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INCIDENCE AND ANALYSIS OF ANOSMIA AND AGEUSIA IN PATIENTS WITH COVID-19: A CROSS-SECTIONAL STUDY

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Abstract: The Covid-19 pandemic, declared on March 11, 2020 by the World Health Organization, has brought a series of worldwide socioeconomic and demographic repercussions. Therefore, several studies have emerged to understand its mechanism of action, its clinical findings and sequelae during and after the disease period. As with viral conditions in general, the most common symptoms found so far are fever, cough, nasal congestion, fatigue, which can progress to more severe inflammatory conditions, such as pneumonia and acute respiratory distress syndrome, and even coursing with peculiarities known as anosmia and ageusia, the loss or alteration of smell and taste, respectively. The SARS-CoV-2 virus entry mechanism leads to a pro-inflammatory environment. Therefore, this viral artifice can disturb the functions of the olfactory and gustatory receptors, since these impulses added to the somatosensory factor are directly linked to the gustatory sensation to be more effective, bringing with it the symptom of anosmia and ageusia. As these symptoms are poorly studied at qualitative and quantitative levels and generate a lot of discomfort in affected individuals, this present study aims to investigate the incidence and characteristics of these conditions for a better understanding of this topic. After authorization through the Certificate of Ethical Appreciation Presentation number 52262821.9.0000.5496, an online questionnaire was carried out through the Google Forms platform, together with the consent form, which reached a total of 101 individuals affected by Covid-19 as of 2020. The results showed that 75.2% of those affected by Covid-19 had anosmia/ageusia, 87% had both symptoms at the same time and there are reports of their spread to the present day. Finally, this work tends to contribute to a better understanding of the behavior of this condition in patients affected by Covid-19,

since these symptoms generate discomfort and can affect the affected individual in the long term.

Keywords: Ageusia. Anosmia. Covid-19.

INTRODUCTION

The Covid-19 pandemic, a disease caused by the single-stranded RNA virus called SARS-CoV-2, was declared on March 11, 2020 by the World Health Organization (WHO, 2020), which generated several global impacts at global levels. collective and individual, leading to an incessant search for more information, treatments and prevention for this pathology.

SARS-CoV-2 infects alveolar epithelial cells of the lung using receptor-mediated endocytosis via angiotensin-converting enzyme II (ACE2) as an entry receptor, which leads to widespread infection and oxidative stress, leading to the so-called "storm of cytokines", a condition closely linked to severe tissue damage (VELAVAN et al., 2020; DELGADO-ROCHE et al., 2020). Consequently, such an infection culminates in nonspecific signs and symptoms, similar to other respiratory viral infections, such as fever, cough with or without sputum, rhinorrhea, dyspnea, myalgia, diarrhea, headache, anosmia/hyposmia and ageusia/dysgeusia. It can also result in complications, such as chronic inflammatory conditions, pneumonia and acute respiratory distress syndrome (VELAVAN et al., 2020; DELGADO-ROCHE et al., 2020; KUMAR et al., 2021).

The senses of smell and taste have important adaptive functions and are essential for a perfect adaptation of the human being to the environment. It is a peculiar fact that, although they are not considered vital, these senses can have an important alarm function in situations such as the ingestion of spoiled food or the perception of a fire, despite being only valued when altered or lost in some way, altering the quality of life. life significantly (KUMAR et al., 2021). The loss or alteration of smell and taste are commonly the result of neurological diseases, but viral infections can also affect these pathways (FRANCO, 2018; KUMAR et al., 2021).

Particularly, olfactory and gustatory dysfunctions, in addition to a high incidence of Covid-19 infection, were most notably observed in the early stages of the disease (VAIRA et al., 2020; KUMAR et al., 2021). One study reported that 30% of confirmed COVID-19 cases in South Korea had anosmia as their primary initial symptom; in a letter to the editor sent to the journal Obesity, Jean-François Gautier and Yann Ravussin claimed to have observed cases of anosmia in patients after two to three days of fatigue and headache (GAUTIER et al., 2020). In the literature, one of the first studies reporting these findings, analyzed the frequency of neurological manifestations in 214 infected patients and found anosmia in 11 (5.1%) and ageusia in 12 (5.6%) cases (MAO et al., 2020).). In a single-center study with 72 patients, olfactory disturbances were reported in 61.1% of the sample during SARS-CoV-2 infection (VAIRA et al., 2020). Thus, there is an important search for understanding the mechanism of these symptoms and recovery, considering that they lead to great discomfort for patients, since quantitative and qualitative reports that assess neurosensory disorders in patients affected by the disease are rare.

