SCIENTIFIC REVIEWS AND LECTURES

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OLFACTORY DYSFUNCTION AS A KEY SYMPTOM OF COVID-19: A REVIEW BASED ON CURRENT RESEARCH

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The 2019 coronavirus pandemic (COVID-19) has caused a large-scale epidemic and a global crisis around the world. The growing scientific evidence suggests that olfactory dysfunction (OD) is present in COVID-19 patients. It can occur on its own or in combination with other symptoms of coronavirus infection. In patients with COVID-19, the main clinical manifestations are fever, cough, accompanied by lymphocytopenia and changes in the lungs with computed tomography of the chest (lesions of the lung tissue in the form of "ground glass"). Also, patients with a severe form of infection may develop neurological disorders, such as acute cerebrovascular diseases, impaired skeletal muscle function, and loss of consciousness. However, the pathogenetic mechanism and clinical characteristics of anosmia in COVID-19 patients remain unclear. Due to the unique anatomical localization of the olfactory system, including the olfactory bulb and olfactory nerve, coronaviruses are able to penetrate and infect the central nervous system through the cribriform (ethmoid) plate. Numerous studies have shown that the incidence of olfactory dysfunction in patients with COVID-19 correlates from 33.9% to 68%, and in women much more often. Anosmia (loss of smell) and dysgeusia (taste disorder) are often associated symptoms in patients with coronavirus infection. Patients with COVID-19 may experience sudden olfactory dysfunction without any other symptoms. Before the onset of anosmia, other symptoms in the form of a dry cough may be present. Otolaryngologists should pay attention to the symptom of anosmia on an outpatient basis in order to diagnose COVID-19 as quickly as possible. To avoid cross-infection, a physician may consider a remote sense of smell assessment for a patient with this diagnosis. In this article, we have reviewed the relevant evidence based on the current literature. Many questions that are somehow related to the loss of smell in coronavirus infection remain unresolved to date.

Keywords: SARS-CoV-2, COVID-19, anosmia, olfaction, dysgeusia.

Introduction. In December 2019, an outbreak of coronavirus infection (COVID-19) occurred in Wuhan, Hubei province (China) and spread very quickly around the world [13,22,39]. On February 12, 2020, WHO named the disease caused by the novel coronavirus as COVID-19 [40]. Clinical studies have shown that SARS-CoV-2 can be transmitted from person to person [13]. Researchers found a high concentration of SARS-CoV-2 RNA in the air in some public areas of 2 Wuhan hospitals during the COVID-19 outbreak [23]. They suggested that the SARS-CoV-2 pathogen may have an aerosol transmission type [23]. The number of COVID-19 cases has skyrocketed worldwide over the last 2020. As of January 27, 2021, WHO reports that since the beginning of the pandemic, 98.2 million cases and 2.1 million deaths have been registered worldwide. [39]. The COVID-19 pandemic has put tremendous pressure on global health systems and the economic stability of all countries in the world.

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In patients with COVID-19, the main clinical manifestations are fever, cough, accompanied by lymphocytopenia and changes in the lungs on computed tomography of the chest (lesions of the lung tissue in the form of “ground glass”) [22]. Also, patients with a severe form of infection may develop neurological manifestations such as acute cerebrovascular diseases, skeletal muscle injury and impaired consciousness [26]. In addition, some patients experience respiratory symptoms such as pharyngolaryngitis, sore throat, rhinorrhea, and changes in the sense of smell [24,25]. Olfactory dysfunction (OD), including anosmia and hyposmia, is very common among all symptoms in patients with COVID-19 [42]. However, the degree of manifestation of OD in COVID-19 remains unclear to date.

To find out the relationship between the development of OD in COVID-19, we conducted a broad search in the literature databases: PubMed, Google Scholar, Web of Science, Wiley Online Library and Nature. The key sample of words included the concepts: anosmia, hyposmia, olfactory dysfunction, COVID- 19. We also looked at the preprint databases (Medrxiv, Biorxiv) to get updated information on research. **This review summarizes the results of studies published on the problem of olfactory dysfunction in patients during the COVID-19 pandemic, as well as examines the mechanisms of its occurrence.**

Etiology of the pathogen

There are 7 types of coronavirus pathogens that can cause disease in humans: SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 [41]. The genome sequence of SARS-CoV-2 is represented by single-stranded unsegmented RNA [4]. SARS-CoV-2 and SARS-CoV belong to the genus Betacoronavirus of the coronavirus family and have 82% similarity in the gene sequence [45].

