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Review Article

Anosmia and Ageusia in COVID-19: Updating its Pathophysiology, Diagnosis and Treatment

Enrique Arturo Lombana Salas[I*], Moisés Andrés Lombana Salas[2], María Camila Miranda Jiménez[2], Michelle Bedoya Coronel[2], Wendy Yulieth Herazo Madera[I], Andres Felipe Ducuara Hernandez[2]

[1]General Medical, University of Sucre, Sincelejo – Sucre- Colombia. [2]5th Year Medical Student at the University of Sucre, Sincelejo- Sucre- Colombia

ABSTRACT

Infection caused by the new coronavirus SARS-CoV-2 produces different clinical manifestations, including anosmia and ageusia, which can occasionally be persistent after the disappearance of other symptoms, which is the reason for the current review, with the aim of presenting the pathophysiology, diagnosis and management of these alterations in an updated manner. Through a search in scientific databases and worldwide recognized organisms in Health, evidence published since 2019 was compiled, where answers were found to new physio pathological bases that explain such disorders, such as the cofactor Neurolipin 1; and effective subjective methods for the diagnosis, as well as objective tests generally used by specialists, finally in terms of treatment there are described varieties ranging from olfactory training to the use of corticoids. In conclusion, the aspects studied related to the manifestations of COVID19 are constantly providing pathophysiological answers and therapeutic alternatives.

Keywords: *anosmia, ageusia, COVID-19, sensory dysfunction*

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***Corresponding Author**

Enrique Arturo Lombana Salas
General Medical, University of Sucre, Sincelejo – Sucre- Colombia
Email: Enrilombana19@gmail.com

INTRODUCTION

Infection by the new coronavirus (COVID19) was declared a pandemic by the World Health Organization (WHO) in March 2020[1] and has caused deaths in millions of people.[2] Emergency vaccination against SARS-CoV-2 has been available since December of the same year, since when thousands of vaccines have been administered; however, infections and their fatal outcomes continue.[3] Approximately 153 million people have been infected and 3.2 million were reported dead as of May 1, 2021.[4]

SARS-CoV-2 is a single-stranded RNA virus composed of an envelope, membrane, and spike that binds with high affinity to the angiotensin 2 receptor (AGT2) expressed in various tissues of the human body.[5] The infection has different clinical manifestations: fever, dry cough, dyspnea, myalgias, nausea/vomiting or diarrhea, headache, weakness, rhinorrhea, anosmia and ageusia,[6] the latter two are considered manifestations of great negative impact due to the importance of mentioned senses in the interaction with

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the environment,[7-9] which has led to the initiation of several studies, one of which showed that 79% and 54% of the patients had loss of smell and taste respectively, and in 32% of the cases the first manifest symptom was loss of smell, which would indicate that in addition to the repercussions in daily life, these disorders could be considered an early marker of infection.[10]

Due to its repercussions and considering that in some patients there are persistent presentations, ageusia and anosmia caused by COVID19 are conditions that deserve to be reviewed in light of the scientific literature, therefore, the following article aims to provide a literature review with a view to elucidate aspects such as: pathophysiology, diagnosis and treatment, leaving updated information to serve as a reference for medical personnel.

Bibliographic review

A literature search was performed in scientific databases: PubMed, WorldWideScien, SciELO, LILACS collecting information from 2019 to 2021, using the following descriptors: anosmia OR ageusia AND COVID19, anosmia AND COVID19, ageusia AND COVID19, Anosmia OR COVID19 AND treatment, ageusia AND COVID19 AND treatment. Original articles, clinical trials, meta-analyses, systematic reviews, clinical practice guidelines, expert recommendations, letters to the editor, mini-reviews, and review articles were selected; in addition, we searched the web pages of international health organizations: World Health Organization (WHO) and Pan American Health Organization (PAHO).

