

Literature Review

Olfactory and Taste Disorders in Patients Suffering from Covid-19, a Review of Literature

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ABSTRACT

Corona virus epidemic has caused a widespread disaster around the world. In studies, there are pieces of evidence of olfactory and taste dysfunction in patients with Covid-19. These symptoms occur independently or can be associated with other symptoms such as dry cough. The mechanism of the above-mentioned disorders and also its clinical features in patients are not yet known. The rate of incidence of olfactory dysfunction (OD) in patients has been varied from 29.64%-75.23% and the rate of incidence of taste dysfunction among the people can be different from 20.46% to 68.95%. Therefore, clinicians including ENT specialists and dentists should pay attention to the symptoms of anosmia and ageusia in outpatients so that the diagnosis is not delayed and/or does not lead to inappropriate treatments in patients. In this article, the available studies regarding this issue are mentioned. In this review article, data collection by searching the available articles in the domestic and foreign journals using databases such as: PubMed, PubMed Central, Medline, EBSCO, Google Scholar and Embase with key words of Anosmia, Ageusia, Dysgeusia, Covid-19, Coronavirus occurred between 2019 to 2020. Among the relevant references, 38 authoritative articles were chosen. It seems that olfactory and taste function disorders are the obvious symptoms of Covid-19 which can occur independently or with other symptoms, but the pathogenesis is not well-specified yet. Therefore, further studies are required to achieve a reliable result in this area.

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Introduction

In December 2019, the Corona virus broke out in Wuhan, China and spread rapidly throughout China and then around the world; Therefore, World Health Organization called this disease Covid-19 on February 12, 2020 [1].

In patients with this virus, the main symptoms include dry cough, shortage of breath and lymphocytopenia, along with the observation of a radiopaque examination on a chest CT-scan [2]. Patients with severe infections can also develop neurological symptoms such as skeletal muscle damage and memory impairment [3]. Among these symptoms, olfactory dysfunction (OD),

including anosmia, hyposmia, as well as taste dysfunction, such as ageusia and dysgeusia, especially prominent in patients with Covid-19 appear. The clinical examination of these symptoms in patients, today has attracted much attention, because their evaluation does not require interventions and can only be achieved with the help of questionnaires or screening algorithms. It's not clear whether olfactory and taste disorders are a recurrent symptom in patients or are in the group of prognostic factors of this disease [4].

Many studies have been done around the world today to examine these disorders. For example, recent studies in Iran show that there has been a significant

increase in the number of patients who have completely lost their sense of smell with the onset of Covid-19. Similar results can be seen in studies conducted in other countries of the world [5].

This article provides an overview of articles related to these disorders.

Search Strategy

In preparing a review article of databases such as PubMed, PubMed Central, Medline, EBSCO, Google Scholar and Embase were used and 60 articles including 49 English articles and 9 Persian articles between 2019 and 2020 which had one of the keywords such as Anosmia, Ageusia, Dysgeusia, Covid-19, Coronavirus in their titles were selected and studied. The inclusion criterion was the year of publication, the name of the first author and the degree of relevance of the title and purpose of the related articles. The exclusion criterion was excessive information. 33 English articles and 5 Persian articles were selected by the researcher for the final analysis and writing of the review article.

Discussion

The Corona virus family includes 7 viruses, of which the SARS-Cov-2 virus is said to be the cause of Covid-19. The receptor of this virus in the human body is called HACE2, and its receptors are located in the lungs, digestive system, nasal mucosa, urinary tract, lymphatic tissues, reproductive organs, vascular endothelium, brain and kidneys. Among these cases, the virus is mainly absorbed through the nasal mucosa or digestive system due to the higher protein of HACE2 [6]. Symptoms of the disease appear when the virus binds to the receptor. The main clinical manifestation of this disease is severe pneumonia, which is commonly reported in the elderly those who have been exposed to the virus before. The virus causes chronic inflammation of the lungs, severe shortage of breath, fever, dry cough and cyanosis, and in vulnerable patients causes complete lung failure. Recent studies, however, have shown that patients with mild symptoms such as anosmia and other neurological problems indicate the aggressive neurological nature of the virus [7].