The pathogenesis is thought to occur through direct damage of the virus to olfactory and gustatory receptors in acute COVID-19 infection, explained by the high expression of ACE2 and transmembrane serine-2 protease (TMPRSS-2) in nasal epithelial cells allowing entry viral, and invasion of the olfactory bulb causing damage to olfactory sensory neurons. (KUMAR et al., 2021). The explanation of these mechanisms is based on imaging findings,

presented in studies, such as, for example, a prospective study by the Association of University Radiologists involving 23 patients, which showed opacification of the olfactory cleft on computed tomography (CT), observed in 73.9 % of cases with middle and posterior segment dominance. 43.5% of the cases had olfactory bulb volumes below normal and 60.9% had shallow olfactory sulcus. Of the total, 54.2% of the cases presented alterations in the normal shape of the inverted J of the bulb. 91.3% of cases showed abnormality in the signal intensity of the olfactory bulb in the forms of diffuse increase in signal intensity, scattered hyperintense foci or micro-hemorrhages (KANDEMIRLI, 2020).

Therefore, this descriptive analytical cross-sectional study aims to more consistently assess the patterns of these symptoms, such as the incidence, onset, duration period and sequelae in relation to the olfactory and gustatory pathway in individuals who have already been affected by Covid-19. in order to generate more data to contribute to this line of research in the search for a better understanding of these phenomena and to promote a more specific recovery for these patients.

PHYSIOLOGY OF SMELL AND TASTE

The nasal epithelium contains olfactory epithelium (EO) and olfactory sensory neurons (NSOs). EO contains basal stem cells responsible for the renewal of the sustentacular (or support) cells that structurally support sensory neurons, detoxify and maintain salt and water balance. There are also mucus-secreting microvillar cells and Bowman's gland cells (ZHANG et al., 2020).

The olfactory process begins when odor molecules bind to NOS in the OS located in the nasal cavity, which later transmits this information through its axons to the olfactory bulb in the brain, located in the anterior cranial fossa. This way, there is a triggering of synapses in the glomeruli that promotes different odorant patterns for each type of odoriparous molecule, thus recognizing the odor (MUTIAWATI et al., 2021 ROMANO et al., 2021).

The tongue contains between 2,000 and 5,000 taste buds responsible for five basic taste sensations: sweet, salty, bitter, sour and umami. In addition, it has a tactile function of texture perception, allowing the stimulus to be conducted to the brainstem, where it synapses in the nucleus of the solitary tract, where there are interactions with olfactory stimuli and previous experiences. Thus, there is a modulation of taste perception in structures such as the brainstem itself, gustatory cortex, central nucleus of the amygdala and hypothalamus, thus allowing the triggering of physiological responses and sensations in relation to food (ROMANO et al., 2021).

PATHOPHYSIOLOGY OF ANOSMIA AND AGEUSIA IN COVID-19

Initially, it was hypothesized that, like other viral infections, the coronavirus resulted in anosmia due to nasal congestion, disrupting the interaction between odor molecules and olfactory receptors. However, this theory was discarded after studies reported that the presence of anosmia was more prevalent than nasal congestion in patients with COVID-19. Furthermore, nasal obstruction in viral infection occurs as a subsequent event after damage to the mucociliary system, thus inhibiting nasal discharge and leading to nasal obstruction.

Today, SARS-CoV-2 is believed to infect cells through the interaction between its spike protein (S) and ACE2 on target cells. This interaction requires cleavage of the S protein by the cell surface protease TMPRSS2. Thus, it

is suggested that SARS-CoV-2 can infect EO that contain sustaincular cells, leading to EO damage and disrupting the function of NSOs. The loss of sustentacular cells and the inability to regenerate OS over time can result in long-term anosmia. Furthermore, damage to microvillar cells in OS can alter iron gradients and thus affect sensory neuron function. Damage to Bowman's gland cells can cause disruption of the olfactory neuroepithelium (ZHANG et al., 2020).

Although the attack on receptor neurons is considered to be the main mechanism of disturbance in the sense of smell, this hypothesis remains under debate. Several recent studies have reported the absence of ACE2 and TMPRSS2 in NSOs, the main factors responsible for the entry of the virus into the cell. Furthermore, when analyzing the duration of anosmia in COVID-19 patients and the cellular regeneration process of NSOs, it was found that anosmia disappears within 1-2 weeks, while the regeneration of dead NSOs requires more than 2 weeks. However, there is evidence that SARS-CoV-2 causes disruption of the olfactory center, starting from the olfactory bulb, the trajectory of the axons of NSOs (MUTIAWATI et al., 2021).