Key points of olfactory perception

The process of olfactory perception involves the interaction between odoriferous substances and chemoreceptors located in olfactory sensory neurons (OSN), which are activated and allow the passage of the nerve impulse to the olfactory bulb, the amygdala, the hippocampus, and then to the primary olfactory cortex where it is interpreted.[11]

For the pathophysiological understanding of SARS-CoV-2 infection and its underlying olfactory disorder, it is necessary to name key points of the olfactory epithelium (OE), a crucial structure in the explanation of such clinical manifestation. The OE is composed of sustentacular cells, olfactory sensory neurons, stem or basal cells, microvillous cells and Bowman's gland cells, see Figure 1.[12]

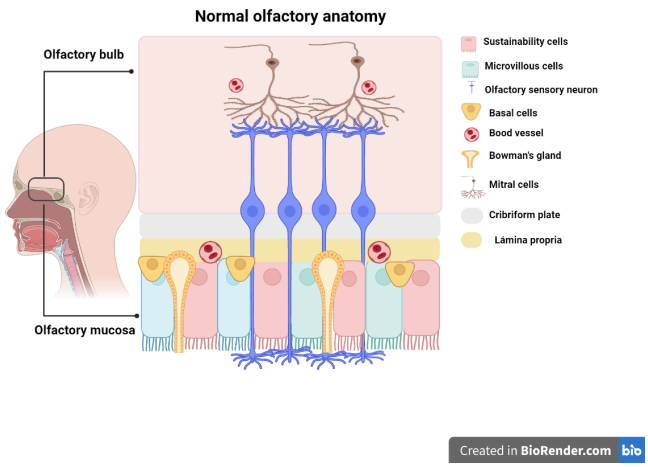

Figure 1: Normal olfactory anatomy.
The sustentacular cells: they have microvilli in their apical part and play an important role in the protection and isolation of the OSN due to their detoxifying function when there is inhalation exposure to toxic substances, they also play a role in the regulation of the hydro electrolytic balance and glucose supply to the cilia. Microvillous cells: they have microvilli in their upper portion, and these reach the nasal cavity, their function in the EO is not clearly identified. Olfactory sensory neuron: they are described as specialized bipolar cells, and their formation is given by "a single dendrite from which the cilia protrude into the mucosal layer of the surface epithelium and a myelinated axon that projects into the olfactory bulb". Basal cells play a very important role in the regeneration of the EO, coming to divide and differentiate into any cell that makes up the EO. Bowman's gland cells, which perform various protective, immunological, and mucus-producing functions; where odor-binding proteins are found, which are responsible for carrying odorous particles to the OSN cilia, generating odor detection.[13] Created with BioRender.com

Pathophysiology

Entry of the virus into the host organism

The entry of SARS-CoV-2 occurs through the interaction of its peak protein (S) with the angiotensin converting enzyme 2 (ACE2), and with the help of the transmembrane protease type 2 (TMPRSS2), which is responsible for separating a specific point of this protein generating a direct connection between the C-terminal domain (CTD) of the peak and ACE2.[5,14] Other transmembrane and intracellular proteases have been named as possible mediators in the virus infection process in the host cell, such as: TMPRSS4 and Cathepsin L (CTSL).[14,15] Recent studies have shown that the presence of Neuropilin-1 (NRP1) is crucial in the infectivity of SARS-CoV2, making it a new cofactor that potentiates the binding of the virus peak protein with ECA2.[16]

The presence of ECA2 in a tissue generates greater susceptibility for it to be infected by SARS-CoV-2; in the human body there are many organs that express ECA2: "the lung parenchyma, gastrointestinal tract, nasal mucosa, renal and urinary tract, epithelium of the human respiratory tract, lymphoid tissues, reproductive organs, vascular endothelium and brain".[17] It is believed that SARS-CoV-2 infection initiates in the nasal mucosa following the route of the olfactory nerve, then to the olfactory bulb, to finally disseminate in the central nervous system (CNS), a situation that was demonstrated in studies performed in mice[18] Its entry through the nasal mucosa could be explained by the expression in this region of: TMPRSS2, ACE2 and NRP1.[16,17,19]

Anosmia

Previous pathophysiological hypotheses

The pathophysiology of anosmia in COVID19 infection has been explained by different hypotheses such as the association of edema that generates obstruction in the olfactory cleft causing conduction loss,[20] to alterations in olfactory sensory neurons,[21] as well as transient edema of the olfactory bulb.[22]