The Relationship between Olfactory and Taste Disorders with Covid-19

Various documents indicate that OD is one of the most

prevalant symptoms of Covid-19 [8]. The above symptoms have attracted the attention of ENT specialists around the world. A summary of published studies shows that the anosmia and ageusia are an evident symptom SARS-Cov-2 infection [9].

Anosmia

Is described as the absence of the sense of smell, and upper respiratory tract infection is its most common etiology. Also, among the various pathogens, the most prevalent causes are viruses such as Corona virus 229E and SARS-Cov [10]. However, the probability of occurrence of anosmia caused by SARS-Cov-2 may be much higher than SARS-Cov [1]. Patients suffering from Covid-19 may have a sudden onset of symptoms without any other symptoms, or may have other mild symptoms, such as dry cough, before it starts [11-12].

Hyposmia

Means a decrease a sense of smell. Data some various studies suggest that Covid-19 can lead to hyposmia in about 30% of patients. It is also observed in most patients that the olfactory disorder is not associated with nasal obstruction, so the probable sort of this disorder can be considered neurological [13].

Ageusia

Is defined as a lack of sense of taste that is seen in patients with Covid-19 and can appear alone or with other symptoms of the disease [14].

Dysgeusia

Means taste failure; that is, a person has an unpleasant perception of a flavored substance and generally feels a metallic taste in his mouth [15].

Since today, taste and smell disorders are observed in patients with Covid-19, the presence or absence of these symptoms should be included in the evaluation and screening questionnaires of suspicious [16].

Hypogeusia

Means a reduced ability to taste things. Some studies have stated that hypogeusia can be an initial presenting symptom of Covid-19 [17].

In 2020 a study was conducted by Yonghyun Lee *et al.* [14] on 3191 patients. This research showed that in 52% of the patients, the two symptoms of ageusia and anosmia together, in 27.7% of patients only anosmia, and in 20.3% of patients only ageusia appeared (Figure 1) and the average recovery time from anosmia in patients is 7 days, and most patients with anosmia or ageu-

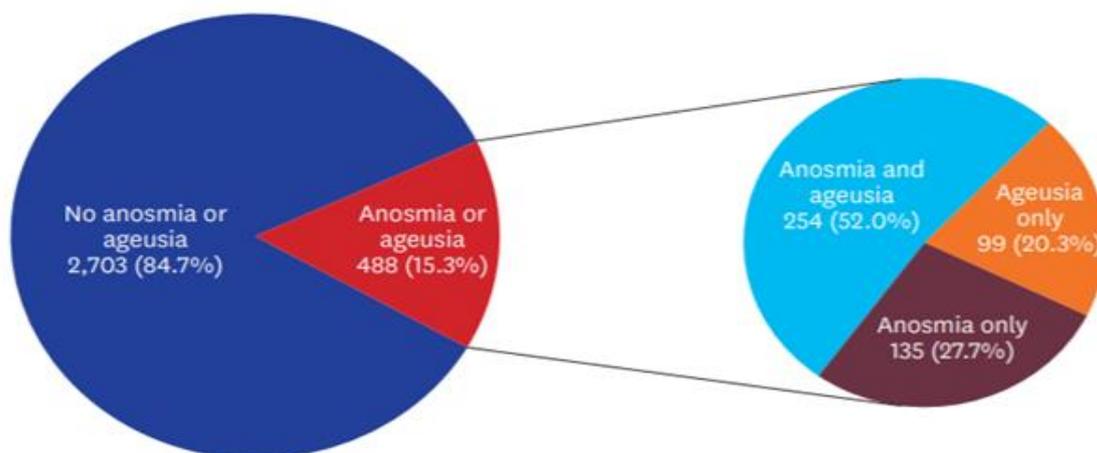


Figure 1: Proportion of anosmia or ageusia in patients with coronavirus disease 2019

sia recover within 3 weeks. In addition, young people, especially those in the age group of 20-39 years, showed a longer duration of anosmia (Figure 2) [14].