The SARS-CoV-2 virus uses the S1 spike glycoprotein, which is found in the envelope of the virus, to attach to and infect host target cells. The receptor for coronavirus on the host cell surface is angiotensin-converting enzyme-2 (ACE2) [4]. ACE2 is a functional receptor for SARS-CoV-2, and its expression and localization in the nervous system is very extensive. Therefore, it is assumed that SARS-CoV-2 can cause neurological disorders in both direct and indirect ways [26]. Due to the unique anatomical localization of the olfactory system, including the olfactory bulb and the olfactory nerve, viruses are also able to penetrate and infect the central nervous system through the cribriform (ethmoid) plate [5,20].

Overwhelming evidence has confirmed that the nasal cavity is a vital area tropic to COVID-19. Using a macaque model of coronavirus infection, the researchers compared the pathogenesis and primary localization of SARS-CoV-2, SARS-CoV, and MERS-CoV [31]. The study showed that these pathogens have different areas of localization of the pathological process: SARS-CoV-2 (nose and throat); SARS-CoV (lungs); MERS-CoV

(type II alveolocytes). The viral load on the nasal mucosa of patients was higher than on the pharyngeal mucosa [47]. These data indicate that the nasal cavity is the gateway for primary infection [47].

Scientists have studied the expression of genes associated with the target for SARS-CoV-2 - ACE2 and TMPRSS2 (Transmembrane protease, serine 2), using immunohistochemical methods. For the study, we used biopsy material from various tissues of the human body: bronchial tree, cornea, retina, esophagus, ileum, colon, heart, skeletal muscles, spleen, liver, placenta, kidneys, testes, pancreas, prostate gland, brain, skin and tissues of the fetus [35]. Goblet and ciliated cells (providing mucociliary clearance) localized in the nasal mucosa are a reservoir of coronavirus infection and possible sources for the spread of COVID-19 in the population [35]. In addition, the pathogen SARS-CoV-2 was isolated from the tears of a patient COVID-19 and can cause infection by spreading through the nasolacrimal canal into the nasal cavity [8,11]. Thus, these data prove the highly virulent and highly pathogenic nature of COVID-19.

Anosmia is defined as complete loss of olfactory function that can be caused by a variety of causes, with upper respiratory tract infections being the most common cause [15].Among the various pathogens, the most common are members of the coronavirus family [15.33]. It has been proven that the type of coronavirus 229E, a common variant of ARVI, is capable of causing hyposmia in humans [3]. During the coronavirus epidemic in November 2002 in southern China, anosmia was reported in a 27-year-old patient diagnosed with severe acute respiratory syndrome (SARS) [16]. However, the incidence of anosmia caused by SARS-CoV-2 is significantly higher than that of SARS-CoV. Researchers believe that post-infectious olfactory dysfunction is caused by damage to the olfactory epithelium or the nerve of the same name [15].

Eliezer M. et al. in a study [9] gave a clinical case of infection with SARS-CoV-2. A 40-year-old woman had an acute loss of olfactory function without nasal obstruction. The patient underwent a CT-scan of the nasal cavity, which showed bilateral inflammatory obstruction of the olfactory fissures, which was confirmed by magnetic resonance imaging (MRI). This inflammation seriously impaired the olfactory function, preventing the penetration of odorant molecules into the olfactory epithelium of the nasal cavity [9].

Anosmia is a clear sign of SARS-CoV-2 infection [14]. Patients with COVID-19 may present with sudden olfactory dysfunction without any other symptoms [14, 27]. Before the onset of anosmia, other symptoms may be present in the form of a dry cough [19]. In a retrospective study [19], 54 (47%) of 114 COVID-19 patients had anosmia. The data also showed that patients developed anosmia 4.4 days after the onset of SARS-CoV-2 infection, with a duration of 8.96 days, and 98% of patients recovered within 28 days [19]. Olfactory dysfunction in patients with a confirmed diagnosis of COVID-19 is often accompanied by dysgeusia [17, 19].

