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Ageusia/Dysgeusia in post-COVID-19 patients

Ageusia/Disgeusia em pacientes pós-COVID-19

Ageusia/Disgeusia en pacientes pos-COVID-19

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ABSTRACT

Objective: Summarizes the current knowledge on ageusia/dysgeusia in post-COVID patients focusing on the taste pathway as a possible gateway for central nervous. **Literature review:** Observational studies have revealed that loss of smell and taste may be more predictive in the diagnosis of COVID-19 than other symptoms such as fatigue, fever or cough. Taste dysfunction was associated with moderate COVID-19 infection. The duration of ageusia/dysgeusia is seven days on average, and almost all recover within a month. However, there are reports of patients whose taste has not returned to normal for prolonged periods after infection and still have alterations in taste for certain flavors. **Final considerations:** The mechanisms by which these alterations occur are not yet well clarified, but it is known that there is a neuroinvasive potential of SARS-CoV-2 that may play a role in the pathophysiology of taste alterations, due to a hyperinflammatory state, viral invasion in the central and peripheral nervous system, as well as post-infection immune reactions.

Keywords: COVID-19, Taste, Ageusia, Dysgeusia, Gustatory dysfunction.

RESUMO

Objetivo: Abordar o conhecimento atual sobre ageusia nos pacientes no período pós-COVID com foco na via do paladar como uma possível porta de entrada para o sistema nervoso central. **Revisão bibliográfica:** Estudos observacionais revelaram que a perda do olfato e do paladar pode ser mais preditiva no diagnóstico da COVID-19 do que outros sintomas, como fadiga, febre ou tosse. A disfunção do paladar foi associada à infecção moderada pela COVID-19. A duração da ageusia/disgeusia é de sete dias, em média, e quase todos se recuperam em um mês. Entretanto, há relatos de pacientes cujo paladar não voltou ao normal por períodos prolongados após a infecção e ainda apresentam alterações no paladar para determinados sabores. **Considerações finais:** Os mecanismos pelos quais essas alterações ocorrem ainda não estão bem esclarecidos, mas sabe-se que há um potencial neuroinvasivo do SARS-CoV-2 que pode desempenhar um papel na fisiopatologia das alterações gustativas, devido a um estado hiperinflamatório, invasão viral no sistema nervoso central e periférico, bem como reações imunológicas pós-infecção.

Palavras-chave: COVID-19, Paladar, Ageusia, Disgeusia, Disfunção gustativa.

RESUMEN

Objetivo: Resume los conocimientos actuales sobre ageusia/disgeusia en pacientes post-COVID centrándose en la vía del gusto como posible puerta de entrada al sistema nervioso central. **Revisión de la literatura:** Los estudios observacionales han revelado que la pérdida del olfato y el gusto pueden ser más predictivos en el diagnóstico de COVID-19 que otros síntomas como la fatiga, la fiebre o la tos. La disfunción del gusto se asoció a una infección moderada por COVID-19. La duración de la ageusia/disgeusia es de siete días por término medio, y casi todos se recuperan en el plazo de un mes. Sin embargo, hay informes de pacientes cuyo gusto no ha vuelto a la normalidad durante periodos prolongados después de la infección y siguen teniendo alteraciones del gusto por determinados sabores. **Consideraciones finales:** Los

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mecanismos por los que se producen estas alteraciones aún no están bien aclarados, pero se sabe que existe un potencial neuroinvasor del SARS-CoV-2 que puede desempeñar un papel en la fisiopatología de las alteraciones del gusto, debido a un estado hiperinflamatorio, a la invasión viral en el sistema nervioso central y periférico, así como a reacciones inmunológicas postinfección.

Palabras clave: COVID-19, Gusto, Ageusia, Disgeusia, Disfunción gustativa.

INTRODUCTION

The symptoms most frequently related to COVID-19 include fever, cough, dyspnea, phlegm, myalgia, arthralgia, headache, diarrhea, nausea/vomiting and sore throat. In addition, several patients with COVID-19 also develop other symptoms, such as loss of taste (ageusia/dysgeusia) (BÉNÉZIT F, et al., 2020; LECHIEN JR, et al., 2020). Also, disorders of smell and taste usually manifest within three days of the onset of other COVID-19 symptoms and have been reported as the initial symptoms in up to a quarter of cases, possibly indicating COVID-19 infection even before the development of other symptoms (KAYE R, et al., 2020).

