

Impairment of olfactory and gustatory sensations in severe acute respiratory syndrome corona virus 2 (SARS-CoV-2 virus) disease

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ABSTRACT

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2 virus) disease had first appeared in December 2019 in Wuhan, China, and since then, it has emerged as a global threat to humanity. An early diagnosis and isolation are the most significant measures required to prevent its spread. Recent anecdotal evidence has suggested impairment of olfactory and gustatory sensations associated with corona virus disease (COVID-19). Angiotensin-converting enzyme-2 is an important aspect for the manifestations seen in this deadly viral disease. The associated olfactory and gustatory dysfunction can also lead to partial and/or complete loss of the ability to smell and taste in the early stages of disease onset. Evidence has also suggested that the presence of SARS-CoV-2 nucleic acid in human saliva makes it the carrier of the infectious viral disease and aids in its diagnosis. The present review focuses on the listed clinical manifestations in the form of olfactory and gustatory impairment in SARS-CoV-2 virus disease.

Keywords: Angiotensin-converting enzyme-2 (ACE-2), asymptomatic infection carrier, corona virus disease (COVID-19), diagnostics, gustatory perception, olfactory impairment, saliva, severe acute respiratory syndrome corona virus 2 (SARS-CoV-2 virus) disease

Introduction

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2 virus) is responsible for causing corona virus disease (COVID-19). Since its outbreak, this deadly, infectious disease has become a serious global threat infecting people worldwide.^[1] SARS-CoV-2 has its roots from Nidovirus family and shares 96.2% genetic

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similarities with the corona virus found in bats, thus, hypothesized to be possessing a possible zoonotic origin.^[2,3] It is also postulated that bat corona virus might have undergone homologous recombination with some intermediate host and has developed the ability to infect humans. The virus mainly spreads via droplets from an infected patient, but can also spread through direct contact and orofaecal route.^[4] Viral genome studies suggest that the majority of samples were infected with S-type while rest with L-type subtypes of SARS-CoV-2 virus.^[4] The possible binding of virus spike protein (a surface glycoprotein) to angiotensin-converting enzyme-2 (ACE-2) expressed in host cells is considered to be the major factor in pathogenesis of this deadly viral disease.^[5] This is the reason why respiratory manifestations are reported commonly amongst the infected hosts as Type 2 pneumocytes present in lungs express the said enzyme in large amounts while infected patients develop pneumonia-like symptoms including shortness of breath and dry cough followed by high fever, and in later stages, acute respiratory distress syndrome with numerous other secondary complications as multiple organ failure. In addition, upper respiratory manifestations including nasal congestion and sore throat are commonly observed in patients exhibiting mild disease.^[6] Since virus accesses host cells via enzyme ACE-2, there has been evidence that superficial stratified epithelial cells of the esophagus, absorptive enterocytes from ileum and colon, cholangiocytes, myocardial cells, renal proximal tubular cells, and urothelial cells of the bladder also act as important host where an active infection can be seen since they all express high amounts of enzyme ACE-2.^[7] The analysis of bulk-seq ribonucleic acid (RNA) datasets also suggests the expression of similar enzyme ACE-2 by oral mucosa, especially, in higher concentrations in the tongue than other oral sites including gingival tissues and cells of the buccal mucosa.^[7] Therefore, there is a high probability that oral mucosa and various other organs excluding lungs are at an increased risk for secondary sites of infection in the pathogenesis of the disease process. In a mice model, this has been further emphasized based on the observation that SARS-CoV-2 virus can enter via olfactory bulbs.^[8] Some of the published literature reports cutaneous and systematic manifestations of SARS-CoV-2 infection in detail, and although there is a paucity of data in relation to the oral manifestations and impairment of olfactory and gustatory sensations in this infectious disease with oral mucosa being a possible source of infection acting as a reservoir for the virus in clinically occult cases. Few studies, on limited available evidence, have reported oral signs and symptoms and olfactory and gustatory dysfunction in the early stages of the disease process prior to the actual symptoms or, even, in asymptomatic cases. Few reports have also indicated that oral signs and symptoms can be independent of olfactory and gustatory dysfunction and vice versa or can manifest simultaneously. The present review focuses on the listed clinical manifestations and olfactory and gustatory impairment in the early stages of SARS-CoV-2 virus disease.

Materials and Methods

The present review was based on a systematic search of PubMed, Google Scholar, and Elsevier databases with key words signs/

symptoms/olfactory and gustatory impairment/early stage/asymptomatic SARS-CoV-2 infection. Quick reading of abstracts was conducted and significant articles were kept for review. In addition, cross references that seemed to be clinically relevant were also accessed. All original articles, letters to editor, case reports, and reviews in English literature were included for review.