Despite the above, some evidence indicates that OSNs do not express RCT2 and TMPRSS2, which are essential in the invasion process by SARS-CoV-2, suggesting that other cells found in this anatomical region that do express RCT2, TMPRSS2 and other genes involved in virus coupling are involved, such as non-neuronal cells: sustentacular cells, basal cells, Bowman's gland cells and perivascular cells.[13,5] From this, the idea that the pathophysiological mechanism of anosmia would not be explained by damage to neuronal cells but to non-neuronal cells is contemplated.[13]

New findings

Recent findings of the role of Neuropilin-1 (NRP1) as an enhancer in the process of virus infectivity suggest a restructuring of the already known pathophysiological processes involved in the appearance of anosmia, supported by a study published in May of this year, performed in hamsters and human autopsies, where by immunofluorescence techniques the presence of SARS-CoV-2 was established in olfactory neuroepithelial cells of the olfactory type: mature and immature olfactory sensory neurons, sustentacular cells and myeloid cells, this could perhaps be explained by the presence of NRP1 in OSNs which would significantly enhance SARS-CoV-2 infectivity.[16,23]

Mechanism of cell injury

The association of SARS-CoV-2 infection in olfactory neuronal and non-neuronal cells with the presence of cytokines and inflammatory mediators such as IL6, Ccl5, Isg20 and Mx1, would explain a local inflammatory process that would lead to the transient loss of the ciliary epithelium of sustentacular cells and OSN. Subsequently, programmed cell death would be generated in infected and non-infected cells, in the former by the cytopathic effect of SARS-CoV-2 and in the latter by the same local inflammatory process.[23]

Current pathophysiological approaches

Taking into account the different physio pathological processes that are not mutually exclusive, the olfactory disorder could be explained as follows: (See Figure 2) firstly, the infectious process in vascular and sustentacular cells would generate local inflammation with release of cytokines and inflammatory mediators causing conduction block with negative effects on OSNs, secondly, damage to sustentacular cells would alter important functions such as: glucose supply to OSN cilia, in addition to a hydro electrolyte imbalance, indirectly affecting OSN functions, thirdly, damage to Bowman cells will decrease mucus production, a process that is crucial for odor transport and finally as recently added evidence, direct damage to OSN by SARS-CoV-2, which would directly hinder the olfactory perception process developed by these.[5,13]

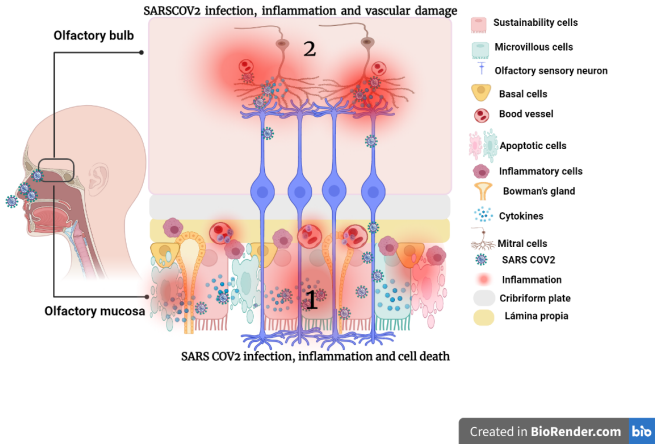

Figure 2: Pathophysiological mechanisms involved in taste loss. SARS COV2 infection of sustentacular cells, microvillous cells, stem cells, Bowman cells, and olfactory sensory neurons, with subsequent cytokine-mediated inflammatory process and induction of cell apoptosis. 2. SARS COV2 infection with subsequent cytokine-mediated inflammation and endothelial damage. The above processes would directly or indirectly hinder the neuronal signaling process resulting in loss of olfaction. *Created with BioRender.com*

Mechanisms involved in the persistence of anosmia

In relation to anosmia, anecdotal studies in hamsters have shown partial recovery from epithelial damage caused by SARS-CoV-2 infection in an average of 14 days. A systematic review published in May of this year found that the average duration of this condition does not extend beyond 14 days in most cases of those who recover, however, it is described that a considerable number of patients reported persistence of anosmia even for a month after the disappearance of the other symptoms.[24,25]