In this context, patients may develop a variability of taste disorders, being classified as quantitative disorders ageusia (complete loss of taste), hypogeusia (partial loss of taste sensitivity) and hypergeusia (increased taste sensitivity). The qualitative disorders observed include dysgeusia (altered taste), which can be divided into parageusia (altered perception of taste stimuli) and phanthongeusia (taste impressions in the absence of stimulus) (RADEMACHER WMH, et al., 2020). Post-COVID-19 syndrome (PCS) is a group of signs and symptoms that occur after SARS-CoV-2 infection and persist for several months. Disturbances of smell and taste are among the most common manifestations associated with this period.

These manifestations can endure beyond the acute phase of SARS-CoV-2 infection, emerging weeks or months later and persisting for varying durations, ranging from weeks to several months or even longer. Their severity can range from mild to extremely severe and may fluctuate over time (BROLA and WILSKI, 2022). Some patients may suffer from lasting impairment of smell and taste. About 10% at a two-month follow-up and 11% at six months did not recover; furthermore, partial recovery was present in only 30% of cases, and no relationship was found between clinical history and the development of symptoms of olfactory or gustatory dysfunction (RIESTRA-AYORA J, et al., 2021).

One study showed that about 25% of patients followed up for up to 36 weeks from the onset of COVID-19 symptoms still had dysgeusia (PELUSO MJ, et al., 2021). This relationship between COVID-19 and alterations in chemosensory functions (smell and taste) raises questions about how SARS-CoV-2 can alter the cells and circuits in charge of detecting stimuli and creating perception. The identification of these pathophysiological mechanisms has important implications for the possible development of treatments, as well as for the development of clinical assessments to detect SARS-CoV-2 infection (COOPER KW, et al., 2020). Thus, this review summarizes the current knowledge on ageusia/dysgeusia in post-COVID patients focusing on the taste pathway as a possible gateway for central nervous system (CNS) involvement by the coronavirus and points out possible associated mechanisms.

LITERATURE REVIEW

Neuroinvasion and damage

The perception of flavors is complex and involves the senses of taste and smell as well as chemesthesis. The precise biological definition of taste, also known as gustation, refers specifically to sensations mediated by a specialized anatomical and physiological chemosensory gustatory system. In addition to taste, consuming food often triggers concurrent sensory responses, including smell, touch, temperature, and irritation.

While distinguishing these sensations perceptually can be challenging, it's important to note that the non-gustatory components are perceived by distinct systems, namely olfaction and somatosensation. Thus the taste system includes taste cells, afferent taste nerves (facial, glossopharyngeal and vagal) and brain structures involved in the central processing of taste (BACHMANOV AA and BEAUCHAMP GK, 2007).

The medial prefrontal cortex is where taste signals are recognized activating working taste memories. The orbitofrontal cortex is where motivational and emotional responses to tastes occur, and the medial parietal cortex (precuneus) is where taste sensations are understood individually (CRAIG, 2002). The gustatory cortex is a dedicated area primarily responsible for perceiving and distinguishing between different tastes. It enables us to differentiate the subtleties of salty, sweet, sour, bitter, and umami (a savory taste often associated with monosodium glutamate), which collectively define the flavor profile of our food.

This area is close to the primary olfactory piriform cortex, correlating anatomically and physiologically olfaction with taste (OBIEFUNA S and DONOHOE C, 2023). All of these sites can be infected by COVID-19, as the virus can travel from the taste sensory ganglion cells to the thalamus and then to the primary sensory cortex ('trigeminal-thalamic-cortical pathway'). These cortical and brainstem areas can be infected trans synaptically after the virus reaches the cranial nerve receptors involved in taste (VITALE-CROSS L, et al., 2022). Autopsy studies performed on the brains of COVID-19 patients have revealed SARS-CoV-2 in different parts of the brain, including frontal lobes, olfactory nerve, olfactory bulb, trigeminal ganglion, medulla oblongata, cerebellum and frontal córtex.

The hypothesis suggests that in individuals infected with SARS-CoV-2, the virus may spread through the bloodstream and breach the brain's blood-brain barrier via endothelial cells in brain capillaries. This mechanism could potentially allow the pathogen to enter the central nervous system (CNS), leading to subsequent neuropathic effects caused by the vírus (PANIZ-MONDOLFI A, et al., 2020). The neuroinvasive potential of the SARS-CoV-2 plays an important role in the pathophysiology of hypogeusia and hyposmia. The suggested mechanism for SARS-CoV-2 causing alterations in taste is its ability to bind to the angiotensin-converting enzyme-2 (ACE2) receptor, expressed in various organs and systems, including the surface of the tongue, salivary glands and oral cavity. This can act as a gateway for infection and lead to the development of ageusia/dysgeusia (LI YC, et al., 2020).

