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Anosmia and ageusia associated with coronavirus infection (COVID-19) - what is known?

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Abstract. In 2020 a new pandemic caused by the SARS-CoV-2 coronavirus is affecting the lives of millions of patients and healthcare workers worldwide. The clinical picture of this infection is in a dynamic process of discovery, and more symptoms emerge as the clinicians observe and diagnose manifestations that affect multiple organs. Anosmia (loss of smell), and ageusia (loss of taste) become more frequently cited as independent symptoms or in association with the most common manifestations of the disease, such as fever, cough and dyspnea. A thorough screening program will prevent most nosocomial and community-acquired infections by promoting efficient triage and specific measures such as isolation of the patients. Therefore, it is important to include frequent symptoms in the anamnesis and questionnaires to select those patients who might benefit from testing, isolation, and treatment. This study summarizes the existing data regarding the association of anosmia and ageusia with the SARS-CoV-2 infection. It also aims to describe manifestations of these, particularly in the clinical picture of all symptomatic patients.

Introduction

The new coronavirus, SARS-CoV-2, determined a highly contagious zoonosis in the eastern Asian countries that rapidly transformed into an ongoing pandemic worldwide, accounts for approximately 262,000 deaths so far as reported by World Health Organisation (WHO) (1).

SARS-CoV-2 belongs to the coronaviridae family alongside with SARS-CoV and MERS-CoV, and it has a single-stranded RNA genome (2). The coronavirus invasion of the target cells is mediated by a transmembrane spike glycoprotein (S). It has two subunits: S1, for binding to the host cell receptors, and S2, for the fusion process with the host cell membrane. These subunits will remain in a prefusion conformation after specific protease cleavage, with the distal S1 subunit comprising the receptor-binding domains (RBD), specifically involved in recognition of human angiotensin-converting enzyme 2 (ACE2) (3,4). The S protein will be further cleaved by host proteases and activated for the membrane fusion. Due to the peripheral location of S proteins, they are the main target for neutralizing antibodies and for new developing therapies (3,5).

The ACE2 is a functional receptor for the SARS-CoV-2 and has a ubiquitous distribution into the human body, but its expression is higher in the nasal mucosa, lung parenchyma, and gastrointestinal tract (6). Some studies suggest a possible link between smoking and enhanced expression of ACE2 receptors (7), thus, smoking could be a risk factor that increases the susceptibility of the patient to contact the new coronavirus.

SARS-Cov-2 is a highly transmissible virus with an incubation period of approximately 14 days, with a median time of 4-5 days from exposure to symptoms onset (8-10). It has been stipulated that the viral transmission is through the droplets, direct contact, contact with an infected individual, fecal, oral, and body fluid routes (11-13).

The most typical symptoms experienced by the patients were fever (83-99%), cough (59-82%), fatigue (44-70%), anorexia (40-84%), shortness of breath (31-40%), sputum production (28-33%) and myalgias (11-35%) (14-16). Less common symptoms reported include headache, confusion, rhinorrhea, sore throat, hemoptysis, vomiting, and diarrhea (<10%) (15,16).

Anosmia (loss of smell), ageusia (loss of taste), acrosyndroms (cutaneous manifestations due to vasomotor disturbances), and skin rashes have also been reported, and more data are needed to understand better their role in

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the clinical picture of SARS-CoV-2 infection (17-19). An increasing volume of empirical data indicates that anosmia, hyposmia, ageusia, and dysgeusia may be possible symptoms of SARS-CoV-2 infection, regardless of, or alongside, classic symptoms.

This report summarizes the evidence regarding the association of anosmia and ageusia with SARS-CoV-2 infection. It also aims to describe these manifestations' particularly in the clinical picture of symptomatic patients.

Materials and methods

A literature search was conducted in MEDLINE, EMBASE, and Cochrane databases using the following keywords, including synonyms, and all the possible combinations of them: anosmia, ageusia, SARS-CoV-2, COVID-19, coronavirus. Studies were included that documented symptoms associated with SARS-Cov-2 infection (up to May 5, 2020).