A study carried out in 121 patients corroborated the duration of these symptoms for more than one month in 21% of them with a mean of 15 days.[26] In another study performed in 89 French patients with anosmia and/or ageusia, 29 patients (32.6%) reported persistence of symptoms up to 60 days.[27]

There are several follow-ups where persistence of anosmia and ageusia is reported, highlighting the one that determined taste and smell disorders up to 125 days after the resolution of the other symptoms.[28]

The persistence of anosmia raises many questions as to the associated pathophysiological mechanisms. Recently, a study provided information in this regard, finding the presence of SARS-CoV-2 RNA in the neuroepithelium of patients with prolonged duration of anosmia or without loss of smell but with long-lasting COVID19 symptoms and negative nasopharyngeal RT PCR tests at the time of consultation, as well as the presence of inflammatory mediators, IL6-type cytokines and apoptotic cells, suggesting an inflammatory process with evident cell death, which was milder in the patient without loss of smell. This leads the investigator to hypothesize that:" the persistence of COVID-19 associated loss of smell is related to inflammation caused by persistent infection".[23]

Ageusia

Key points in taste perception

The transmission of taste sensation occurs from the interaction of chemical substances (flavoring) with taste buds: fungiform, circumvallate and foliated, located in different regions of the tongue and throughout the oral cavity. After interaction, the signal goes through cranial nerves VII, IX and X to the gustatory area (nucleus of the solitary tract) in the midbrain, goes to the thalamus in the region of the central tegmental tract, and finally to the cortex where it is interpreted.[29]

The integration of the sense of smell in the perception of flavors is fundamental because during chewing odiferous substances are released and perceived by the OSNs, adding olfactory sensory information to the food being chewed complementing taste perceptions (sweet, salty, sour, bitter and umami).[30]

The role of ACE2 in taste modulation is not completely defined; apparently, in taste receptors there is an inactivation of G protein-associated proteins and sodium channels in patients taking ACE2 inhibitors (ACE inhibitors) and angiotensin II antagonist (ARA2) drugs, generating taste disorders, which remit after discontinuation of the drug.[31]

Pathophysiological approaches

Due to the perceptual relationship between smell and taste, anosmia resulting from COVID19 could consequently lead to taste dysfunction, but previous data reflect that taste alterations were present alone in 10.2% to 22.5% of the patients.[31,32]

The expression of ECA2 in the oral mucosa with predominance in the lingual epithelium (where the greatest number of taste buds are found) was demonstrated by Hao Xu and collaborators, who support the idea that the interaction of SARS-CoV-2 with these receptors in the oral cavity is not only a gateway for the virus to enter the body, but also the cause of the underlying olfactory dysfunction.[33,34]

An alteration in the regeneration of taste buds secondary to an inflammatory process mediated by proinflammatory cytokines such as TNF-α, IFN-γ and IL-6, cytokines highly expressed in SARS-CoV-2 infection, suggests an explanation for ageusia due to subsequent cell damage derived from this process, which not only affects stem cells in charge of regeneration, but also affects taste cells already mature, hindering the process of taste perception.[33,35]

The affectation in the salivary glands in rhesus macaque monkeys during infection by SARS-CoV-2 suggests that in humans it is possible that there is also an alteration in these, presenting a dysfunction of the salivary flow affecting its quality and quantity causing the subsequent taste alteration.[32,36]

As it was suggested in the pathophysiological mechanism of anosmia with direct affection to neuronal cells, it is possible that in ageusia the cytopathological effect of SARS-CoV-2 generates a direct damage in the cells that express ECA2 of the taste buds and in the neurosensorial chemoreceptors of peripheral taste, or by direct damage to cranial nerves (VII, IX, or X) where the virus affects the tympanic cord by entering the Eustachian tube through the previous infection of the nasopharynx, a situation that would generate dysgeusia.(36)

Other hypotheses that support the neurotropism of the virus suggest that it affects the olfactory and facial nerve, through its passage through the cranial nerves (VII, IX and X) generating alterations in the gustatory sensoperceptive endings.[37]