ACE2 receptor is widely expressed throughout the central nervous system in neurons, astrocytes and oligodendrocytes, and cerebral vasculature, making these cells susceptible to attack by SAR-CoV-2. The ACE2 expression is also highly concentrated in the substantia nigra, ventricles, medial temporal gyrus, posterior cingulate cortex and olfactory bulb. Additionally, there appears to be no significant change in the total expression of ACE2 with age. Consequently, findings underscore the significance of ACE2's spatial distribution within the brain over its overall expression levels (CHEN R, et al., 2021).

What's more ACE2 can also be found in all nerve structures, such as nerve sheaths, endoneurium, connective tissue inside the bundles, small vessels, axons and myelin (VITALE-CROSS L, et al., 2022). In addition to ACE2, the SARS-CoV-2 spike (S) protein has been shown to bind to CD147, also known as Basigin (BSG) or extracellular matrix metalloproteinase inducer (EMMPRIN), whose functional role is to facilitate SARS-CoV invasion into host cells mediated endocytosis, especially in ACE2-deficient cell types (WANG K, et al., 2020).

CD147 expression is higher in most human brain cell lines and in mouse brain tissues compared with lung cell lines. CD147 exhibited higher levels in the hypophysis, cortex, and cerebellum regions of the mouse brain. Symptoms associated with hypophysis issues include frequent headaches, vision changes, and impaired pituitary function. Damage to the cortex and cerebellum can lead to symptoms such as dizziness, ataxia, impaired consciousness, and other neurological disorders. Hence, the vulnerability of these brain regions to SARS-CoV-2 may contribute to cognitive and neurological impairments observed in patients. This also indicates that SARS-CoV-2 may use different routes of entry into central nervous system cells (QIAO J, et al., 2020).

So these findings indicate that CD147 and ACE2 could serve as complementary receptors in facilitating virus infection (WANG K, et al., 2020). It has been suggested various routes through which SARS-CoV-2 could access the central nervous system. These include transmission via transsynaptic neurons (such as the olfactory, trigeminal, glossopharyngeal, and vagus nerves), hematogenous pathways across the blood-brain barrier, immunological mechanisms involving mucosal immune cells, or via the meninges. Additionally, entry

through the cerebral spinal fluid by passing through the choroid plexus or circumventricular organs, as well as a potential enteric route, are also under consideration (CÁRDENAS G, et al., 2022).

During the initial phase of SARS-CoV-2 infection, the virus exhibits significant variability and adept concealment, making it challenging for the body to promptly identify. Inside the body, SARS-CoV-2 releases specific factors that disrupt the initiation of a targeted immune response (WAN, et al., 2020). Once in the CNS, SARS-CoV-2 can trigger an increase in the innate response. An exacerbated systemic infection leads to a massive release of inflammatory mediators, including cytokines, chemokines, interleukins and antibodies, colony-stimulating factors (CSF) and TNF-alpha, resulting in increased blood-brain barrier permeability. CSFs are components of an amplification cascade that ultimately increases the production of cytokines by macrophages at sites of inflammation, thus perpetuating the inflammatory reaction (COPERCHINI F, et al., 2020).

These proinflammatory cytokines serve a dual role: aiding in viral clearance by recruiting mononuclear cells while potentially posing long-term challenges to neuronal function and regeneration. T cells, which migrate from the blood and perivascular spaces, not only play a direct role in controlling acute viral infections through cytokine release but can also establish residence in the central nervous system as tissue-resident memory T (Trm) cells for months or even years. However, the enduring neurological consequences of these Trm cells and antibody-secreting B cells within the CNS remain uncertain. In this way, the exacerbated neuroinflammatory response may promote neuronal damage which, if chronic, may favor the occurrence of neurological sequelae (KLEIN RS, et al., 2019).

A study highlighted that individuals recovering from COVID-19 may experience prolonged elevation of pro-inflammatory cytokines, chemokines, platelet-derived growth factor (PDGF-BB), brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF)-A, and VEGF-D levels for 3 to 6 months post-infection, potentially leading to lasting implications. Notably, an analysis spanning 180 days post-recovery revealed a persistent state of chronic inflammation, marked by heightened levels of IL-17A, IL-12p70, stem cell factor (SCF), and IL-1β. Furthermore, indicators of endothelial repair and angiogenesis, such as increased BDNF, MIP-1β, and VEGF levels, were observed. Remarkably, there were no significant differences in these immune mediator levels among patients with varying degrees of disease severity (ONG SWX, et al., 2021).

