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Research Article

# Olfactory alterations in long COVID

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**Abstract:**

Olfactory anosmia is the complete loss of the sense of smell, while hyposmia is the partial loss of smell. SARS-CoV-2 is the pathogen responsible for COVID-19. The virus is composed of the membrane, envelope, and spike protein. In the physiology of smell, odoriferous substances bind to proteins secreted by sustentacular cells to be processed by olfactory receptor neurons. Olfactory dysfunction is one of the main manifestations of COVID-19. The duration of persistent symptoms in long COVID is longer in patients who presented severe symptoms compared to those with mild or moderate disease. Therefore, all known risk factors for severe COVID-19, such as obesity or advanced age, fit the risk profile for long COVID.

**Keywords:** COVID 19; long COVID; pathophysiology; hyposmia; anosmia

## Introduction

The disease caused by the SARS-CoV-2 virus is known as the novel coronavirus disease (COVID-19). This coronavirus belongs to the subfamily Orthocoronavirinae, of the Coronaviridae family (order Nidovirales). Based on their genetic structure, they are classified into four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. Alphacoronaviruses and betacoronaviruses infect mammals and are responsible for respiratory infections in humans, mainly causing common colds (HCoV-NL63 and HCoV-229E are alphacoronaviruses, while HCoV-HKU1, HCoV-OC43, SARS-CoV, MERS-CoV, and SARS-CoV-2 are betacoronaviruses). Structurally, coronaviruses are spherical viruses with a diameter of 100-160 nm, covered by a lipid bilayer and containing ribonucleic acid (COFRE, 2021).

The disease caused by the novel coronavirus (COVID-19) was declared a pandemic by the WHO in March 2020. Since then, the disease has already claimed millions of victims worldwide, with over 500 million confirmed cases and a mortality rate of around 2% in the period of 2020-2021 and 1.2% in 2022 (AZEVEDO, 2022).

Studies show that the problems caused by the disease do not end with the end of the infection, many people who have recovered from the virus still suffer from the impacts of the illness. According to the World Health Organization (WHO), between 10% to 20% of people who have had Covid-19 suffer from these symptoms after recovering from the acute phase of the disease. The WHO considers "Long Covid" or "Post-Covid Condition" to be symptoms that appear up to three months after contamination, last at least two months, and cannot be explained by an alternative diagnosis (KROLL, 2022).

Among the risk factors identified so far for a more severe progression of the disease are advanced age (over 60 years old) and the presence of comorbidities (such as diabetes mellitus, cardiovascular diseases, arterial hypertension, and lung diseases) (HARAPAN, 2019).

Numerous recent studies have reported olfactory dysfunction in patients with the disease caused by the novel coronavirus (COVID-19). Changes in smell can be classified into quantitative and qualitative changes. Among the quantitative changes, a decreased sense of smell is called hyposmia, and a complete loss of smell is called anosmia. In qualitative changes (known as

dysosmias), there is a distortion in the perception of odors, either in the presence of an olfactory stimulus (parosmia) or in its absence (phantosmia) (COFRE, 2021).

The diagnosis of the disease is based on clinical suspicion associated with laboratory methods. The reverse transcription-polymerase chain reaction (RT-PCR) test has shown higher sensitivity (about 80%) when performed from the third day of symptom onset (WIERSINGA, 2020).

Given the complications related to olfactory dysfunction being present in many people who have been infected with SARS-CoV-2, the aim of this article is to expand knowledge about hyposmia and anosmia in Long COVID, based on publications available in the scientific literature.

## Methodology

The methodology used in this article was a literature review based on secondary sources, characterized by a systematic analysis and synthesis of research on hyposmia and anosmia in Long COVID.

The research question used in this study was: "What is the pathophysiology that explains hyposmia and anosmia in long COVID?". This is a literature review characterized by a systematic analysis and synthesis of research on hyposmia and anosmia in long COVID, with a limited scope and descriptive analysis. The search was conducted using the following keywords: COVID-19, long COVID, physiopathology, hyposmia, anosmia, between 2020 and 2023, in Portuguese, English, and Spanish. The main databases used were: the Virtual Health Library with access to Latin American and Caribbean literature in health sciences (Lilacs); the Medical Literature Analysis and Retrieval System Online (Medline); as well as Scielo and Pubmed. The articles were chosen according to their specificity and content related to the topic.

From this question, a search for articles containing the words "COVID 19", "long COVID", "pathophysiology", "hyposmia", and "anosmia" was conducted, with articles selected from the virtual health library databases with access to Latin American and Caribbean health sciences literature (Lilacs), Medical Literature Analysis and Retrieval System Online (Medline), as well as Scielo and Pubmed. Filters for language (Portuguese, Spanish, and English) and time period (the past 3 years, with 2023 as the reference year) were applied.

After an initial analysis of all the researched material, the articles considered suitable for the type of research developed were selected. A careful reading of the tabulated articles was then carried out to better analyze the data.

