

Review Article

Smell and taste abnormalities: early clinical biomarkers for isolating the positive cases in COVID-19 pandemic

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is an infectious disease of the respiratory tract caused by a novel virus called severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). It primarily spread human to human by droplets which carry virus. The common clinical presentations of the COVID-19 patients are fever, cough, fatigue, gastrointestinal symptoms and dyspnea. Smell and taste abnormalities have recently documented among patient with COVID-19 infection which hypothesize that olfactory mucosa and oral cavity mucosal lining possess SARS-CoV-2 virus. Some COVID-19 patients are also presenting with isolated smell and taste disturbances even without any other respiratory symptoms. Currently there is no effective treatment available for COVID-19 infections. So screening, early diagnosis and isolations are essential in this pandemic. Identifying the early symptoms in COVID-19 patient is priority now in health care system. In COVID-19 pandemic, patient presenting with loss of smell and taste should initiate home isolation and social distancing for avoiding further spread of this disease. This can be confirmed by diagnostic test such as reverse transcriptase-polymerase chain reaction (RT-PCR) when available. Sudden onset of smell/olfactory and taste/gustatory dysfunctions should be considered in routine work up and screening of the patients with COVID-19 infection. This review article focuses on the smell and taste abnormalities among COVID-19 patient which will surely increase the awareness among the front liner clinicians and help them for early diagnosis of the patient and their management.

Keywords: COVID-19 infection, SARS-CoV-2, Smell disturbance, Taste disturbance

INTRODUCTION

COVID-19 is an infectious disease caused by a novel coronavirus called as SARS-CoV-2.¹ The initial COVID-19 infection started at the Hubei region of the China in late 2019 and rapidly spread all over the world and become a pandemic.² This infection often causes respiratory symptoms and even causes respiratory distress and death. Angiotensin converting enzyme 2 (ACE 2) was found as the functional receptor for SARS-CoV-2 in several organs of the human body including the central nervous system.² Rapid spread of the COVID-19 infections currently threatens to the world and also healthcare system. Now the early identification of COVID-19 patient is urgently needed to isolate the

patient and control the spread of the infection. The incidence of the smell and taste dysfunctions in viral infections are not new in clinical practice. There are several viruses such as rhinovirus, parainfluenza, Epstein-Barr virus and some corona virus cause inflammatory reactions of the nasal mucosa, rhinorrhea and olfactory dysfunction.³ However, the smell dysfunction in COVID-19 infections is usually not associated with rhinorrhea. The association between the smell and taste disturbances and clinical outcomes in COVID-19 patients may carry the important implications towards future investigations for understanding the SARS-CoV-2 virus ability to overwhelm the host immune response. The most efficient method for preventing spread of the COVID-19 infection is early identification of the symptoms like smell and

taste abnormalities and isolation of the patient. Currently the smell and taste abnormalities by SARS-CoV-2 are increasing reported in the medical literature in COVID-19 pandemic. The sudden onset of the anosmia or ageusia should be considered as important symptoms in the international forum for early diagnosis of the COVID-19 patients. These symptoms act as a biomarker in this pandemic for early isolation of the patient. The aim of this review article is to discuss on the epidemiology, pathophysiology, clinical outcome, diagnosis and treatment of the smell and taste abnormalities among COVID-19 patients.

METHODS OF THE LITERATURE SEARCH

For searching the published research articles, we conducted an electronic survey of the SCOPUS, Medline, Google scholar and PubMed database. A search strategy using PRISMA (preferred reporting items for systematic reviews and meta-analysis) guidelines was developed (Figure 1). Randomized controlled studies, observational studies, comparative studies, case series and case reports were evaluated for the eligibility. This paper focuses only on the smell and taste disturbances of COVID-19 patients. The search articles with no primary data related to the smell and taste disturbances were excluded. Non-English articles were also excluded. The search terms in the database included smell and taste disturbances, COVID-19 infection and SARS-CoV-2 virus. The abstracts of the published articles were identified by this search method and other articles were identified manually from citations. This manuscript reviews the etiopathology, epidemiology, clinical outcome, diagnosis and treatment of the smell and taste disturbances in COVID-19 patients. This review article presents a baseline from where further prospective studies for smell and taste disturbances in COVID-19 patients could be designed and helps as a spur for further research in this clinical symptom.