Several cross-sectional studies have been conducted on the outbreak of OD in patients with Covid-19 in countries such as Italy [18], Iran [19], England [20], USA [21], Spain [22], France [23] and Germany [24], which showed that the outbreak of OD of patients with

Covid-19 varies in different parts of the world (Table 1) [18-25]. Studies have also shown that people olfactory disorder tend to have a taste disorder, and there is a possible link between these two. In addition, the outbreak of olfactory disorders is higher in women with Covid-19 than in men [25]. Therefore, the presence of anosmia or ageusia may be an important symptom of the differential diagnosis of Covid-19 [4].

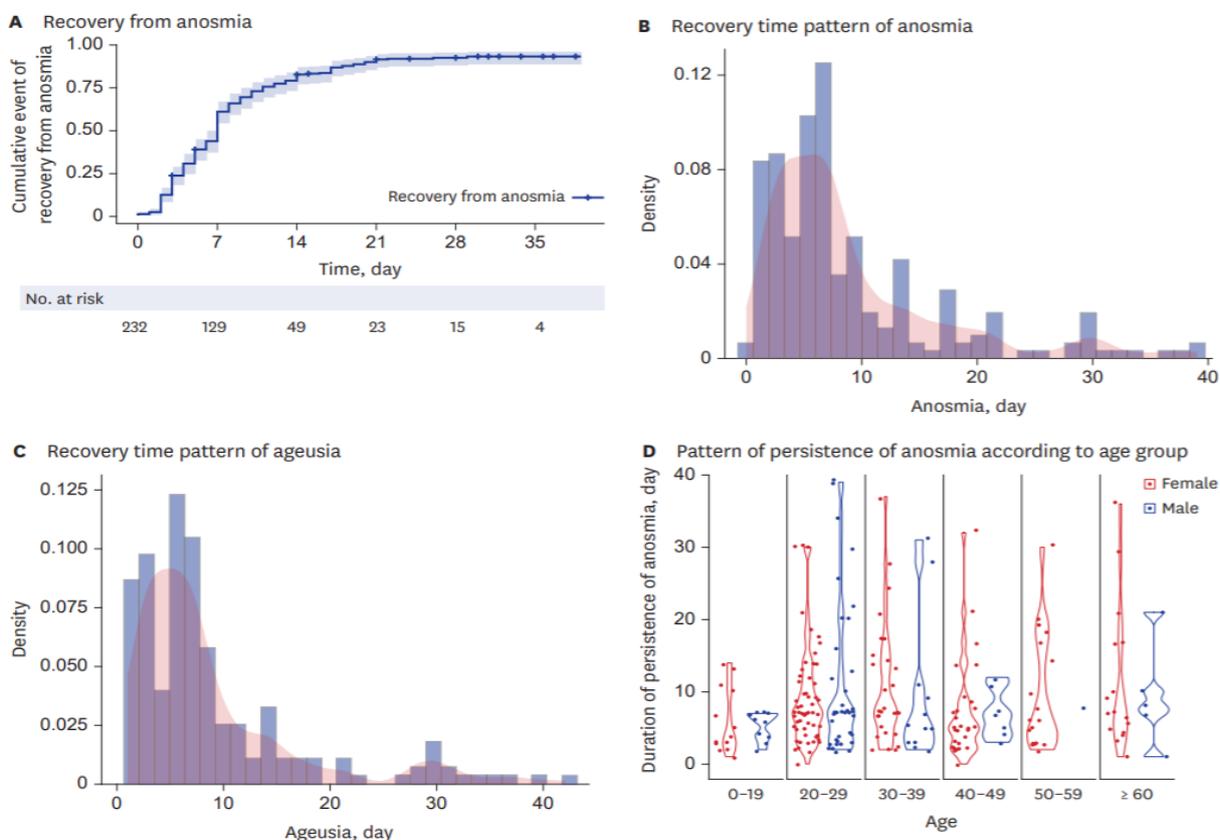


Figure 2: Graph of recovery from anosmia and ageusia among patients with coronavirus disease 2019, **a:** Recovery from anosmia, **b:** Recovery time pattern of anosmia, **c:** Recovery time pattern of ageusia, **d:** Pattern of persistence of anosmia according to age group

