infection.

The incidence of olfactory dysfunction and taste dysfunction ranges 32-87% and 35-89%, respectively, with a concomitant incidence of olfactory and taste dysfunctions reported to be about 35%²⁶⁻²⁹. OD is more frequent in females than in males and is more common in the younger age groups between 20 to 40 years old²⁹⁻³². About 10% of the patients had anosmia/hyposmia and ageusia/hypoageusia preceding the onset of other symptoms, and there have been many patients not even showing other symptoms²⁹. There are reports of differences in the incidences of OD depending on geographic areas, with higher frequencies in Western countries (over 50%), than in Asian countries (about 30% or less)²⁹⁻³³.

According to a report from Doha, Qatar, in a primary care health center, out of 141 respondents this was 24.82% subjects

presented with ageusia, anosmia or both. All subjects had normalization of anosmia or ageusia with an average duration of 6.89 days³⁴. A multicenter study conducted in several countries in Europe at the beginning of the COVID-19 pandemic (from 12 hospitals) which included 417 COVID-19 (263 females/154 males) subjects; 85.6% of patients reported olfactory and 88.0% gustatory dysfunctions with a significant association between both disorders ($p < 0.001$); females were significantly more affected by olfactory and gustatory dysfunctions than males ($p = 0.001$); olfactory dysfunction appeared before the other symptoms in 11.8% of cases. The early olfactory recovery rate was 44.0%³⁵.

In one study from Kathmandu out of 300 patients, prevalence of loss of smell was 54% and loss of taste was 53%. Both of the symptoms were present in 45% of patients. Authors noted that the severity of the disease has a statistically significant effect on the loss of smell and taste whereas gender and smoking history has no significant difference over it³⁶.

In one of the first a meta-analysis (up to 15th March 2021), published in October 2021, the prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized patients recovered from COVID-19 (15,244 hospitalized and 9,011 non-hospitalized patients) anosmia was present in 10–20%, ageusia in 15–20% of analyzed patients³⁷. In another meta-analysis, in which (the CINAHL, PubMed, EMBASE, Scopus, and Web of Science databases were searched from 2019 to August 2021) published in November 2022 (sample included 7623 hospitalised and 1133 non-hospitalised patients) anosmia/ageusia were present in 24% of patients (7%-47%)³⁸.

Galluzzi et al³⁹ did interesting study with aim to determine risk factors for olfactory and gustatory dysfunctions in patients with SARS-CoV-2 infections. They conducted an observational, retrospective study on 376 patients with documented SARS-CoV-2 infection admitted to the San Gerardo Hospital in Monza, Italy, from March to July 2020. They concluded that their study indicates that current smoking and history of allergy (particularly respiratory) significantly increase the risk for smell loss in COVID-19 patients; the latter is also significantly associated to taste loss. Hospitalization has an inverse association with the risk of olfactory and gustatory dysfunctions, suggesting that these may be symptoms characteristics of less severe SARS-CoV-2 infection.

There is also one report on the appearance of taste and smell disorders after vaccination against COVID-19⁴⁰. In this study the anti-SARS-CoV-2 vaccination was performed with Pfizer/BioNTech (106 cases), AstraZeneca (32 cases), Moderna (12 cases), or Johnson & Johnson (three cases) vaccines. Out of the 153 subjects 62.3% and 53.6% reported olfactory and gustatory dysfunction, respectively. Symptom severity was mild or moderate in almost all cases. There were no significant differences in the prevalence of CD between patients who received viral vector or mRNA vaccine⁴⁰.

Etiopatogenesis

Although there is a large number of publications on the widespread frequency of anosmia and ageusia in patients with SARS-CoV-2 infection the mechanism of action of the virus on these smell and taste

abnormalities (STA) is still not fully understood⁴¹. 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.

There is no lot of prior research that studied and explained the mechanism possible association between SARS-CoV-2 infection and the taste alteration^{34,42}. Zhou et al. have been confirmed that SARS-CoV-2 use the same cell entry receptor - angiotensin-converting enzyme 2 (ACE 2)] as SARS-CoV⁴³. Because the fact that enzyme found in the mouth particularly on the tongue, it is possible speculate that the COVID-19 causes STA in the same way as the ACE2 inhibitors^{34,44}. Furthermore, the taste abnormality in the presence of smell disturbance is intimately correlated⁴⁵. 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^{34,46}.

In one 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 olfactory receptor neurons, damage to olfactory neuronal regeneration, and the

inflammatory response, cytokine action, and greater damage to the cortex^{13,47}.

There is also one speculation that suggests that the COVID-19 virus affects the non-neuronal olfactory epithelium causing anosmia and the associated taste dysfunctions. This could be the acceptable mechanism because majority of the patients with SARS-CoV-2 infection are of the mild severity, and most of the smell and taste abnormalities resolve within short period^{34,48}.

Prognosis

A little is known about the clinical course of change in sense of smell and taste after SARS-CoV-2 infection, with inconsistent evidence on the duration of recovery. While most patients are expected to recover their sense of smell or taste within the first three months, a major subpopulation of patients might develop long lasting dysfunction. Although a substantial proportion of patients with covid-19 might develop long lasting of different level of anosmia and ageusia it is uncertain what proportion of patients develop persistent dysfunction⁴⁹⁻⁵¹.

Furthermore, recent studies of long covid have already reported a substantial burden of brain fog, anxiety, and depression, it remains uncertain if persistent smell dysfunction after covid-19 might prognosticate an increased risk of long term neurological sequelae or neurodegenerative disorders⁵²⁻⁵⁴.

Conclusion

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.

Most of the analyzed subjects reported olfactory recovery. However, anosmia and ageusia can last several months or even longer. We do not yet know what long-term neurological consequences these disorders may have and on mental health in general.

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