Results

Viral upper respiratory tract infections frequently determine olfactory dysfunction and taste disfunction. Coronaviruses are the main determinants of the common cold, along with other viruses such as rhinoviruses, influenza, and parainfluenza. Therefore, it is no surprise that the SARS-CoV-2 virus would determine smell alteration in some infected patients.

In a retrospective observational study, Klopfenstein *et al* (20) reported that 54 patients (47%) with confirmed SARS-CoV-2 infection developed anosmia, 4.4 (±1.9) days after infection onset, and that was the third symptom to manifest in 38% (22/52) of the cases. The mean duration of anosmia was 8.9 (±6.3) days, and one patient had not recovered at the end of the follow-up (after 28 days). Anosmia was associated with dysgeusia in 85% of cases (n=46).

Mao *et al* (21) published a retrospective case series at three hospital centers in Wuhan, China. It included 214 patients confirmed with SARS-CoV-2 infection and evaluated the presence of neurological symptoms (central, peripheral) and musculoskeletal symptoms. As for the peripheral symptoms (8.9%), the authors reported that the most common were hypogeusia and hyposmia with 5.6 and 5.1%, respectively.

Although currently there are no guidelines that recommend testing of the persons with symptoms such as anosmia or ageusia, some authors suggest testing and isolation for those patients who experience these symptoms alongside with hyposmia and dysgeusia in the absence of other explanatory conditions (22,23).

Recent studies suggested that the different variants of the virus could determine the extent of susceptibility and clinical course for the infected patient, so that different cohort of patients may have a polymorphic clinical presentation (24).

Li *et al* (25) demonstrated that some ACE2 variants might prevent the association with SARS-CoV-2 S-protein. However, scarce data are currently available, and more research could lead to a proper understanding of this topic. On the other hand, Cao *et al* (26) demonstrated the genetic polymorphisms of the ACE2 receptor and the specific prevalence in the European and Asian populations suggesting the possibility of different clinical courses for these patients.

Pathophysiology

Few studies described the pathophysiological mechanisms of the olfactory and gustatory dysfunction in the SARS-CoV-2 infection. Available data indicate the virus has a neural spread and a cytopathic effect on the neurons. It affects mainly neurons in the cortex and hypothalamus (27).

Some authors reported three mechanisms for anosmia in COVID-19 patients: i) local infection of support cells and vascular pericytes in the nose and olfactory bulb that may affect the function of bipolar neurons or mitral cells; ii) damage to support cells in the sensory epithelium that may indirectly influence the signaling pathway from sensory neurons to the brain; and iii) damage to sustentacular cells and Bowman's gland cells that could lead to diffuse morphological damage to the olfactory sensory epithelium and altering of smell perception (28,29).

In scientific literature, two syndromes with different outcomes are described. One is the olfactory cleft syndrome, which involves a conductive loss due to mucosal obstruction of the olfactory cleft. The other is post-viral anosmia syndrome, which implies a neural loss, due to the destruction of the olfactory sensory neurons (30). The first syndrome has a relatively rapid resolution of anosmia, while the second one can be associated with a persistent olfactory deficit.

Netland *et al* (31) detected the coronavirus 60 h after exposure to SARS-CoV-2 in the olfactory bulb and after four days, its dissemination to the pyriform cortex and dorsal nucleus of the rafe. This aspect suggests a rapid viral propagation to the brain structures.

Recent studies found that SARS-CoV-2 could be detected in saliva and that it is possible to measure the viral load in this fluid (32,33).

