



Review Article

Sudden onset of olfactory and gustatory dysfunctions in coronavirus disease 2019 (COVID-19) is momentous marker

Himani Tiwari Chaturvedi^{a*}, Chandrashekher Chaturvedi^b

^aDepartment of Oral Pathology,
Dharmsinh Desai University,
Nadiad, Gujarat, India,

^bDepartment of General Surgery,
Care Multispecialty Hospital,
Vadodara, Gujarat, India

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ABSTRACT

Coronavirus disease 2019 (COVID-19) presenting as global pandemic left no boundaries untouched worldwide. There are conglomerates of clinical and pathological presentation depending on population and geographic distribution. However amidst of such variable presentations, the sudden onset of olfactory and gustatory dysfunctions, if present, remains the most consistent and reliable symptoms of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) infection. Olfactory and gustatory dysfunctions can be present either isolated or as a part of the spectrum of common symptoms such as fever, cough, dyspnea, and fatigue in COVID-19. The pathophysiology of olfactory and gustatory loss is thought to be due to the neural and cytopathic effect of SARS CoV-2 on nasal and tongue mucosa and olfactory neuroepithelium. This review intends to provide a concise description of recent evidence for structure, pathophysiology, prognosis, and treatment for smell and taste dysfunction in SARS CoV-2-infected patients, subjected to further studies and research. Vigilant screening of anosmia and ageusia could probably be an important tool in the fight against the COVID-19 pandemic.

KEYWORDS: *Ageusia, Anosmia, Coronavirus disease 2019, Olfactory and gustatory dysfunction, Severe acute respiratory syndrome coronavirus 2*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) was first discovered in China in late 2019 has rapidly transformed as global pandemic worldwide [1]. SARS CoV-2 belongs to coronaviridae family and has a single-stranded RNA genome, enveloped virus. Based on early reports, bat is a natural origin of SARS CoV-2 [2,3]. Common clinical manifestations of COVID-19 infection include headache, fever, dry cough, fatigue, myalgia, anorexia, shortness of breath, sore throat, nasal congestion and less common are nausea, vomiting, and diarrhea [2-5]. Recently, several surveys and reviews proposed that acute taste and smell dysfunction in COVID-19 infection is a noteworthy finding [6-15]. This review summarizes the evidence regarding the association of anosmia and ageusia with SARS-CoV-2 infection.

STRUCTURE OF VIRUS AND MECHANISM OF ACTION

SARS CoV-2 has four structural proteins: spike (S) protein, nuclear capsid (N) protein, membrane matrix (M) protein, and envelope (E) protein, gathering of these proteins into infectious virion leads to distinct toxicity of coronavirus. The

coronavirus invasion of the target cells is mediated by trimeric S protein with two domains, S1 for binding to the host cell receptors and S2 for the fusion process with the host cell membrane. The S1 upper lobular domain contains an angiotensin-converting enzyme 2 (ACE 2) receptors binding feature that engages the host cells to initiate entry into the cell. S2 domain contains the machinery required for the virus to fuse with the host cell membrane. S proteins are the main target for neutralizing antibodies and for new developing therapies because of their peripheral positioning [16,17].

SARS CoV-2 uses the ACE2 as receptor, which has ubiquitous distribution into the human body. ACE 2 receptors display the highest expression on type II alveolar cells, upper and stratified epithelial cells, absorptive enterocytes from ileum and colon, myocardial cells proximal tubule cells of kidney, bladder uroepithelial cells, glial cells and


*Address for correspondence:

Dr. Himani Tiwari Chaturvedi,
Department of Oral Pathology, Dharmsinh Desai University, A1/57,
Darshanam Greens, BH Baroda Public School 2, Near Nathdwara
Residency, Dabhoi Waghodia Ring Road, Vadodara - 390 019,
Gujarat, India.
E-mail: himanicsc@gmail.com

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neurons [18-20], oral tissue cells (highly express on the tongue rather than buccal and gingival) [5], and nasal epithelial cells [21].

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. The main route of SARS CoV-2 transmission is by infected fluid droplets secreted by the respiratory system of infected individuals. The virus spreads by droplets while sneezing, coughing, or talking without covering the mouth and nose. Other transmissible methods are direct contact, contact with infected individual, contacting contaminated surface or objects, touching mouth, eyes, nose with contaminated hands, fecal, oral, and body fluid routes [16,17].

New data regarding this pandemic disease is continuously unfolding. Several studies globally have emerged on the loss of smell and taste as notable early symptoms in the majority of COVID-19 patients [8-12].

Severe and sudden alteration of taste and smell without rhinorrhea or nasal obstruction can be reliable symptoms in the early stage of COVID-19 [11,22]. Neurotropic or neurovirulent and cytopathic effect of SARS-CoV-2 infection hypothesized the pathological basis of targeting the gustatory or olfactory systems.

PATHOPHYSIOLOGY OF SMELL AND TASTE DYSFUNCTIONS [FIGURE 1]

The exact pathogenesis of SARS CoV-2 with which it could impair the smell and taste remain unclear.