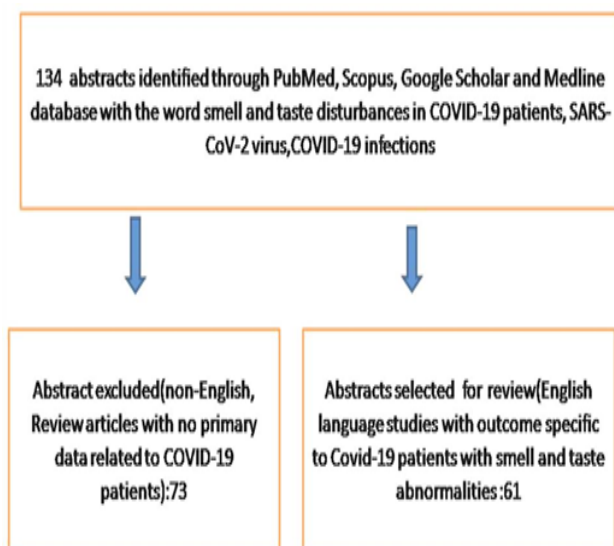


Figure 1: Method of literature search.

EPIDEMIOLOGY

The first case of the COVID-19 pandemic was detected in December 2019 at Wuhan, China.¹ The disease was progressively spread to other Asian countries, Iran, European countries such as Italy, France, Spain, Germany and UK. Later this infection spread to USA, Mexico, Brazil and Argentina. By 10th May 2020, approximately 4 million population globally in 215 countries became positive for SARS-CoV-2 infection.⁴ Till early August 2020, COVID-19 infection affected 18 million people and caused deaths of more than 700,000 all over the world.¹ The world health organization (WHO) declared this disease as a global pandemic on March 11, 2020. Incidence of the olfactory and gustatory dysfunctions is well established after viral infections and found to be key symptoms in COVID-19 patients. In previous study by Chinese author, smell and taste disorders in COVID-19 patients was estimated to be around 5% and these data were documented retrospectively from the medical files, which may lead to underestimation of the true prevalence.⁵ However, the European data showed a very high frequency of chemo sensitive dysfunctions in COVID-19 patients with ranges from 19.4 to 88%.^{6,7} One study reported high rates of olfactory and gustatory dysfunction (98%) by quantitative analysis of the COVID-19 inpatients but only approximately 25% of them showed complete loss of the smell and taste and 35% of them self-reported.⁸ A recent study at USA showed a prevalence of 13.5% for impairment of the smell, 17.3% for impairment of the taste sensation and 2.2% for both smell and taste impairment in adult population.⁹ This discrepancy between quantitative analysis and self-reported smell and taste disturbances are thought to be related to the underreporting or unawareness of these symptoms. The decreased awareness of these smell and taste disturbances in COVID-19 patients may lead to more severe symptoms like respiratory failure.

COVID-19 VIRUS

SARS-CoV-2 virus is a large, encapsulated or enveloped positive strand RNA virus (Figure 2) which can be classified into four genera such as alpha, beta, delta and gamma. Out of these four types alpha and beta are known to infect human beings.¹⁰ The size of corona virus varies from 60 to 140 nm with spike like projection from the surface as a crown like appearance under electron microscope, so the name corona virus.¹¹ The spikes over outer surface of the virus are made up of glycoprotein which act as critical for binding to the host cell receptors and play an important role in severity of the infections of the patient.¹⁰ The majority of the host or human receptors for glycoprotein of this virus, human angiotensin converting enzyme 2 (ACE2) is found mainly in the lower respiratory tract rather than upper respiratory tract.¹¹ Because of scarcity of the receptors in the upper respiratory tract, the clinical symptoms related to upper airway is minimal. The incubation period of COVID-19

ranges from 1 to 14 days with a median of 5-6 days. Although recent study document that the incubation period may extend to maximum 24 days.¹¹ A longer incubation period has implication in quarantine policies and prevention of the spread of the infection. This virus primarily transmitted from human to human via droplets but also it is seen in blood and stool, so raising question regarding the multiple modes of transmission.¹²

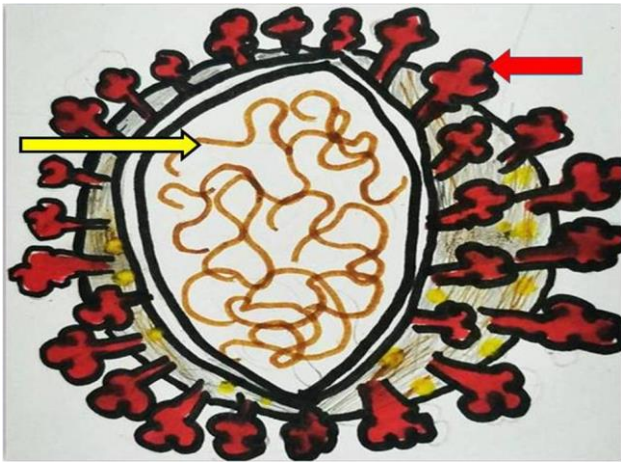


Figure 2: Structure of the COVID-19 virus (red arrow is spike protein over lipid membrane, yellow arrow indicates RNA).