Furthermore, viral interaction with ACE2 receptors in neurons can result in significant damage to neurons, even without the association with inflammation previously seen with SARS-CoV infection. The spike protein of SARS-CoV-2 binds to the host cell's common receptor at least 10 times more strongly than the corresponding spike protein of the severe acute respiratory syndrome (SARS)-CoV. This strong binding affinity for human ACE2 potentially facilitates the apparent ease of transmission from one human to another (WRAPP D, et al., 2020). The neurological lesions observed in the brains of COVID-19 patients result from a combination of factors.

These include direct cytopathic effects caused by SARS-CoV-2 replication, as well as indirect effects stemming from hypoxia, cytokine overreaction, compromised immune responses, and cerebrovascular injury induced by viral infection. It should also be pointed out that, in addition to this acute neurological effects seen in COVID-19, SARS-CoV-2 could potentially trigger delayed effects and possibly contribute to the onset of neurodegenerative diseases during the chronic phase of infection. (BRATOSIEWICZ-WĄSIK J, 2022). In addition, experiments involving tissue culture, the infection of cortical and hippocampal neural cells with human coronavirus demonstrated that cell death can occur through apoptosis in both infected and adjacent uninfected cells.

Moreover, the release of TNF-α by infected cells, a known apoptosis inducer, likely contributed to apoptosis in uninfected cells and triggered the proliferation and activation of microglia (AGHAGOLI G, et al., 2021). Evidence has suggested that the SARS-CoV-2 Spike (S) protein directly induces inflammatory and pro-coagulation responses. This, coupled with immune dysregulation leading to cytokine release syndrome (CRS), may precipitate acute cerebrovascular or neuroinflammatory diseases. Moreover, CRS-induced compromise of blood-brain barrier (BBB) integrity in specific brain regions could prompt the release of proinflammatory

mediators by neural cells, potentially impacting long-term brain function even after the acute infection has subsided (KLEIN RS, et al., 2022). Ageusia can also be explained not only by viral damage to neurons or ischemic damage in the CNS but also by marked increases in IL-6 (interleukin-6) concentrations in sensory neurons.

IL-6 is known to play a role in cytokine storm formation, promoting the induction of acute phase proteins and activation of the blood coagulation cascade, with disseminated intravascular coagulation. It has been shown that the rapid restoration of taste functions can be explained by a simple decrease in IL-6 concentration that occurs on recovery (GROMOVA OA, et al., 2021). A variety of clinical and radiographic signs and symptoms have been observed in patients with inflammatory syndromes in the CNS, including acute demyelinating encephalomyelitis in the post-infection period, or transverse myelitis, as well as unusual haemorrhagic changes. It has been hypothesized that SARS-CoV-2 may degrade the CNS by stimulating T-lymphocyte-mediated autoimmune reactions against CNS antigens, and this could alter the taste function (PATERSON RW, et al., 2020).

Self-reactive T lymphocytes breach the blood-brain barrier, entering from the peripheral circulation. T lymphocytes proliferate and express cell adhesion molecules (CAMs) and cytokines, intensifying damage to the BBB and an abnormal increase in its permeability. This infiltration initiates an inflammatory cascade, ultimately resulting in demyelination. This process starts with viral factors penetrating nerve tissue, causing proteins to appear on the membranes of oligodendrocytes and myelin sheaths. Subsequently, an autoimmune response targets these myelin antigens, disrupting their recognition system (PIVNEVA TA, 2009).

Demyelination can be caused by inflammatory processes, impaired cerebrovascular flow, viral demyelination, hypoxic-ischemic forms demyelination and damage to oligodendrocytes and myelinated axons. Viral proteins in oligodendrocyte membranes and myelin sheaths cause the primary activation of T cells. In addition, cytokines trigger the activation of microglia, macrophages and astrocytes. Thus, microglial and astroglial cells also start secreting inflammatory cytokines. As a result, myelin sheaths and oligodendrocytes are damaged, leading to disruption of their function and death of neurons and axons (KHODANOVICH MY, et al., 2022; KHODANOVICH MY, et al., 2018).

Although myelin renewal is continuous throughout adulthood and is important for repairing damage to myelin sheaths, neural circuit plasticity and cognitive learning, the process of remyelination depends on the ability of oligodendrocyte progenitor cells to proliferate, migrate and ultimately differentiate into myelinating oligodendrocytes (KHODANOVICH MY, et al., 2022). Magnetic resonance imaging (MRI) demonstrated demyelination in various white matter structures. In addition to reductions in cortical thickness and the volume of various subcortical structures, alterations in the microstructure of the cerebral cortex were also observed 3 to 10 months after COVID-19 in patients who had severe and mild infections without neurological manifestations in the acute phase, and following a 10-month recovery period, severe cases continued to exhibit a more extensive and profound reduction in nuclei volume compared to mild cases (QIN Y, et al., 2021; TIAN T, et al., 2022).