## Discussion

According to the World Health Organization (WHO), individuals with a history of probable or confirmed SARS-CoV-2 infection whose symptoms appeared up to three months after infection, lasted for at least two months, and without an alternative diagnosis, can be diagnosed with "post-COVID-19 condition" or "long COVID." These symptoms can fluctuate and recur over time (BRASIL, 2021).

At the beginning of the pandemic, olfactory disorders such as anosmia or hyposmia (partial loss of smell) were not considered relevant symptoms; however, some studies indicated a possible relationship between these symptoms and Covid-19. After the disease spread, it became clear that these symptoms were part of the investigation for the diagnosis of the disease. Therefore, the World Health Organization (WHO) included olfactory dysfunctions as symptoms of Covid-19.

According to Raveendran (2021) and Nalbadian (2021), the pathophysiology of Long COVID or Post-COVID involves multiple factors that interact with each other, such as sequelae of target organ injuries due to viral toxicity, hyper-inflammation of cellular tissues, dysregulation of the autoimmune response, microvascular endothelial injury, hypercoagulation, secondary infections, prolonged hospitalization, especially in ICU (critical patients), decompensation of clinical comorbidities, adverse effects of medications used in treatment, post-traumatic stress, and other psychological conditions, social and financial impact.

SARS-CoV-2 virus is the causative agent of COVID-19. According to Gaurav (2020), there are two differences between SARS-CoV-1 and SARS-CoV-2. The first difference is the alteration of two viral hotspots, hotspot 31 and hotspot 353. These salt bridges became more stabilized at the binding site of SARS-CoV-2. The second difference is a change in the ACE2 binding structure caused by a motif of four residues, resulting in a more compact and stronger contact. These differences make SARS-CoV-2 have a higher affinity to the host ACE2 receptor and, as a consequence, increase its virulence.

According to Rafal (2020), epidemiological factors such as age and lifestyle directly interfere with the prevalence of olfactory disorders. Studies have shown a correlation between the expression of the ACE2 receptor and age, with ACE2 being more prevalent in adults than in children. Regarding lifestyle habits, it has been found that smokers have a higher chance of developing olfactory disorders due to Covid-19, which is a consequence of increased expression of the ACE2 receptor stimulated by the nicotinic acetylcholine receptor (nAChR). Another set of evidence showed that women are more likely to develop olfactory disorders than men. One possible explanation is that incomplete inactivation of the X chromosome contributes to increased expression of ACE2.

According to Bertrand (2020), conductive anosmia occurs due to nasal obstruction, which is common in many viral conditions, and may be accompanied by rhinorrhea and symptoms of rhinitis. However, studies suggest that loss of smell in Covid-19 occurs in most cases independently of these symptoms. Thus, this hypothesis, in the case of SARS-CoV-2, can be ruled out as the main mechanism causing anosmia. Olfactory epithelium injury is the mechanism identified as the most likely cause of olfactory disorders caused by SARS-CoV-2, which may be exacerbated by damage to the central nervous system.

Cindy (2022) agrees with the above author that in SARS-CoV-2 infection, there may also be a conductive disorder that produces a mechanical blockage of odor molecules when they reach the chemoreceptors of the olfactory epithelium. This mechanism could also be responsible for generating olfaction disorders in patients with local symptoms. Patients with olfactory alterations present a significantly higher frequency of neurological symptoms. One of the proposed mechanisms for the spread of SARS-CoV-2 to the central nervous system is through the cribriform plate, which affects the olfactory nerves and the olfactory bulb and leads to a viral encephalitis condition. Such a pathophysiological mechanism could explain the presence of prolonged headache in some individuals with olfactory alterations for a few weeks.

Cindy (2022) also states that the development of post-viral hyposmia/anosmia would be through the increased production of cytokines. Elevated levels of IL-6 were identified in nasal mucus and plasma in individuals with these symptoms after a cold, compared to controls (29.7 vs. 11.6 pg/mL; $p < 0.001$). This interleukin could regulate the activity of olfactory neurons and glial cells. In severe cases of COVID-19, the serum concentration of this substance is increased. On the other hand, in mild cases, there may be a localized increase in this mediator, which thus promotes localized inflammatory processes and leads to dysfunction in the olfactory system.

Bertrand (2020) describes that in experiments with hamsters infected with SARS-CoV-2 via nasal instillation, massive damage to the olfactory epithelium was found just two days after infection. By the fourth day after infection, most of the epithelium had disappeared. After 14 days, the epithelium showed signs of recovery but had not yet returned to normal. It was found that in regions where the damage was most intense, the axons of olfactory receptor neurons were practically in contact with the external

environment. The main observations in this experiment were: the infection and shedding of the olfactory epithelium, the virus's preference for sustentacular cells rather than neuronal cells, and the intense recruitment of immune cells.

Gonzalez (2021) agrees with the other authors when stating that olfactory deficit is generally caused by damage to the olfactory epithelium and/or the corresponding sensory pathway to the rhinencephalon. Damage to the receptors can result from injuries to supporting cells, and SARS-CoV-2 can compromise the functionality of supporting cells or stem cells in the olfactory epithelium, thereby limiting the replacement of epithelial cells, sensory cells, and tissue regeneration.