Discussion

SARS-CoV-2 virus is a nonsegmented, *positive-sense, single-stranded* RNA wrapped in a nucleoprotein (N). The viral envelope (E) surrounds this helical nucleocapsid while matrix protein (M) is embedded in the viral envelope. Spike (S) protein is responsible for attaching, fusing, and infecting particular host cells and this forms the pathogenesis of this highly contagious viral disease. Several of beta corona viruses also possess haemagglutinin esterase protein.^[9] Also, RNA genomes code for four structural proteins (E, N, S, M) and one protein for viral replication/transcription (RNA-dependent RNA polymerase, RdRp).^[9] The viral S glycoprotein attaches to the enzyme ACE-2 expressed in various host cell types including cells from lungs, kidneys, heart, gastrointestinal tract, and oral mucosa, which facilitates entry of virus into host body.^[9] The entry and binding processes are then followed by fusion of viral and host cell membranes.^[10] After fusion occurs, Type 2 transmembrane serine protease present on the surface of host cell membrane clears enzyme ACE-2 and activates receptor-attached spike-like, S protein.^[11] Once the virus enters host cell, viral genome (mRNA) is ready for translation and uses enzyme RdRp for synthesis of necessary proteins.^[11] Since oral mucosa also expresses enzyme ACE-2, chances of oral manifestations as well as alteration in ability to taste and smell cannot be denied.^[7]

In a letter to editor, it has been stated that SARS-CoV-2 RNA has been detected in saliva of infected hosts, even before lung lesions appeared.^[12] Vinayachandran and Balasubramanian^[13] also reported possible oral symptoms including hypogeusia, xerostomia, and chemosensory alterations in infected hosts in SARS-CoV-2 infection. Seo *et al.*^[14] also observed olfactory and gustatory dysfunction in around 24.2% of positive patients presenting with mild SARS-CoV-2 infection in their study. Evidence has also suggested that 95.8% of infected hosts of SARS-CoV-2 infection present with symptom of anosmia. In addition to anosmia, other common manifestations of SARS-CoV-2 infection include ageusia and dysgeusia which, too, have been reported frequently. The possible explanation behind anosmia seen as a manifestation of SARS-CoV-2 infection could be either due to viral involvement in central nervous system (CNS) causing damage to nasal ducts or local tissues affecting olfaction; although the exact phenomenon behind this still being unclear.

Another possibility behind olfactory and gustatory dysfunction in SARS-CoV-2 infection is due to SARS-CoV-2 virus entering via the olfactory nerve or peripheral trigeminal nerve carrying infection to the CNS, thereby, causing dysosmia and dysgeusia.

Existing literature also suggests that Epstein–Barr virus and some of the corona viruses may cause smell and taste disorders. In addition, upper respiratory tract infections due to virus can induce a permanent disorder leading to a partial or complete loss of olfactory senses. Fewer studies, have also suggested that postinfection anosmia can be stabilized in few of the cases.^[8,15,16]

In a case series published by Martín Carreras-Presas *et al.*,^[17] out of three patients including two suspects and one confirmed case of SARS-CoV-2 infection, pain, dysgeusia, and enlargement of lymph nodes were reported as the major clinical presentations in confirmed SARS-CoV-2 infection even before the onset of intraoral lesions. In another case reported by Ciccarese *et al.*,^[18] patient reported cutaneous and oral manifestations including hyposmia and oropharyngeal lesions on the seventh day of onset of symptoms. The characteristic findings in said patient included sudden onset anosmia with asymptomatic cutaneous and oropharyngeal lesions, which later evolved into frank oral erosions and ulcerative lesions on the inner surface of lips and palatal and gingival tissues. In a similar case study of another confirmed SARS-CoV-2 infection published by Cebeci Kahraman and Çaşkurulu,^[19] patient presented oral symptoms on the tenth day after onset of symptoms while an interesting finding in said patient was that the patient reported altered olfactory and gustatory functions before onset of oral lesions.

In a similar report by Gane *et al.*,^[20] it was mentioned that a 48-year-old male patient experienced sudden onset anosmia without significant comorbidities when only two days later, he was diagnosed SARS-CoV-2 positive. In another meta-analysis study by Chen *et al.*^[21] including a total of 108 confirmed cases, 47.2% of the patients reported amblygeusia. In another similar analysis of 131 SARS-CoV-2 patients by Abalo-Lojo *et al.*,^[22] 55% of patients reported both olfactory and gustatory dysfunction, while 3.8% patients only olfactory and 1.5% only gustatory dysfunction. Also, 39.7% of patients reported none of above symptoms while the other common SARS-CoV-2 infection-associated symptoms included dry cough, asthenia, myalgia, headache, and diarrhea. Another notable finding in said study was that 13.9% of patients developed symptoms on day one, 70.9% on day 3, while the remaining 15.2% on day 4 of onset of infection [Table 1].