Even though these studies did not examine other aspects such as cognition and function, it may help in understanding the maintenance of sensory disturbances over a prolonged period post-Covid, once neuronal injury was detected. Severe SARS-CoV-2 infection can also result in dysautonomia and sympathetic storms due to autonomic nervous system (ANS) dysfunction. This infection may disrupt the morphological and functional stability of the cholinergic system (CS) by affecting cholinergic receptors. Nicotinic receptors (NRs) exert crucial anti-inflammatory effects, while muscarinic receptors (MRs) can promote inflammation by triggering the release of pro-inflammatory cytokines.

Notably, the SARS-CoV-2 spike protein bears resemblance to neurotoxins, capable of binding to nicotinic acetylcholine receptors (nAChR) within both the autonomic nervous system (ANS) and the brain. The cholinergic dysfunction observed in COVID-19 arises from the dysregulation of nAChR by SARS-CoV-2, consequently driving central sympathetic activity and culminating in sympathetic storms (NADWA EH, et al., 2022). Thus, the manifestations of COVID-19 may be due to impaired cholinergic neurotransmission

associated with the regulation of neuroinflammation. This hypothesis is based on the fact that the cytokine storm in COVID-19 can be explained by the dysfunction of anti-inflammatory cholinergic signaling pathways. Therefore, α7 nicotinic acetylcholine receptors are potentially involved in modulating the secretion of pro-inflammatory cytokines.

Thus, the clinical manifestations of COVID-19, such as anosmia and thromboembolic complications, may also be linked to dysfunction of the nicotinic cholinergic system (FARSALINOS K, et al., 2020). Mitochondria also participate in the pathogenesis of Covid-19. Another theory suggests that dysfunctional mitochondria and associated altered bioenergetics in infected host cells lead to altered energy metabolism in the brain of Covid-19 patients. The interaction between viral proteins and mitochondrial proteins also provides evidence for mitochondrial involvement in SARS-CoV-2-induced brain dysfunction (MAURYA SK, et al., 2022). Mitochondria act as essential regulators in various biological processes, including innate and adaptive immune responses, development, maintenance and activation of immune cells.

They exert a significant influence on signalling and transcription pathways in immune cells, modulating ATP levels, metabolic pathways and releasing reactive oxygen species and mitochondrial DNA signals. Mitochondria can dynamically influence macrophage (M) phenotypes, changing from pro-inflammatory (M1) to anti-inflammatory (M2) states by adjusting respiration patterns. In addition, the outer mitochondrial membrane harbours the mitochondrial antiviral signaling protein (MAVS), activated by the retinoic acid-inducible gene I (RIG-I) of the viral RNA sensor, contributing to antiviral defense mechanisms. In macrophages infected with RNA viruses, MAVS interacts with the antiviral protein viperin, affecting interferon levels.

The proper functioning of the MAVS mitochondrial response is very important in COVID-19 infection because the survival and replication of the virus depend on the energy production of the host's mitochondria, which can be affected by the virus itself, highlighting the complex interaction between mitochondrial function and SARS-COV-2 infection (KLOC M, et al., 2020).

In this sense, mitochondrial defects and dysfunction may create an intracellular environment capable of aiding SARS-CoV-2 replication and assembly in specific cells. Thus, the severity of SARS-CoV-2 among patients with primary and secondary COVID-19 mitochondrial disease is potentially linked to high SARS-CoV-2 replication and assembly. Finally, it is interesting to note that cytokine storms may be mediated due to impaired mitochondrial vitality resulting from several factors, including oxidative stress, environmental chemicals, and biological agents, including viruses (SHARMA NK and SARODE SC, 2022).

FINAL CONSIDERATIONS

The physiological basis of the neurological and sensory disturbances arising from COVID-19 is not yet fully understood. The probable mechanisms of the development of ageusia/dysgeusia in COVID-19 include hyperactivation of inflammatory processes in the nervous tissue, such as direct damage to taste sensory neurons by viral particles and impairments in taste function. Thus, the degree of impairment of the taste system may establish the duration of taste disturbances. On the other hand, ageusia and anosmia may be seen as a missing link in the neuroimmunology of COVID-19, because although the CNS is an immunocompetent area, the disease caused by coronavirus has demonstrated that these CNS immune barriers may be impaired by viral mechanisms not yet fully elucidated. Nevertheless, several important questions related to the molecular aspects of the severity of SARS-CoV-2 infection still need to be answered. A better understanding of the neuroinvasive properties of SARS-CoV-2 and the neurological complications of COVID-19 will be important to improve patient outcomes.

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