Cell signaling pathways have been proposed as triggering factors of ageusia, involving Toll-like receptors and their interaction with SARS-CoV-2, where programmed cell death is generated with abnormal papillary regeneration and gustatory distortion.[32]

Other hypotheses suggest that the binding of SARS-CoV2 to the receptors of cyanoic acid, which fulfills protective functions to the transport of taste molecules, could generate an accelerated destruction of these molecules, generating the subsequent olfactory affection.[32,33]

Diagnosis

The evaluation of olfactory and gustatory perceptual disturbances is predominantly performed subjectively, a systematic review showed that self-report establishes a high prevalence of olfactory and taste disturbance in patients with COVID19, compared to other viral infections or controls.[38]

In turn, objective evaluations are also useful in the search for the aforementioned perceptual dysfunctions, with psychophysical tests for diagnosis.[24]

Regarding the application of both, a higher prevalence of ageusia and anosmia has been demonstrated in subjective tests, compared to psychophysical tests, in addition to 50% sensitivity and 80.59% specificity for the former, versus 19.44% and 95.52% respectively for the latter, according to the study conducted in a Mexican Hospital.[39] In another publication that took results from 2013 European patients with mild to moderate COVID19, self-reported tests yielded a higher prevalence of taste and smell disorders.[40]

Likewise, a prospective multicenter study supports obtaining subjective information: "the high predictive value and specificity of self-reported loss of smell and/or taste, among other classic symptoms, could help to make a presumptive diagnosis of COVID-19".[41]

Evidence also yields data in favor of the use of objective tests such as a case series, where using a Q-SIT" test (individual, disposable tear-off cards each containing three microencapsulated odor strips"), It was determined that "it is possible to detect more subtle degrees of olfactory dysfunction in COVID19 than patients subjectively report".[42]

A cross-sectional study that also used objective tests identified that in a relevant number of patients where loss of smell was not a reported symptom, the presence of this dysfunction could be ascertained by the application of the objective test; Furthermore, the finding of an olfactory dysfunction rate of 83%, which is high in comparison with those reported up to the time of the publication of this study, stands out.[43]

From the above it is established that, in spite of having objective tests that measure the perceptual dysfunction in taste and smell, the patient's subjectivity is a valid resource for the diagnosis of such alteration.[24] Diagram 1 shows some subjective and objective tests that are available.

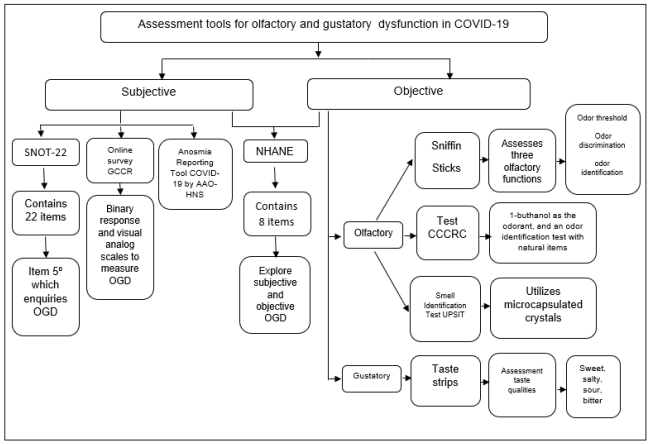

Diagram 1: Subjective and objective tests analyzed in: "Olfactory and gustatory dysfunctions in SARS-CoV-2 infection: A systematic review". SNOT22: Sino-nasal outcome test. OGD: Olfactory and gustatory dysfunction. GCCR: Global Consortium for Chemosensory Research. AAO-HNS: American Academy of Otolaryngology-Head and Neck Surgery. NHANES: National Health and Nutrition Examination Survey. CCCRC: Connecticut Clinical Chemosensory Research Center Test. UPSIT: University of Pennsylvania Smell Identification Test.[24,29,42]

Treatment

The recovery of the olfactory and gustatory function in patients who have had COVID19, in most of the cases takes no more than 20 days, in these patients a specific treatment for these conditions is not necessary, however in patients in which the dysfunction of smell and taste is persistent for more than two weeks it is necessary to consider the application of a therapy.[32,44] Different treatments have been proposed for the treatment of these conditions, which are described in Table 1.