The impact of SARS-CoV-2 on smell is one of those responsible for the change in taste perception, while it has previously been shown that viruses, including coronavirus, can spread to the olfactory bulb or piriformis complex, although the mechanisms exact action are unknown. This is because the sensation of flavors is enhanced with a combination of gustatory, olfactory and somatosensory impulses together (ZHANG et al., 2020). Furthermore, taste alteration is directly related to ACE2 expressed in tongue epithelial cells and pro-inflammatory cytokines, which will be further explored in the discussion of the present study (NAJAFLOO et al., 2021).

METHODOLOGY

The understanding of this topic required a physiological understanding of the olfactory and gustatory system, more specifically at the neuronal level, in addition to the analysis of studies previously carried out in relation to the subject, mainly the mechanism of the pathogenesis of viral infections, as in Covid-19, and the way in which it affects in these two important senses for the human being, since it is a social being that deals with these stimuli constantly. Therefore, the primary search was performed in the PubMed and Google Scholar databases for articles from 2018 that covered the subject in question, 16 of which were selected for the construction of this research.

Therefore, given that the sudden loss of smell presents 65% and 97% of sensitivity and specificity, respectively, in the diagnosis of Covid-19, which has a great impact on the positive predictive value, that is, if positive, it is unlikely that the individual is not, in fact, sick (HAHNER et al., 2020) and as he was still in a critical period of the pandemic, a consent term was sent for data collection that covered the socio-demographic area, in addition to the term of free and informed consent and an online questionnaire on the subject in question through the Google Forms platform after authorization through the Presentation Certificate of Ethical Appreciation number 52262821.9.0000.5496 on December 16, 2021 and carried out through the Scientific Initiation Program of Unimar. The same was disclosed in social network groups at the University of Marília, as well as other study groups, such as academic leagues and university extensions related mainly to the health area. In the end, 101 individuals over 18 years of age affected by Covid-19 were analyzed. Questions were raised about the decrease in smell and taste during the period of infection by Covid-19, whether anosmia

and ageusia actually occurred, when they started, how long it lasted, if there is still change in these senses until the present day. and, finally, reports and explanations were requested for this last question.

Data collection took place from February to April 2022. Thus, the collection was completed and the responses were tabulated using Excel, using parametric and non-parametric tests according to the variables to, finally, have a validation of the final records and a complete development in relation to the analysis and conclusion on the topic.

RESULTS

After checking the data, it was observed that 75.2% reported anosmia/ageusia during the period of infection, with a mean age of 24,327. The results were arranged in tables and graphs comparing the variables, shown below.

DISCUSSION

In fact, it is observed that the majority (75.2%) of those affected by Covid-19 in this research presented anosmia/ageusia. As well as in other research carried out, as reported by Zheng et al., when analyzing the susceptibility of K18-hACE2 mice to SARS-CoV-2. In this research, one of the tests performed was the buried food, in which each mouse had 4 minutes to find the food and the data were analyzed by the χ 2 Fisher's exact test. In the end, it was observed that they were widely affected, identifying a brain involvement by the virus, including the olfactory bulb, cerebral cortex, putamen, thalamus, hypothalamus and ventral striatum. Virus replication in the upper respiratory tract was also evaluated, which was detected in the respiratory and olfactory epithelium, in nerve bundles underlying the olfactory epithelium and occasionally in the vascular endothelium and Bowman's glands. At the sites of antigen positivity in the olfactory epithelium and maxillary sinus, we observed cell death and cell debris, which progressed to cell desquamation and loss of cellularity, which leads us to the conclusion that anosmia is interconnected between the direct involvement of the upper airway, as well as the nervous system itself (ZHENG et al., 2021).

In addition to smell, the loss or alteration of taste is related to ACE2 expressed in epithelial cells of the tongue. In the present study, 87% of those who reported anosmia also reported ageusia during the current period of infection. This is because this enzyme was detected as the functional receptor for the Covid-19 virus and is increased in the infection in sustentacular cells, which leads to a pro-inflammatory environment and acts directly on the alteration of smell and taste, either through obstruction. by nasal edema/congestion resulting from the inflammatory process or even directly by the release of cytokines in the OS, such as tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6), represented in Figure 1 (NAJAFLOO et al., 2021).