There have been several cross-sectional studies on the prevalence of OD in COVID-19 patients in countries such as Italy, Spain, United Kingdom, France, Belgium, the United States and Iran [6,12,28,34,44]. These surveys were conducted by non-contact methods such as online questionnaires and telephone polls [6,21,34]. The incidence of anosmia in COVID-19 patients varied widely among these studies, from 33.9% to 68% [6,12,28,34,44]. Survey data showed that people with OD also have a taste disorder, which suggests a possible probabilistic relationship between them [6,12,28,34,44]. In addition, most studies have shown that the incidence of olfactory disorders in patients with COVID-19 is higher in women than in men [6,12,34]. The female predominance in the experiments is consistent with the findings of previous studies, where olfactory dysfunction was also caused by an upper respiratory tract infection [18].

To date, two case-control studies have been conducted on the relationship between OD and COVID-19 [7,29]. Moein et al. [29] conducted an odor identification test at the University of Pennsylvania (UPSIT). The experiment involved 60 patients with diagnosed coronavirus infection and 60 subjects as a control group corresponding to the age and sex of the patient group [29]. The study showed that 59 (98%) of 60 patients with COVID-19 had some olfactory dysfunction, 35 of 60 patients (58%) had pronounced anosmia [29]. Another study, using a questionnaire, analyzed the prevalence of smell and / or taste disorders in 19 patients with COVID-19 and a similar number of patients with influenza [7]. It was proved that the level of the occurrence of OD in patients with COVID-19 was significantly higher than in patients with influenza by 39.2% and 12.5%, respectively [7]. The main drawback of this study is the lack of an odorant test. The results are interpreted only on the basis of the questionnaire data, which may contribute to some bias on the part of the medical community.

The odor identification test is key in the diagnosis of olfactory dysfunction. However, most of the studies did not give patients such tests. After analyzing the literature data, we found only 3 such studies in which odorant tests were carried out [29,30,36].

Ottaviano G. et al. in their study reported that hyposmia was the only, and in some cases the main symptom in 6 patients with COVID-19, confirmed by 6 smells of the olfactory test called “le nez du vin” (collection of wine aromas “Nose wine ") [30].

Moein et al. [29] in their experiment, they first performed a 1: 1 case-control comparison using a 40-odorant odor identification test to obtain more reliable results between groups. The study showed that 59 (98%) of 60 patients with COVID-19 showed different variants of OD, only 21 (35%) of them were aware of this testing, which allowed us to identify a more accurate frequency of occurrence of OD, compared to the previous study [29]. Importantly, these data provide solid evidence that OA is often associated with COVID-19. In a study [36], 33 quarantined patients diagnosed with COVID-19 were remotely assessed. At home, they had to independently conduct an odorant test using a solution of denatured ethyl alcohol with a decreasing concentration [36]. As a result, the results were as follows: chemosensitive dysfunctions were registered in 21 patients (63.6%). Specifically, 13 patients (39.4%) reported combined taste and olfactory disorders. In 4 patients (12.1%), only a decrease in taste (dysgeusia) was observed, while in the remaining 4 patients (12.1%), isolated hypo / anosmia was observed.

Specialists at the Mayo Clinic (USA) used artificial intelligence with advanced technology of deep neural networks to identify and analyze the clinical features of the pathogen SARS-CoV-2 [37]. The study found that the prevalence of anosmia in COVID-19 (+) - patients was 28.6 times higher than in patients with similar respiratory infections, and OD was one of the earliest symptoms of COVID-19 [37]. Susceptibility to SARS-CoV-2 infection depends to some extent on the host genotype; the heritability in anosmia was 47% [38].

According to current research, olfactory dysfunction has a high incidence in patients with COVID-19 in European and American countries, while it is rare in patients in China [19,25].