Studies confirmed that SARS CoV-2 uses ACE-2 as the receptor for host cell entry mainly through endocytosis and uses the transmembrane serine protease 2 (TMPRSS2) for S protein priming along with activation. Although some discrepancies regarding this showed that nasal cavity respiratory cells have low level of ACE-2 and TMPRSS2 proteins as compared to the lower part of respiratory organs. Hence, this may be one reason why lungs are the primary target organ in COVID-19 [14].

Many viruses such as rhinovirus, coronavirus, parainfluenza virus, and Epstein–Barr virus make transient changes in smell perception and responsible for olfactory dysfunctions [23].

Loss of smell without any significant nasal inflammation in COVID-19 may be due to: (1) Direct damage of olfactory receptor neurons located on olfactory epithelium by virus, (2) cytokine storm (uncontrolled or marked increase of immune cells and cytokine release) and affect nervous system include sensory organs of smell, (3) nonneuronal cells located in the olfactory epithelium express both, ACE-2 and TMPRSS2 protein receptors, required for efficient SARS CoV-2 infection in humans. The nasal epithelium has both neuronal and nonneuronal cells. ACE-2 and TMPRSS2 proteins are essential for SARS CoV-2 entry; however, which are neither displayed by olfactory sensory neurons nor by olfactory bulb but present on stem cells, supporting cells and perivascular cells. This suggests that virus does not directly attack olfactory sensory neurons and olfactory bulb but instead may attack olfactory epithelium supporting and stem cells and vascular pericytes [14,17]. Hence, primary infection of nonneuronal cell types may be the cause to anosmia in COVID-19 patients possibly by three ways [14,24].

1. Local infection of supporting cells and vascular pericytes leads to significant inflammatory responses, which may cause change in olfactory mucus or ion imbalance, and can alter or modulate the function of olfactory sensory or bulb neurons [24,25]
2. Supporting cells damage has the potential to change ion ingredients, which may indirectly impact on signaling from olfactory sensory neurons to the brain [24,26].
3. Damage to the sustentacular cells and Bowman’s gland cells in mice models leads to olfactory sensory neuron death, which can disturb smell function [24,27].

Several studies suggest the virus has neural spread and cytopathic effect on neurons, mainly in the cortex and thalamus [20,28,29].

According to Xu *et al.* reported high ACE 2 receptors expression on the oral cavity mucosa and epithelial cells of the tongue, so SARS CoV-2 may have an effect on taste buds or receptors directly [5].

Loss of taste might be linked to binding between SARS-CoV-2 and sialic acid receptors, a component of saliva that protects the glycoproteins responsible for the transport of molecules stimulating taste in the taste pores, which leads to degradation of taste particles with an alteration of taste sensation [11,17].

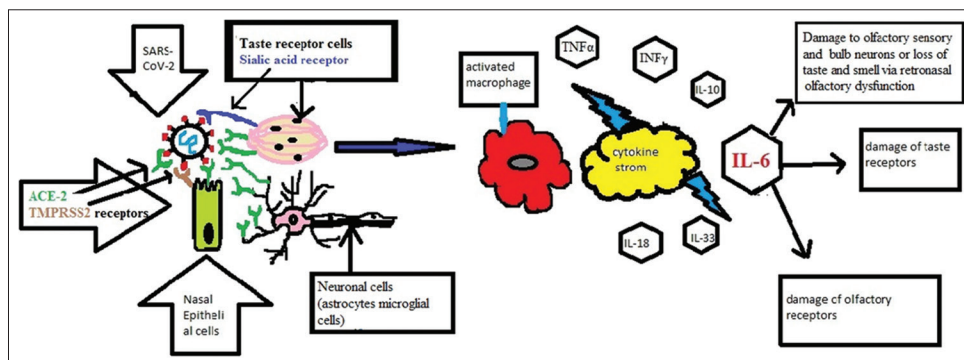


Figure 1: Pathogenesis of loss of taste and smell due to severe acute respiratory syndrome coronavirus 2

The ability to separate flavors, including odor's smell, taste, temperature and texture, depends on the retronasal stimulation pathway. Some authors say, loss of taste can be linked to loss of smell because the brain combines the perceptions of taste from the mouth, so mostly loss of taste due to retronasal olfactory dysfunction [11,14].

In COVID-19, the dysregulated immune system responds by secreting cytokines (small proteins interleukin-6 [IL-6], IL-8, IL-10, tumor necrosis factor-alpha, IL1 β , IL-18, IL-33) in an uncontrolled manner leads to cytokine storm which can develop into a severe acute respiratory distress syndrome and multiple organ damage. It has been suggested that IL-6 is the most common type of cytokine released by activated macrophages and rise sharply in the severe manifestations of COVID-19. Study on 67 patients demonstrates a close correlation between the level of IL-6 and taste and smell dysfunctions. Reduction of disturbances accompanied by a progressive reduction of IL-6 level, which return to normal value when disturbance disappears [11,30].