Table 1. Anosmia treatment and evidence reports

Treatment	Evidence Reports
Olfactory training	Based on brain neuroplasticity with poorly elucidated cellular mechanisms,[45] it is the only current treatment for olfactory dysfunctions, which has shown improvement in patients with post-infectious olfactory disorders in meta-analyses.[46,47] The classic treatment consists of exposure to 4 odors (phenyl ethyl alcohol, eucalyptol, citronella and eugenol) for 5 minutes twice a day, which has been shown to improve olfaction for 12 weeks or more.[48] A modified training proposed in 2015 by Atuldang et al. proposes exposure for 5 minutes, 2 times a day of the 4 odors used in the classical method for 12 weeks, followed by 12 more weeks of exposure to (menthol, thyme, mandarin and jasmine) and a final 12-week exposure of 4 more odors (green tea, bergamot, rosemary and gardenia).[49] Another olfactory training proposed by Whitcroft and Hummel consists of using odors such as rose, lemon and eucalyptus for 20 weeks each, twice a day for at least 90 days. In addition to meta-analysis, olfactory training is supported by the British Rhinological Society (BRS) consensus for use in patients who persist with olfactory loss for more than 2 weeks.[50]
Corticosteroids	Corticosteroids used in post-infectious olfactory dysfunction have shown benefits,[44] a limitation in their use is that their improvement effect is only maintained while the treatment is used.[32] There are studies against and in favor of the use of corticosteroids for the treatment of olfactory dysfunction, against is a study that compared a nasal spray of mometasone furoate as a topical corticosteroid vs. olfactory training, the former did not demonstrate benefits of superiority in olfactory scores, duration of anosmia and recovery rates.[51] In favor is a randomized multicenter study conducted in 18 patients suffering from COVID19 with hyposmia or severe anosmia of more than 30 days duration, who were administered oral corticosteroids (prednisone) and nasal irrigation with betamethasone, ambroxol and rinazine for 15 days of administration, the study concluded that corticosteroids in association could reduce the prevalence of these olfactory disorders.[52] Recommendations in favor of the use of corticosteroid nasal sprays and drops are those of the BRS consensus, which suggest their use in patients with more than 2 weeks of anosmia, but do not recommend the use of oral corticosteroids.[50] On the other hand, the lack of clear evidence to support the use of oral or topical corticosteroids for patients with anosmia could limit their use, as stated by the consensus of the Clinical Olfactory Working Group.[48]
Caffeine	Caffeine improves the sense of smell and taste in patients with COVID19, the effect of this depends on whether the patient has (hypertension, diabetes and heart disease) or not comorbidities, if he has the efficacy is presented in 2 to 4 days and if he does not have, it is presented in 5 to 7 hours[32] Studies described by Stafford and Orgill, where the effects of caffeine in inhalation tests were investigated, demonstrated that the effects on the odorous threshold may be greater in patients who are habitual consumers of caffeine and in older subjects, based on the A2a adenosine receptors for which caffeine has affinity, which could participate in olfactory dysfunctions, these would be temporarily reverted by caffeine.[32,53]
Vitamin A	Vitamin A with its metabolite: retinoic acid which participates as a transcriptional regulator in the development and regeneration of tissues function may be useful in the regeneration of the olfactory neuroepithelium and olfactory bulb in patients with COVID19 who have lost their sense of smell.[44,32] A study described by Neta and collaborators have shown benefit of the use of vitamin A in patients with post-infectious and post-traumatic loss of olfactory function and even more if associated with olfactory training.[32] On the other hand, a double-blind, randomized, placebo-controlled clinical trial concluded that "Systemic application of vitamin A at a dose of 10,000 IU per day for 3 months does not appear to be useful in the treatment of post-infectious or post-traumatic olfactory loss".[54] The BRS consensus does not recommend the use of vitamin A for this purpose, as do Hura and colleagues.[55]