Lovato A. et al. Reviewed 5 articles on the clinical picture of COVID-19 patients

from China, including 1556 cases; no studies have reported on the manifestation of OD in patients [25]. Mao L. et al. In a study [26] retrospectively analyzed the neurological symptoms of 214 patients in Wuhan, China, and found that 5.1% (n = 11) of patients had a sense of smell impairment [26]. To our knowledge, this article is the only study to date describing OD in COVID-19 patients in China.

Several reasons explain that the incidence of OD in patients varies across countries. First, SARS-CoV-2 is able to mutate, which causes its increased virulence and pathogenicity [43]. In a study [10], the authors performed a phylogenetic analysis of the SARS-CoV-2 genome and found the 3 most common variants with an altered amino acid sequence [10]. Genotypes A and C of SARS-Cov-2 have a significant population of Europeans and Americans, however, type B is the most common genotype in East Asia. It is assumed that strains of type A and C are highly pathogenic for the olfactory epithelium of the human nasal cavity, which leads to an increase in the prevalence of OD in European and American countries. Secondly, a species-specific pathogenetic predisposition to SARS-Cov-2 is possible, and it can also circulate in the population. However, there is no evidence to support this assumption. Third, due to the COVID-19 outbreak that originally occurred in China, doctors were poorly informed about the infection, highlighting only the primary life-threatening symptoms, but leaving out the history of olfactory disorders.

Since anosmia may be the only clinical manifestation of COVID-19 in patients without any other significant signs, it highlights the differentiation of coronavirus infection by an otolaryngologist [14]. Otolaryngologists should always be vigilant when working with outpatients to diagnose COVID-19 on time. To avoid cross-infection, a physician may consider a remote sense of smell assessment for a COVID-19 patient with OD [36]. Also an important problematic issue is that many infectious diseases of the upper respiratory tract, for example, rhinosinusitis are very often accompanied by anosmia / hyposmia [1]. This can contribute to the difficulty in making the correct diagnosis, especially during a pandemic.

Among other things, during the COVID-19 pandemic, it is necessary to remember about the timely detection of rare hereditary pathologies. Thus, in the article [2], the authors describe a clinical case in a patient with Rendu-Osler disease (congenital hemorrhagic telangiectasia). The patient experienced intense nosebleeds during stress.Thanks to timely diagnosis, including detection of telangiectasias on the skin and mucous membranes; family nature of the disease; the absence of pathology of the hemostasis system, the doctors managed to correctly diagnose and begin timely therapy.

Otolaryngology is a high-risk unit for COVID-19, especially for physicians over 60 years of age [32]. The main prerequisite is that it is important for the medical personnel to comply with the rules of personal protection in the first place [46]. With the exception of urgent emergencies, telemedicine in ENT is a good option for reducing COVID-19 cross-infection [27].

Current confusion and future directions. Many current studies lack longitudinal results on olfactory dysfunction in COVID-19 patients from disease onset to full recovery. Therefore, the question of whether OD in a patient with coronavirus infection is temporary or permanent remains to be seen. What is the exact prevalence of anosmia / hyposmia in COVID-19 patients worldwide? Can indicators of olfactory dysfunction be used as a valuable indicator of diagnosis and prognosis of infection?

Uncovering these problems in the future will require more extensive research, both basic and clinical. Macaca mulatta monkeys are a good experimental model for studying the correlation of pathogenesis and olfactory dysfunction in COVID-19. The high similarity with humans lies in the fact that the course of infection with SARS-CoV-2 in monkeys is exactly the same. The olfactory epithelium can be biopsied for ultrastructural observation to better understand the pathology of OD in patients with COVID-19 [18]. Once the COVID-19 pandemic has been contained, an epidemiological study should be conducted involving patients from different countries and races.

Conclusions. OD is a characteristic feature of COVID-19 in patients that can occur on its own or with other symptoms, but its pathogenesis is not well understood. In-depth studies are needed to elucidate the clinical features and pathogenesis of the SARS-CoV-2 pathogen in patients with OD. Otolaryngologists and therapists need to be aware of anosmia in COVID-19 to avoid misdiagnosis and thereby contribute to the COVID-19 pandemic.

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