Recent studies are now supporting that acute onset of loss of taste and smell could be important presenting symptoms of SARS-CoV-2 infection. Olfactory and gustatory disorders may occur at varying intensities and before the general symptoms of COVID-19 and even in mild cases, should be considered as a part of clinical features. Still, there is no scientific evidence of specific treatment for such disorders in COVID-19 [31].

Incidence of olfactory and gustatory dysfunctions was higher in European (34%–86%), North America (19%–71%), and the middle east (36%–98%) as compared to the Asian population (11%–15%) [7-10,12,32]. This clinical difference in COVID-19 patients may be due to variation of the affinity of SARS CoV-2 to different tissue sites in the different ethnic groups, as explained by Lechien *et al.* or alternatively, genomic mutation in Europe and North America could be the possibility [7].

DIAGNOSTIC TOOLS FOR ANOSMIA AND AGEUSIA

We can use questionnaire for clinical diagnosis and follow-up in anosmia and ageusia patients.

Studies usually include SARS-CoV-2 polymerase chain reaction confirmed cases and evaluated for anosmia and ageusia using numerous validated questionnaire based on smell and taste components [7-9,12].

In one study, the olfactory and gustatory function was objectively tested by using common odorants and salt, sweet, sour, bitter taste, respectively [10].

However, more data are needed to provide quantitative data on the incidence and severity of these symptoms in association with SARS-CoV-2 infection.

CORRELATION OF ANOSMIA AND AGEUSIA WITH OTHER CLINICAL SYMPTOMS

Despite so many researches, there is very less information available on the association of anosmia and ageusia correlation with other symptoms of COVID-19. Olfactory

dysfunction was described to be the first symptoms of COVID-19 in 2.9%–11.8% of patients [7,33]. The severity of loss of smell is highly correlated with loss of taste. Only 4.8% of patients with olfactory dysfunctions experienced no symptoms of fever, cough, or shortness of breath compared to 95.2% of patients with olfactory dysfunctions who had at least one of these symptoms. However, fever and cough did not correlate with Olfactory dysfunction either, but patients with olfactory dysfunctions had more severe shortness of breath as compared to those without olfactory dysfunctions [33]. Loss of smell and taste significantly correlated with fever, younger age, and female sex [7]. Hence, correlation between anosmia and ageusia and other presenting symptoms for their possible prognostic role is subjected to further advance studies and researches.

TREATMENT

General treatment has been considered for anosmia and ageusia in patients with COVID-19 infection; paracetamol, nonsteroidal anti-inflammatory drugs, nasal saline irrigations, chloroquine, mucolytics, and oral corticosteroids. For olfactory dysfunction, the most frequently used methods were nasal saline irrigations, nasal and oral corticosteroids and vitamins and noncorticoid decongestants and trace elements. Gustatory dysfunction was treated by L-carnitine, trace elements, and vitamins [7].

The use of caroverine, alpha-lipoic acid, or Vitamin A is also useful for treating olfactory dysfunction [14]. More studies need to be performed before the use of these treatment regimens.

Olfactory training is simple, safe, and readily available method in the context of social distancing, performed by patients themselves two times a day for 12 weeks. They exposed to 4 intense odors, phenyl ethyl alcohol: rose, eucalyptol: eucalyptus, citronellal: Lemon and eugenol: clove and the studies confirmed the efficacy of training. The pathophysiology is not clear, but it is hypothesized that repeated odorant smelling might have the potential to promote the regenerative capacity of olfactory neurons [14,17]. Over 90% of COVID-19 patients with loss of smell may recover that sense of smell within the 1st month and olfactory training is strongly recommended if smell has not recovered after that period but can be started early [34].

RECOVERY RATE

Short-term olfactory and gustatory recovery rate is approximately 44%–74% in COVID-19 patients is quite a good prognosis [14].

Lechien *et al.* confirmed that anosmia function recovered within the first 8 days following the resolution of disease in 67.8% of cases and it believes that 25.5% of patients, at least, recovered both olfactory and gustatory functions throughout the 2 weeks after resolution of general symptoms [7].

Nevertheless, it is still too early to assess long-term olfactory improvement in COVID-19 patients, as well as gustatory improvement.

CONCLUSION

COVID-19 presented as a dreaded challenge globally because of its multifacial presentations, rapidly changing viral strains and life-threatening organ damages, along with a little and limited handful of knowledge about pathogenesis leading to fatal complications. Hence, restricted and very narrow window of available treatment options has left us with more number of questions than answers. This review article supports the recent reports that SARS CoV-2 may infect oral and nasal tissues and cause olfactory and gustatory dysfunctions. Concluding that far more miles to go to understand the disease and anosmia and ageusia, when present, can be reliably considered as an effective tool for early suspecting or diagnosing or screening of COVID-19 and with prompt treatment positively effecting the further prognosis and course of the disease, subject to further studies and researches.

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Conflicts of interest

There are no conflicts of interest.

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