Hu *et al* (32) studied the cellular distribution of taste cells and ACE2 receptor distribution. They found that the percentage of ACE2 positive cells was higher in taste cells, which indicated that SARS-CoV-2 might invade them and lead to ageusia in these patients. However, data regarding the exact mechanism by which SARS-CoV-2 determines ageusia is limited. The virus may bind to the sialic acid receptors and occupy and accelerate the degradation of the gustatory particles, leading to a decrease in taste sensation (34).

Diagnostic tools

Medical imaging and neuropathology studies evaluate changes in the olfactory bulb, cranial nerves, and brains of the infected patients. Thus, magnetic resonance (MR) imaging of the olfactory bulb can be used to assess the patients with anosmia (35). The main MR findings in anosmia secondary to upper respiratory infection are reduced olfactory bulb and tract volume, which correlate with the olfactory function (35).

Anamnesis and personal reports of anosmia and ageusia are also necessary. One can use questionnaires for clinical diagnosis and follow-up in anosmia or ageusia patients. In a prospective study, Lechien *et al* (24) evaluated anosmia and ageusia using questionnaires based on smell and taste component of the National Health and Nutrition Examination Survey, and the short version of the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS). These authors

found a substantially higher prevalence of olfactory and gustatory dysfunction in European COVID-19 patients. More, the olfactory disorder may appear before the rest of the complaints. They identified a significant association between olfactory and gustatory dysfunctions.

In a cross-sectional study by Bagheri *et al* (36), 10,069 participants responded to an online checklist that evaluated the sense of smell and taste. The results indicated a significant correlation between anosmia and SARS-CoV-2 infection, decreased taste sensation, and decreased quality of life.

We found numerous validated questionnaires and tests for assessing anosmia and ageusia. However, more data are needed to provide quantitative data on the incidence and severity of these symptoms in association with SARS-CoV-2 infection.

Treatment

According to a report of the French Society of Otolaryngology, patients must avoid corticosteroids for the treatment of the SARS-CoV-2 infection (37).

On the other hand, clinicians frequently use empirical oral steroids for the treatment of anosmia, to decrease inflammation and edema. We suggest that individualized case management and treatment should be applied, considering the increased risks of immunosuppression associated with these drugs.

The relative risk seems to be reduced in the case of intranasal steroids use. Here, the main concern is the exacerbation of an upper respiratory tract viral infection (38).

Lechien *et al* (24) reported that the most frequently used treatments for olfactory dysfunction in SARS-CoV-2 infected patients were nasal saline irrigations, followed by nasal and oral corticosteroids. As for gustatory dysfunction, clinicians used l-carnitine or trace elements and vitamins.

Smell training is a simple, safe, and readily available method in the context of social distancing for smell recovery in different forms of anosmia (39-41).

There is no therapeutic regime for ageusia. The condition may either improve gradually on its own or may remain the same. In patients with associated xerostomia, a therapeutic option could be artificial saliva.

Expected recovery

Scarce data reported in the literature suggest that most patients will achieve smell recovery up to 14 days after resolving the disease.

In the study conducted by Lechien *et al* (24), 67.8% of the anosmic patients recovered olfactory function within the first eight days following the resolution of the disease, and it seems that, at least, 25.5% of the patients recovered both olfactory and gustatory functions throughout the two weeks after the resolution of general symptoms.

Conclusions

Further research is needed to demonstrate the association between anosmia and ageusia with SARS-CoV-2 infection, the clinical manifestations determined by variants of ACE2 receptor, and recovery rates of olfactory and gustative dysfunction, and specific treatment protocols of these manifestations.

Anosmia and ageusia are symptoms that require further investigation during a clinical consultation, due to the increasing evidence of their association with the new coronavirus. Careful screening and prevention must be offered to avoid nosocomial and community infection.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

IAT and DN designed the study. IAT, DN and AC retrieved the data. CM, AC and DBN contributed to data extraction and quality assessment. CM, DBN and REB were responsible for the analysis and discussion of data. IAT and DN drafted the manuscript. CM, AC, DBN and REB revised critically the manuscript and made substantial intellectual contributions to the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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