PATHOPHYSIOLOGY

The exact pathophysiology for smell and taste disturbances in COVID-19 infections are not clear. There are controversies regarding the etiology of impaired smell and taste disturbances in COVID-19 patients whether by infecting directly or by neurological disease or other infections or direct damage of the organ itself. There are two potential mechanisms for explaining the olfactory dysfunctions such as: mechanical blockage of the olfactory function due to inflammation, as found in the olfactory cleft syndrome or neuro-epithelial injury occurred when the olfactory epithelium and sensory neurons damaged by the infections.^{13,14} The nasal airflow odorants reach the neuro-epithelium of the olfactory fossa of the nasal cavity which covers a surface of 8 to 10 cm² where they bind or activate the olfactory receptor proteins. The olfactory neuro-epithelium possesses 5 to 30 million receptors neurons and these express up to 350 different olfactory receptor proteins.¹⁵ On the other hand the taste sensation is conveyed via only five taste receptors such as salt, sweet, bitter, acidic/sour and umami/sodium glutamate expressed at the tongue and palatal gustatory buds. Currently, it has been suggested that damage of the olfactory epithelium by the virus or its transmission into the central nervous system can cause smell and taste disturbances among the COVID-19 patients.¹⁶ The direct transmission of the SARS-CoV-2 virus via the nasal mucosa to the olfactory bulb occur by angiotensin converting enzyme 2 receptor and transmembrane protease serine 2 (TMPRESS2).¹⁷ The

two proteins ACE2 and TMPRESS2 are needed for the host cell entry which facilitates replication, accumulation and binding of the SARS-CoV-2 and expressed in the sustentacular cells, receptor neurons of the olfactory neuro-epithelium which have potential role in loss of smell in COVID-19 patients.¹⁸ The gustatory dysfunction has not been thoroughly investigated in upper airway infections.

The neuro invasive property of the SARS-CoV-2 might have role for pathophysiology of smell and taste disturbances.¹⁹ As the olfactory mucosa is found at the roof of the nasal cavity, a direct or indirect effect of the SARS-CoV-2 in situ may be another explanation for these clinical manifestations. The SARS-CoV-2 is infecting the olfactory epithelium in the nasal cavity and causes localized inflammation there which lead to olfactory dysfunction. Such phenomenon may cause rapid recovery of the olfactory function along with resolution of the viral infection.²⁰ The SARS-CoV-2 can cause death of the neurons in a mice model which has been proved experimentally. This happened when the virus entered to the central nervous system via the olfactory epithelium.²¹ Previously the research has already confirmed the expression of the ACE2 receptors in the nervous tissue like glia and neurons.²² In viral rhinitis, mechanical obstruction may occur due to hypertrophy of the turbinate's and cause anosmia. The anosmia due to mechanical obstruction of the nasal cavity during rhinitis is usually resolved within three days.²³ However the duration of the anosmia in COVID-19 infections is longer period.

CLINICAL OUTCOME

COVID-19 infection currently continues to affects the individuals of all age groups and the symptoms ranges from asymptomatic to fatal presentations like respiratory failure and even death.²⁴ The most common clinical symptoms of the COVID-19 patients are fever, myalgia, cough, fatigue and dyspnea. In addition to these symptoms, losses of smell and taste have also reported as the important presentations of the COVID-19 patients.²⁵ If the clinical symptoms are neglected, patients may land in respiratory failure and death. ²⁶ The old age patients with COVID-19 infections are more susceptible to acute respiratory distress syndrome (ARDS) and cytokine storm.²⁷ The clinical presentations of the COVID-19 patients may appear 2 to 14 days after exposure to the viral infections as per the incubation period of the SARS CoV-2 virus.²⁵ It has been documented that SARS-CoV-2 may manifest smell and taste disturbances without any nasal congestion and nasal discharge unlike to other viral infections of the upper respiratory tract.²⁸ This behavior of the SARS-CoV-2 is considered as contrary to the observations in patients infected with other upper respiratory tract viral infections. There is growing number of the literature about the loss of smell and taste strongly correlates with prevalence of the COVID-19 infections.²⁹ Patients those present with influenza like