IL-6 plays a significant role in these sensory changes by activating apoptotic pathways through TNF-α and directly inhibiting olfaction. Significant correlations were found between decreased levels of IL-6 and the time required for recovery from anosmia secondary to COVID-19, which opens the door to thinking about prolonged cases of anosmia/ageusia in some patients (CAZZOLLA et al. 2020).). In the current research, the absolute number of people who did not have sequelae is higher than those who did. However, the number of people in whom there was maintenance of olfactory and gustatory sequelae, concomitantly, predominates in relation to sequelae exclusively of smell or taste. This can be explained by molecules such as cytokines, including IL-6, IL-12, IL-15 and TNF-α, which are increased in virus-infected

Of those who had a change in smell, how many also had a change in taste?	
71	had an altered sense of smell (including Yes and Sometimes)
62	of them also had taste alterations (including Yes and Sometimes)
87%	of people who had a smell change also had a taste change

Table 1: Absolute value and percentage of people with taste alteration in relation to those who had olfactory alteration.

Of those who had a change in smell, how many had sequelae?
71 had an altered sense of smell (including Yes and Sometimes)
24 of them maintained olfactory impairments (including Yes and Sometimes)
34% of people who had a change in smell maintained sequelae in smell

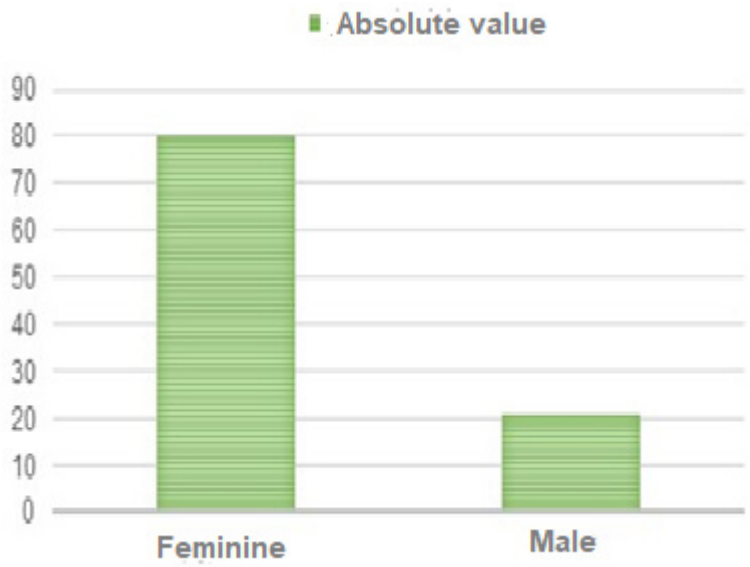
Table 2: Absolute value and percentage of people with maintenance of olfactory sequelae.

Of those who had taste alterations, how many had sequelae?
67 had taste alteration (including Yes and Sometimes)
16 of them maintained sequels in the taste (including Yes and Sometimes)
24% of people who had taste alterations maintained taste sequelae

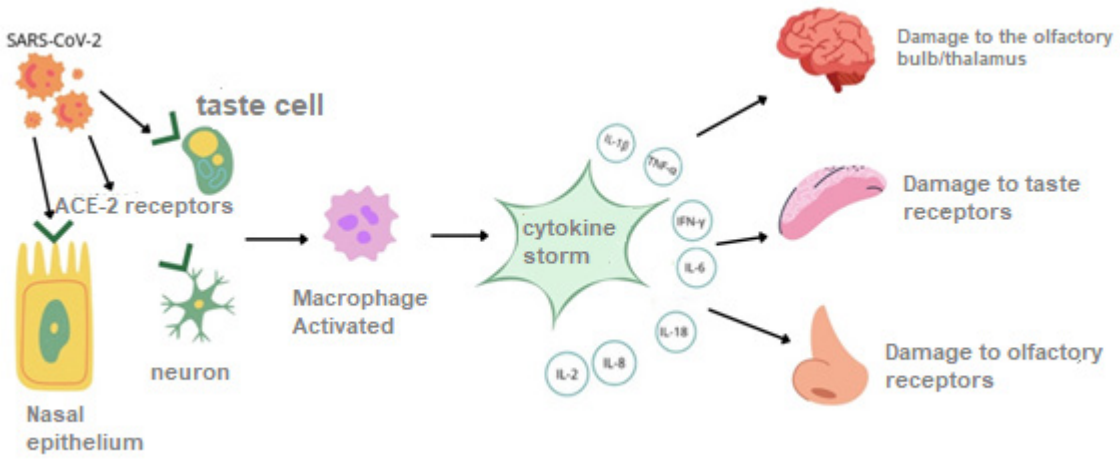
Table 3: Absolute value and percentage of people with maintenance of taste sequelae.

Change in smell and taste in days		
	Smell	Taste
Average start	5,7	5,8
Average duration	4,9	5,1

Table 4: Estimating time in days of onset and duration of symptoms.