A validated controlled trial conducted in the University of Pennsylvania on 60 confirmed SARS-CoV-2 patients by Moein *et al.*^[23] also confirmed olfactory dysfunction in 98% of patients. Furthermore, 23% of positive patients reported gustatory dysfunction as an early symptom of SARS-CoV-2 infection [Table 1]. In another larger scale research from Europe by Lechien *et al.*^[24] on 417 confirmed SARS-CoV-2 patients, 85.6% and 88.0% of patients reported olfactory and gustatory dysfunction, respectively. Furthermore, olfactory dysfunction appeared before other symptoms in 11.8% of cases while females were affected more for both olfactory and gustatory dysfunction. Also, phantosmia and parosmia were reported in 12.6% and

32.4% of patients, respectively, while among the patients who did not complain of nasal stuffiness and rhinorrhoea, rates of anosmia and hyposmia reported were found to be 66.2% and 13.5%, respectively [Table 1].

Interestingly, in a web-based questionnaire study on 140 quarantined subjects, 38.3% and 32.8% of patients reported impaired sense of smell and taste, respectively, as initial symptoms while 25.8% of patients reported olfactory and gustatory dysfunction in the absence of other symptoms. Moreover, more than 50% of patients reported xerostomia and dysgeusia both as prominent oral manifestations of SARS-CoV-2 infection.^[25] The findings of xerostomia and dysgeusia in confirmed cases of SARS-CoV-2 infection can be explained by the fact that olfactory and gustatory sensations are necessary for stimulation of saliva secretion. Thus, any grade of olfactory and gustatory dysfunction leads to impairment of neurological stimulation resulting in xerostomia and secondary dysgeusia in affected patients.^[26,27]

Melley *et al.*,^[28] in their report of a 59-year-old female patient also suggested hypogeusia and hyposmia as early symptoms of infection with hyposmia later turning-out to complete anosmia with the passage of time. Similarly, in a literature of European Journal of Case Reports in Internal Medicine, two aged patients including an 85-year-old male and an 80-year-old female patient reportedly presented with sudden onset anosmia and fatigue in the asymptomatic stage of infection with a concomitant history of ageusia actually preceding complete anosmia in patients.^[29] Another letter to editor in Spain also suggested similar finding of anosmia which persisted for more than two weeks in a 40-year-old female patient and was more prominent than other clinical symptoms associated with SARS-CoV-2 infection.^[30] Walker *et al.*^[31] in their study using Google trends in eight different countries hypothesized that increase in searches for anosmia and onset of SARS-CoV-2 infection could be correlated with a surge in cases reported for anosmia in the current pandemic. Evidence also suggests that isolated anosmia could be one of the most common initial symptoms of SARS-CoV-2 infection without manifestation of other SARS-CoV-2 infection-associated symptoms.^[32]

In another questionnaire-based study in Spain by Beltrán-Corbellini *et al.*,^[33] 31.65% of patients reported olfactory dysfunction while 35.44% patients reported gustatory dysfunction. Furthermore, early onset disease was seen in 35.5% of patients presenting with olfactory and gustatory dysfunction [Table 1]. The numbers of patients affected with olfactory and gustatory dysfunction were found to be even more in another retrospective analysis done by Klopfenstein *et al.*^[34] in France who reviewed 114 records of confirmed SARS-CoV-2 patients and reported olfactory dysfunction in 47% and gustatory dysfunction in 85% of patients [Table 1].

Infections of influenza and parainfluenza viruses, rhinoviruses, and other endemic corona viruses including common cold and