Table 1: Proportion of Covid-19 patients with anosmia or dysgeusia in different countries

Country	Proportion of Covid-19 patients with anosmia or dysgeusia
Spain	83.9%
USA	64.4%
UK	59%
France	45.3%
Italy	33.9%
Germany	13.5%
Iran	10.6%

Possible Hypotheses of Pathogenesis of Anosmia

The first possible hypothesis could be that the anosmia occurrence is due to damage caused by the virus to the olfactory pathways. Evaluations performed on mouse models of SARS with anosmia showed a very low destruction of the olfactory epithelium. Decreased lifespan of neurons in the epithelium is the most likely cause of decreased food support of the olfactory bulb of sensory neurons, and it can lead to mitral cell loss or lack of surviving mitral cell dendrites. Moreover, the virus may inflict its primary damage on the surface of the olfactory bulb rather than the epithelium, causing symptoms such as anosmia. However, the Corona virus used in these studies were specially modified in the laboratory, and this is not necessarily the case for SARS-Cov-2 [26].

However, recent reports of cases of Covid-19 indicate a high rate of recovery after the onset of olfactory dysfunction. Moreover, it seems that the frequency of central nervous system symptoms is about 25% lower than olfactory disorders among these patients [27]. Nerve cells may not be the main target of the virus, but non-neurons that include ACE2 receptors, such as the olfactory epithelium and olfactory bulbs, may be the main target of the virus [28].

The second possible hypothesis is based on a study conducted by Brann *et al.* [28]. This research concluded that infection of the epithelium and olfactory bulb cells caused by the virus could alter the function of the olfactory neurons and cause loss of the sense of smell. Stem cells involvement (which expresses lower levels of ACE2 receptors) can be the basis of long-term olfactory disorders [28-29].

Possible Hypothesis of Pathogenesis of Ageusia

The first possible hypothesis of ageusia is since the ACE2 receptor is known as a cellular receptor for SARS-Cov-2 and is expressed diffusely on the mucous membrane of the whole oral cavity, especially on the tongue, and its role in modulating taste perception in

many studies has been tested and proven, It is now believed this receptor is involved in the development of taste disorders in Covid-19 [26].

The second possible hypothesis of ageusia is that the Middle East respiratory syndrome (MERS) Corona virus may bind to sialic acid receptors [30]. This ability has also lately been seen in the pathogenesis process of SARS-CoV-2. Sialic acid is one of the elemental components of the salivary mucin, and it protects the glycoproteins which carry gustatory molecules inside the taste buds from premature enzymatic degradation. Hence, SARS-CoV-2 could accelerate the degradation of the gustatory particles by occupying the binding sites of sialic acid on the taste buds [26].

Diagnosis Tests Used for Olfactory and Taste Disorders

The first diagnosis test used for diagnosing Covid-19 patients with anosmia is Olfactory Function Test. Olfactory function test has been and is the chief basis for the diagnosis of OD disease [31-32].

In this test, which is performed in a quiet room, the patient's olfactory threshold and his/her ability to distinguish various odors are evaluated. This test is performed by the ortho-nasal olfactory device, which is a simple and reliable device.

Evaluation of a person's olfactory threshold is done with the help of butanol, by preparing eight bottles with different concentrations of n-butanol in deionized water. The maximum concentration of butanol is 4% placed in 60 milliliters of deionized water (Bottle 0). Other bottles (from 1 to 8) have a diluted concentration of butanol. To perform the test, patients are provided with two identical incompressible bottles, one containing n-butanol solution and the other containing deionized water. The patient is then asked to close one nostril and immediately squeeze the bottle under his/her nostril and repeat this for the next bottle. The patient is now asked which of the two bottles smells more. If the patient answers all 4 questions correctly, his/her olfactory function is healthy. In case of error, the next bottle with the highest concentration of butanol is given to the patient and he/she is asked again. Finally, each of the two nostrils is assigned a score between 0 and 8 for the last bottle with the lowest concentration that has been correctly identified, and the average of these two is considered as the total score. To test the patient's ability to distinguish different odors, common odors are placed in 180 milliliter opaque pots

covered with gas and will be exposed to the patient at once in the same way as it was presented in the olfactory threshold assessment test. The patient is asked to identify the available fragrances, which include 10 items, thus score between 0 and 10 for each of the person's nostrils, based on the number of correct odors guest, will be obtained. The 10 most common scents used in this test include baby powder, chocolate, coffee, ammonia, Vicks-VapoRub, fruit gum, ketchup, black pepper, soap and orange [32].