In the olfactory epithelium, a cascade of cellular events occurs that may explain the transient anosmia in COVID-19. In addition, evidence suggests that the SARS-CoV-2 virus uses a nose-brain pathway that ultimately affects the rhinencephalon. The nasal epithelium has been shown to have a higher viral load than the lower respiratory tract epithelium (GONZALEZ, 2021).

According to Lima (2022), infection of sustentacular cells leads to loss of cilia in olfactory receptors, which results in the inability to transmit olfactory stimuli and thus detect odors.

Lima (2022) also states that damaged olfactory cells release inflammatory factors that lead to changes in the microenvironment and deterioration of neurons. Injured astrocytes usually release inflammatory modulators and cytokines (both neuroprotective and neurotoxic) and various neurotrophic factors. This hypothesis attempts to explain that SARS-CoV-2 infection of sustentacular cells is the cause of olfactory dysfunction. The consequent loss of epithelial trophism also leads to a weak basal cell renewal, which prolongs the duration of this dysfunction, sometimes for months after healing.

After reading and interpreting the above-mentioned articles regarding the topic, it was concluded that there is a global consensus among the authors regarding the entry route of SARS-CoV-2, which requires an ACE2 receptor. Additionally, olfactory disorders such as anosmia and hyposmia can be caused by COVID-19, and the main pathophysiological mechanism is related to damage to the olfactory epithelium, targeting predominantly non-neuronal cells. However, neuronal cells can also be affected, worsening the olfactory loss.

## Conclusion

It was found that hyposmia and anosmia in long COVID are very frequent, affecting more women, elderly individuals, and those with comorbidities. The physiopathology is based on injury to the olfactory epithelium. Diagnosis should be made quickly, and treatment should be individualized.

According to large studies, olfactory changes in long COVID-19 patients have a significant impact, with the underlying pathophysiology being the injury to the olfactory epithelium. Additionally, it has been identified that risk factors for these changes are female individuals, the elderly, and people with comorbidities. Therefore, it is crucial to understand the pathophysiological mechanisms of hyposmia and anosmia in long COVID-19, as early diagnosis and individualized treatment are necessary to minimize the damage caused by the disease.

## References


1. AZEVEDO, Helena Moraes Jardim de. (2022). Persistence of symptoms and return to work after hospitalization for COVID-19. United Metropolitan Faculties, São Paulo (SP).
2. BERTRAND Bryche, A.S. Albin, S. Murri, S. Lacôte, C. Pulido, M.A. Gouhl, et al. (2020). Massive transient damage of the olfactory epithelium associated with infection of sustentacular cells by SARS-CoV-2 in golden Syrian hamsters. Brain Behav Immun, 579-586.
3. BRAZIL. (2021). World Health Organization.
4. CINDY V.M.; JOSÉ A.M.N.; FABIO A.S.; MARLON S.O.; HUGO M.N.; SÉRGIO R. N. (2022). Smell dysfunction in Covid-19: marker of good prognosis?. braz. j. otorhinolaryngol. 88(3).
5. CHEST, Ana R. et al.(2021). OLFACTORY AND GALATÓRIA DYSFUNCTION IN PATIENTS WITH COVID-19 FROM ARGENTINA. rev. argent. public health, Buenos Aires.
6. GAURAV Das; NABANITA Mukherjee; SURAJIT Ghosh. (2020).Neurological Insights of Covid-19 Pandemic.
7. ACS Chem Neurosci,1206-1209.
8. GONZALEZ AGUILAR, Vivian; CAMANO CARBALLO, Liset; PEPPER CONCEPTION, Ivan. (2021).Physiopathological mechanisms of smell and palate alterations in patients with covid-19. University and Society, Cienfuegos.
9. HARAPAN H, ITOH N, YUFIKA A, WINARDI W, KEAM S, TE H, et al.(2020). Coronavirus disease 2019 (COVID-19): a literature review. J Infect Public Health,13(5):667-73.
10. KROLL, Rebecca. (2022).Covid Longa: Unpredictable and debilitating. Arco magazine, scientific and cultural journalism UFSM.
11. LIMA, Mateus Henrique de Las Casas.(2022). Physiopathological relationship between Covid-19 and olfactory dysfunction: a systematic review. Federal University of Vale São Francisco (Univasf), Paulo Afonso, BA.
12. NALBANDIAN, A. et al. (2021).Post-acute COVID-19 syndrome. Nature Medicine.
13. RAVEENDRAN, A.V. et al.(2021). Long COVID: An overview. Diabetes Metab Syndr.
14. RAFAL Butowt; KATARZYNA Bilinska; CHRISTOPHER S Von Bartheld. (2020).Chemosensory Dysfunction in Covid-19: Integration of Genetic and Epidemiological Data Points to D614G Spike Protein Variant as a Contributing Factor. ACS Chem Neurosci, 3180-3184.
15. WIERSINGA WJ, RHODES A, CHENG AC, PEACOCK SJ, PRESCOTT HC.(2019). Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. NEVER,324(8):782-793.

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