Table 1: Pattern of olfactory and gustatory impairment in SARS-CoV-2 infection

Author/Reference	Patient's Mean Age/Gender Distribution/ Sample size	Comorbidities/ Severity of SARS-CoV-2 infection	Impairment of Olfactory and Gustatory Sensations. Clinical Outcomes/Early Onset of Impairment of Olfactory and Gustatory Sensations (Before Other Symptoms or, Hospitalization)	SARS-CoV-2 Infection-Associated Other Symptoms
Abalo-Lojo <i>et al.</i> ^[22]	Mean age 50±4 years; Males 42.6%; Females 57.4%. Sample size: 131	Not mentioned. Not mentioned.	55% reported both olfactory and gustatory dysfunction; 3.8% only olfactory dysfunction; 1.5% only gustatory dysfunction; 39.7% reported none of above. On day one, 13.9% cases reported with symptoms, on day 3, 70.9% while the remaining 15.2% after day 4.	Dry cough, asthenia, myalgia, headache, diarrhea, odynophagia, fever (>38°C), anorexia, dyspnea, expectoration, chest tightness, dizziness, nausea, abdominal pain, vomiting, and conjunctivitis.
Moein <i>et al.</i> ^[23]	Mean age 46.55±12.17 years; Males 66.7%; Females 33.3%. Sample size: 60	Diabetes with hypertension. Mild to severe.	98% reported olfactory dysfunction including 58% complete anosmia, 33% severe microsmia, 27% moderate microsmia while 8% mild microsmia; 23% reported gustatory dysfunction.	Fever (n=46, 77%), cough (n=35, 58%), shortness of breath (n=31, 52%), headache (n=22, 37%), myalgia (n=5, 8%), increased sweating (n=2, 3%), chills (n=2, 3%), anorexia (n=2, 3%), stomach-ache (n=1, 2%) and tinnitus (n=1, 2%).
Lechien <i>et al.</i> ^[24]	Mean age 36.9±11.4 years; Males 37%; Females 63%. Sample size: 417	Allergic rhinitis (20%), asthma, hypertension, hypothyroidism. Mild to moderate.	85.6% and 88.0% of patients reported olfactory and gustatory dysfunction respectively. Olfactory dysfunction appeared before other symptoms in 11.8% of cases. Females were more affected as compared to males for olfactory and gustatory dysfunction. 47% reported olfactory dysfunction (anosmia) while 85% reported dysgeusia.	Cough, myalgia, loss of appetite, diarrhea, fever, headache and asthenia.
Klopfenstein <i>et al.</i> ^[34]	Mean age 47±16 years; Males 33%; Females 67%. Sample size: 114	Hypertension, cardiovascular disease, asthma. Not mentioned.	31.65% reported olfactory dysfunction including 45.7% complete anosmia, 29% hyposmia and 6.5% dysosmia among 31 SARS-CoV-2 patients with olfactory and gustatory dysfunction; 35.44% reported gustatory dysfunction including 45.2% complete ageusia, 22.6% hypogeusia and 25.8% dysgeusia among 31 SARS-CoV-2 patients with olfactory and gustatory dysfunction. Early onset disease was seen in 35.5% of the 31 SARS-CoV-2 patients presenting with olfactory and gustatory dysfunction.	Fatigue (93%, n=50), cough (87%, n=47), headache (82%, n=44), fever (74%, n=40), myalgia (74%, n=40), arthralgia (72%, n=39) and diarrhea (52%, n=28).
Beltrán-Corbellini <i>et al.</i> ^[33]	Mean age 61.6±17.4 years; Males 60.8%; Females 39.2%. Sample size: 79	--	Not mentioned.	Not mentioned.
Giacomelli <i>et al.</i> ^[8]	Median age 60 years; Males 67.8%; Females 32.2%. Sample size: 59	--	11.9% reported complete anosmia while an equal number of patients, 11.9%, reported hyposmia; 13.6% reported ageusia while 15.3% dysgeusia. 20.3% reported olfactory dysfunction while 91% gustatory dysfunction as early onset disease symptoms.	Fever, cough, dyspnoea, sore throat, arthralgia, coryza, headache, asthenia and abdominal symptoms.

flu viruses have all been associated with a characteristic olfactory dysfunction.^[35,36] Recent anecdotal and scientific reports have also provided evidence that SARS-CoV-2 infection-associated chemosensory impairment is limited not only to olfactory but also to a gustatory dysfunction as well in addition to *chemesthesis*.^[37] Not to forget, all recent data and research are based on a limited sample size while case reports published are merely anecdotal

evidences and based on suspected SARS-CoV-2 infection without a confirmed laboratory diagnosis. Furthermore, evidence has also suggested that olfactory dysfunction in SARS-CoV-2 patients can be an initial manifestation before the actual onset of other significant SARS-CoV-2 infection-associated symptoms while it can be seen alone or in association with gustatory dysfunction and vice versa.

Conclusion

In the limited number of studies available to date, SARS-CoV-2 infection has been reported to be associated with varied manifestations. In this context, during the pandemic, possibility of SARS-CoV-2 infection should be carefully evaluated, particularly, in patients presenting with characteristic findings. On the other hand, it should be kept in mind that the disease may also show findings related to viral infections, in general, with or without a prodrome. A timely and accurate identification of the relevant clinical manifestations, thus, may play a key role in the early diagnosis and management of such patients. Data from more research work, however, are always mandated to know further the true etiopathogenesis of this deadly disease process and its varied clinical manifestations. An in-depth analysis of the manifestations is also required to further confirm the role of saliva and other mucosal exudates and infected secretions in the spread of this deadly infection. It is but obvious that extensive research work is mandated to understand the exact relationship between SARS-CoV-2 infection and the associated manifestations attributed to it.

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Conflicts of Interest

There are no conflicts of interest.

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