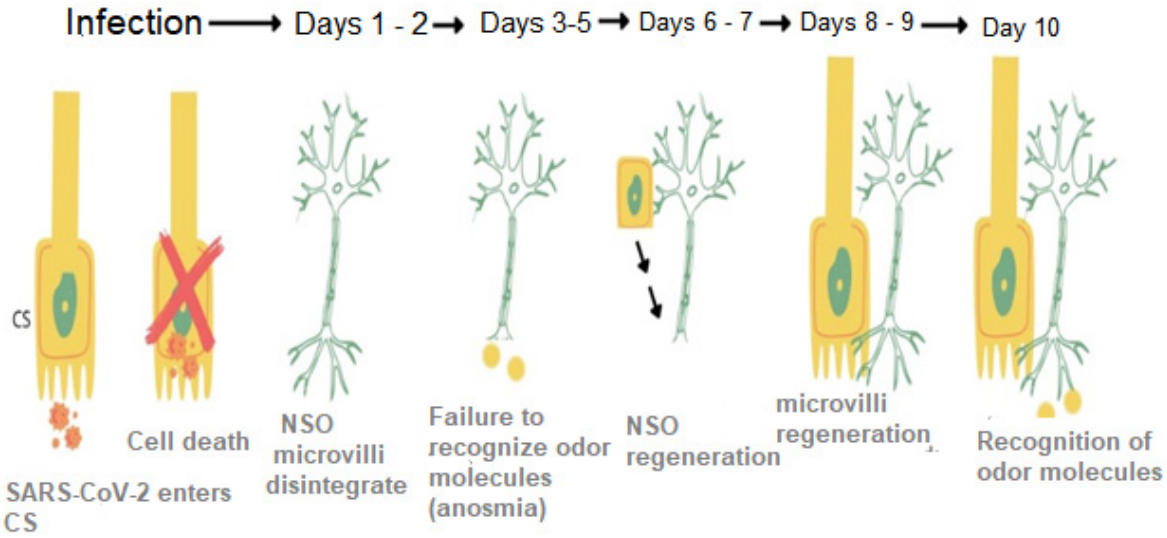


Graph 1: Amount participating in absolute value by sex.



Notes: ACE-2, Angiotensin II Converting Enzyme; IFN-γ, Interferon-γ; IL-1β, Interleukin-1β; IL-2, Interleukin-2; IL-6, Interleukin-6; IL-18, Interleukin-18; TNF-α, Tumor necrosis factor α.

Figure 1: Interaction of SARS-CoV-2 with ACE2 receptors representing the cytokine storm and its respective damage.



Notes: CS, Sustacular cells; NSO, Olfactory sensory neurons.

Figure 2: Evolution and pathophysiology of anosmia according to the period of infection.

cells, which are part of the cytokine storm caused. Therefore, the combination of this pro-inflammatory environment, combined with early apoptosis of the olfactory epithelium and neuronal damage of these sensory pathways, results in prolonged changes in smell and taste, with a slower recovery time, going beyond the period of infection of the disease (CAZZOLLA et al. 2020; NAJAFLOO et al., 2021).

In addition, there have been many specific reports about changes in smell and taste. It was reported from the reduction of smell to the change of this sense in situations that were previously pleasant odor and became unpleasant, even promoting other symptoms such as nausea. Some reported that odors such as garlic, perfume and fuel became odors reminiscent of "burning" or chemical smells such as alcohol. There were five patients who persisted with altered smells compared to what they felt before infection.

In terms of taste, many foods were described as bitter. Foods that were once pleasant have been reported to be unpleasant after infection. Coffee and cola soft drinks were shipped with chlorine/bleach flavor. Until the present day, some refer that they still need to use more seasonings in their food for a better taste sensation and it was also mentioned that certain foods could never be ingested again due to a persistent change in taste, such as meats, citrus fruits and soft drinks. Glue.

It is also observed that people who showed changes in both senses, the time of onset was approximately the same for changes in smell and taste. The duration was also very similar. According to the model by BUTOWT et al., (BUTOWT et al., 2021), there is a pathophysiology according to the days of SARS-CoV-2 infection, from cell death to regeneration, which is outlined in figure 2.

CONCLUSION

In Covid-19 there are several symptoms that corroborate the severity of this disease. Among some characteristic symptoms, anosmia and ageusia is present in most people affected by SARS-CoV-2. This work allowed a better visualization and behavior of how these olfactory and gustatory phenomena occur, as well as their patterns and duration in patients. While these symptoms cause discomfort to the affected individual, since they are directly linked to memory, protection and pleasure, either personally or even at a collective level, this work tends to promote greater knowledge so that there are more studies on how these sequelae can be mediated.

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