The second diagnosis test used for diagnosing Covid-19 patients with dysgeusia is Taste Function Test. This test includes a standard and valid test that assesses the ability to perceive the four main flavors (sweet, salty, sour and bitter) which is used to evaluate the taste function of patients with Covid-19. Initially, four solutions of each are prepared to measure each of the main flavors as follows:

Salt solution (30 grams of ordinary salt in one liter of deionized water), sweet solution (30 grams of refined sugar in one-liter deionized water), sour solution (90 milliliters of 100% commercial lemon juice in one liter of deionized water) and bitter solution (decaffeinated coffee and without sugar). Each should be noted that deionized water is used as the control.

During the test, one milliliter of each solution is poured onto the patient's tongue center. Also, for each solution, a different swab is used and then disposed of. The patients are then demanded to cite whether the perceived flavor is sweet, salty, bitter, sour or neutral. In this experiment, solutions are given to the patient at random, and the only exception is the bitter solution, which is always presented last because it changes the patient's perception of the next taste.

Finally, patients' answers are recorded as correct or incorrect. The score of each question varies from 0 to 4 and allows the patients to be classified into 4 groups as: normal (score 4), mild hypogeusia (score 3), moderate hypogeusia (score 2), severe hypogeusia (score 1) and ageusia (score 0) [32].

Existing Treatments for Olfactory and Taste Disorders Associated with Covid-19

If olfactory and taste disorders persist for more than two weeks, it may be acceptable to consider a special treatment. The effectiveness of existing treatments for Covid-19 is unknown regarding olfactory disorders, but

targeted disinfection therapies may be helpful for this disorder [33].

Frequent and intentional inhalation of a set of scents (lemon, rose, clove and eucalyptus) is usually recommended twice a day, each time for at least 20 seconds for 3 months (if possible) because this method is effective and has few side-effects and it is low cost [34].

Some medications including oral and intra-oral Corticosteroids, Alpha Lipoic Acid (600 mg/day), Vitamin A (10000 U/day) and systemic Omega 3 (2000 mg/day) can also be used to treat this disorder [35-36].

Despite all these cases, until today, there is no evidence that these treatments are effective in patients with OD associated with Covid-19 [32]. There is a hypothesis for taste disorder that states that changes in Zinc cellular homeostasis in mouth taste cells are caused by the body's immune response to SARS-Cov-2 viral replication, and thus by the creation of a hypozincemia mode, the person can suffer from dysgeusia. Therefore, according to this hypothesis, taking supplementary Zinc pills or syrups (75 mg/day) can be effective as soon as dysgeusia symptoms appear [37].

The Relationship between Olfactory and Taste Disorders with Dentistry

In 2020, a research was done by Huaqiu Guo *et al.* [38] on 2537 dental patients. This study indicated that at the beginning of the COVID-19 outbreak, 38% patients went to the dental offices. The results of this study greatly suggest that COVID-19 highly influenced the smell and gustatory perception of the patients who visited these dental offices. Therefore, there are very strong documents which show that in the post-COVID-19 era, people with olfactory and gustatory disorders visit dental offices first. As a result, all the members of dental team should be alerted to these symptoms [38].

Conclusion

Olfactory and taste disorders can be important symptoms of Covid-19, which can be seen solely or with other symptoms. The pathogenesis of this disease is not well-specified and requires further studies in this area. Hence, the clinicians, dentists and ENT specialists should pay attention to this important diagnostic symptom of the disease so that the diagnosis of the disease is not delayed or does not lead to inappropriate treatments in patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

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