Zinc sulfate	Zinc deficiency as a micronutrient that regulates immune responses can lead to loss of smell and taste, as zinc-dependent carbonic anhydrase, which is involved in the perceptual processes of taste and smell, is found to be low.[56,32] This is supported by a clinical trial described by Neta et al. in which patients with COVID19 infection who received zinc therapy showed improvement in smell in a significantly shorter time.[32] However, the consensus of the Olfactory Clinical Working Group led by Addison described that all studies involving the use of zinc sulfate for the treatment of post-infectious olfactory loss did not demonstrate statistically significant improvement.[48]
Theophylline	Theophylline would function by inhibiting phosphodiesterase and increasing secondary messengers such as cyclic adenosine monophosphate and cyclic guanosine monophosphate thus achieving regeneration of the olfactory neuroepithelium.[48] Several studies mentioned by Neta and collaborators corroborate the benefit of theophylline in patients with olfactory dysfunction and even more if it is used intranasally where it decreases systemic effects and acts on the stem cells of the olfactory epithelium generating regeneration of this.[32] Hura and collaborators on the contrary recommend the realization of randomized controlled trials with theophylline since the existing ones did not involve control groups.[55,32]
Alpha Lipoic Acid	"A-lipoic acid (ALA) is a fatty acid that is mainly used in the treatment of diabetic neuropathy. It stimulates the expression of nerve growth factors, substance P and neuropeptide Y, and has antioxidant and neuroprotective capabilities."[48] ALA can decrease the presence of inflammatory cytokines from reducing NADPH activity, in addition to decreasing the activity of angiotensin II converting enzyme and avoiding the replication of SARS COV2.[32] In turn, a prospective study where ALA was used in patients with post-infectious loss of smell, reported an improvement of 61% of patients, the limitation of this study is that it was not controlled.[57] In contrast, the BRS consensus states that "it is not recommended for a patient with LOS of more than 2 weeks as an isolated symptom or after the resolution of any other symptom of COVID-19"[50] , similar to that stated in the consensus of the Olfactory Clinical Working Group, which does not recommend the use of alpha lipoic acid for the treatment of olfactory disorders secondary to COVID19.[48] Omega-3 fatty acids Omega-3 fatty acids could generate a recovery process in the olfactory nerve through their anti-inflammatory and neuroregenerative effects and also function as adjuncts in olfactory therapy.[44,58] The BRS consensus states that omega-3 acids "are optional for a patient with isolated olfactory loss of more than 2 weeks as an isolated symptom or after resolution of any other COVID-19 symptom".[50]
Intranasal sodium citrate	Its beneficial effect is based on modulation of the olfactory receptor transduction cascade.[32] Two trials conducted by Whitcroft and collaborators in different years demonstrated, the first one an improvement in the olfactory threshold with the use of sodium citrate and the second one focused on patients with post-viral olfactory loss, where a significant improvement in the threshold plus a better identification of the compound was found after using sodium citrate, However, it was not superior to placebo, and the latter concluded that "more basic and clinical work is required to fully delineate the effect of intranasal sodium citrate in the treatment of post-infectious olfactory loss".[59,60] Regarding Hura et al, they state that sodium citrate offers benefits of temporary and short-term improvement with minimal side effects such as rhinorrhea, sore throat and nasal congestion but more studies of its long-term use are needed.[55]
N-methyl D-aspartate antagonist	The mechanism of action of carverine is not fully elucidated, it is believed to act in the olfactory bulb by inhibiting the feedback mechanism. Studies described by the Olfactory Clinical Working Group report significant improvement in patients with post-infectious olfactory loss who were treated with Carverine, however, this same group led by Addison states that well-designed randomized controlled trials are needed.[48]