symptoms with smell and taste disturbances are six to ten times more likely to be infected with SARS-CoV-2.³⁰ About 59 to 86% of COVID-19 patients are self-reported with smell and taste disturbances.³⁰ Post-viral olfactory dysfunction is common in female than male and has favorable prognosis unlike other neurological causes of the anosmia.³¹ The smell and taste disturbances in COVID-19 infection has significantly affect the quality of life (QoL) and also cause decreased ability for detecting the noxious environmental materials such as gas leaks, fire, spoiled food, reduced appetite, malnutrition, lowering the immunity and worsening of the medical illness. Olfactory and gustatory dysfunctions are also associated with increased mortality. Some patients may present with isolated smell and taste disturbances even without having any respiratory symptoms. The partial or complete loss of smell and taste has a wide differential diagnosis. However, there are several current literatures showing impaired smell and taste could be manifestations by the COVID-19 infections. The international and national authorities should also consider about the isolated smell and taste disturbances as a sufficient basis for testing the patient with RT-PCR and/or isolate the patient for limiting the spread of the infection.

DIAGNOSIS

A COVID-19 patient is diagnosed on the basis of the positive result of the real time reverse transcriptase polymerase chain reaction (RT-PCR) assay from nasopharyngeal and oropharyngeal swab specimens. There are several tests available for smell and taste abnormalities. Although the objective tests for smell and taste are more sensitive to determine the degree of loss of smell and taste and also for recovery and the self-reporting for loss of smell and taste are relatively accurate.³² Sense of the smell are tested by asking the patient to smell of the lemon, peppermint, rose, cloves and garlic for each side of the nose separately with eye closed. The taste sensations of the patients are tested by using table sugar (for sweet), table salt (for salt), citric acid (lemon juice) for sour and coffee for bitter test. In COVID-19 patients, olfactory and gustatory assessment can be done by: (a) written or online questionnaire but this test is more qualitative than quantitative; (b) visual analogue scale (VAS, 0-10 cm), this is easy to perform and fast, safe and quantitative method used for daily clinical practice; (c) a subjective olfactometry but this is not recommended to be used in a face to face use in COVID-19 patient because of the chance of transmission of infection to the patient and health care professional.¹⁵ By proper training, some of these tests can be done by help of the video consultations through telemedicine, which are safe for both patient and examiner. Individual assessment for smell sensation such as University of Pennsylvania smell identification test (UPSIT) could be considered, however being culturally dependent and should be properly validated in different country and populations.³³ Chemical gustometry is helpful to

differentiate between different smell and taste but because of the chance of infections, only individual disposable kits are advised in COVID-19 patients.

TREATMENT

The effective treatment options for the COVID-19 patients are currently under the urgent investigation. Currently there is no evidence of the randomized clinical trials regarding the specific treatment which improves the patient outcome in COVID-19 infection.^{34,35} According to world health organization (WHO) recommendations, everybody should protect themselves against COVID-19 infection which will protect also other people. Currently there are no effective treatment and vaccine for COVID-19 infection available. The screening, rapid diagnosis and isolations of the COVID-19 patients are essential for further spread of this disease.³⁶ The current evidence-based treatment option for post-viral olfactory dysfunction is olfactory training.³⁷ The olfactory function is usually modulated by repeated exposure to different odors. Olfactory training improves the sensitivity the odors used during the training process.³⁷ More than 90% of the COVID-19 patients with smell disturbances may recover within first month and the olfactory training is strongly advised if olfaction has not recovered after that period of the time but also can be started earlier. Post-viral smell and taste disturbances are common cause for permanent olfactory and gustatory dysfunctions. There are no specific pharmacological options for treatment of the smell and taste disturbances in COVID-19 infection. The common treatment in COVID-19 patients include nasal saline irrigation, paracetamol, non-steroidal anti-inflammatory drugs either, mucolytic, nasal and or oral corticosteroids, vitamins, non-corticoid decongestants and their trace elements. The role of topical and systemic corticosteroids for post-viral smell and taste loss is not clear although these are used as first line therapy for a potential virus exacerbation of allergic rhinosinusitis than post-viral condition. If the patients are treated with corticosteroids for Sino nasal inflammatory disease in COVID-19 pandemic, discontinuation of the treatment is not advised.^{38,39}

CONCLUSION

Smell and taste disturbances are often found in COVID-19 patients. These symptoms may be presented as the first and/or only symptoms by COVID-19 patients. During the COVID-19 pandemic, the patients presenting with smell and taste disturbances, clinicians should consider COVID-19 as a differential diagnosis for achieving early identification, avoid delayed diagnosis and prevention of the transmission of the virus. So, the screening of these smell and taste disturbances in the community may facilitate for early diagnosis of the SARS-CoV-2 infections. Impaired smell and taste in COVID-19 patients would allow for self-isolation and urge a signal to their health care workers for prompt management.

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