DISCUSSION

Taste and olfactory dysfunctions in the course of COVID19 disease are prevalently high, which is why it is necessary to look at specific aspects of these. Firstly, with respect to olfactory alterations, their pathophysiology is currently defined by a series of factors that may converge and not be mutually exclusive; however, it is important to highlight the role of recent research in seeking to add new host factors as a gateway to SARS-CoV-2 and not just limit itself to what has already been established, Thus, according to the current evidence presented in this review, Neuropilin1 protein plays a fundamental role, which has been found in the olfactory epithelium and is believed to be related to SARS-CoV2 infectivity, in association with other factors such as ECA2 and TMPRSS2 receptors already known previously.[16,17,19]

The recently published study cited in this publication, carried out in hamsters and humans, which demonstrates the direct damage of SARS-CoV-2 on the neuroepithelium apparently due to the presence of NRP1, changes the hypothetical concept previously put forward on this damage mechanism. Currently, thanks to this study it is possible to propose a process of cell damage to the olfactory neuroepithelium, which added to the presence of cytokines, inflammatory cells, cell apoptosis generated by the damaging effect of the virus, in addition to the underlying inflammatory process, all of the above converge and end up generating death in non-infected cells.[23] Regarding this mechanism of cellular lesion, it is indicated to be the cause of the persistence of the loss

of smell in the patient who has recovered from COVID19, this is explained by a persistent process of inflammation with the presence of the virus in the neuroepithelium, situation that opens the possibilities of treatment.[23]

Ageusia is attributed to different mechanisms ranging from the specific such as the use of ECA2 receptors by the virus, the use of cyalic acid receptors, Toll-type signaling pathways and less specific mechanisms such as direct damage to the nerves responsible for the process of taste perception, in addition to taking into account the complement of the sense of smell in the perception of flavors.[32] Despite this, taste dysfunction occurs less frequently than smell dysfunction, perhaps due to the different taste perception pathways that exist involving different nerves, which give the sensation of temperature and texture of the food, not being limited only to the use of one mechanism of perception as it happens in the sense of smell.[32]

Ageusia and anosmia in the context of COVID19 infection have generated controversy as to how to make the clinical evaluation, either using objective tests or subjective tests, since the evidence supports the subjective one to make a diagnosis with good specificity, sensitivity and adequate negative predictive values, situation that raises questions about the objective tests that at the same time provide good specificity and sensitivity,[39,40,41] in any case the latter become part of the tools used by specialists in otolaryngology, and as for the general practitioner, he could stay with the subjective evaluation using the questionnaires mentioned in this review.

Finally, in terms of treatment, there is no specific therapy for these disorders, even less for ageusia. However, different therapies have been proposed in search of the resolution of these symptoms.[32]

In turn, corticosteroid treatment mediates the persistent inflammation caused by the presence of the virus in the neuroepithelium.[51] Although there is controversy about its benefit, the BRS consensus recommends that corticosteroids be considered in patients who persist with loss of smell for more than 15 days.[50]

This same consensus as well as the Olfactory Clinical Working Group agree in recommending olfactory training as a treatment, which seeks to expose the olfactory receptor neurons to different odors for a certain period of time, generating in them a greater growth and in turn greater expressiveness of olfactory receptors. Thus, taking advantage of the characteristics of the functional plasticity of the olfactory system, which could be the explanation for the success of olfactory training.[45,50]

With respect to other therapeutic options such as omega 3 fatty acids that would generate a recovery process of the olfactory nerve, it would be a treatment to consider ordering in patients who persist for more than 2 weeks with loss of smell according to the BRS consensus.[50]

The rest of the treatments such as caffeine, alpha lipoic acid, vitamin A, Zinc sulfate, sodium citrate, theophylline, carveline, all of them seem to be promising in terms of treatment of olfactory dysfunction, in fact the mentioned studies suggest their effectiveness, however, experts such as the Clinical Olfactory Working Group and BRS consensus suggest the realization of randomized controlled studies.[48,50]

CONCLUSION

In conclusion, anosmia and ageusia, as well as most aspects associated with SARS-COV-2 infection, are constantly updated. In this review, recent aspects of the medical evidence that allow elucidating new pathophysiological mechanisms and therapeutic approaches were added with the aim of improving the patient's quality of life during and after COVID-19. Regarding the objective / subjective diagnostic approach of the alteration in sensory perception, the controversy continues, however, in those countries with limited resources it has been demonstrated that the subjectivity of the patient in the context of the infection has a significant predictive value. Finally, in treatment, the current recommendations focused on the plasticity of the olfactory epithelium constitute a therapeutic approach with good results in the disorder of anosmia and open opportunities for future research in the management of ageusia.

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