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Oral Manifestations and Olfactory and Gustatory Dysfunction in Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-Cov-2 Virus) Disease: A Systematic Review

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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 has been spreading quickly throughout the world since then. Since then, the outbreak of this severe viral disease has become 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 oral manifestations with or, without olfactory and gustatory impairment in association with corona virus disease (COVID-19). Angiotensin converting enzyme-2 (ACE-2) is expressed in oral mucosa in large amounts and can, thus, contribute in the early manifestations of this deadly viral disease. The oral manifestations of corona virus disease can occur in the form of irregular ulcerative lesions in relation to different parts of the oral cavity and particularly, in relation to the attached mucosa in the hard palate region as well as inflammation and subsequent, atrophy of the various tongue papilla. The associated olfactory and gustatory dysfunction can, also, lead to partial and/or, even a complete loss of the ability to smell and taste in the early stages of the disease onset. Evidence has, also, suggested the presence of SARS-CoV-2 nucleic acid in human saliva making it the carrier of the infectious viral disease as well as aiding in its diagnosis. We have systematically searched medical database for the same and have reviewed all the literature available up to 29th of the June 2020.

Keywords: Oral Manifestations; Olfaction; Gustatory Dysfunction; Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-Cov-2 Virus) Disease; Corona Virus Disease (COVID-19)

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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 1,00,55,037 people worldwide while 4,99,892 deaths have been reported till date. In India alone, 16,095 deaths with 5,28,859 people infected have been reported till date [1]. SARS-CoV-2 has its roots from Nidovirus family and shares 96.2% genetic 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 oro-faecal route [4]. Viral genome studies of 103 samples suggest that around 30% of them were infected with S-type while the rest, with L-type subtypes of SARS-CoV-2 virus [4]. The possible binding of the virus spike protein (a surface glycoprotein) to the angiotensin-converting enzyme-2 (ACE-2) expressed in the host cells is the major factor in the pathogenesis of the viral disease [5]. This is the reason as to why the respiratory manifestations are reported commonly amongst the infected hosts as Type 2 pneumocytes present in the lungs express the said enzyme in large amounts while the infected patients develop pneumonia-

like symptoms including shortness of breath, dry cough followed by high fever and in later stages, acute respiratory distress syndrome (ARDS) 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 the virus accesses host cells via the enzyme angiotensin-converting enzyme-2 (ACE-2), there has been evidence that the superficial stratified epithelial cells of the oesophagus, absorptive enterocytes from the ileum and colon, cholangiocytes, myocardial cells, proximal tubular cells from the kidneys and urothelial cells from the bladder, also, act as important areas where an active infection can be seen since they all express high amounts enzyme ACE-2 [7]. The analysis of public bulk-seq RNA datasets suggest that the mucosa of oral cavity, also, expresses the same enzyme ACE2 found in higher concentrations in the tongue than other oral sites as compared to the gingival tissues and cells of the buccal mucosa and can, thus, lead to active manifestations of this deadly viral disease in the early stages of infection [7]. Therefore, there might be a high probability or, possibility that oral mucosa as well and organs excluding lungs are, also, at 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, as well [8]. Some of the published literature reports the cutaneous and systematic manifestations of SARS-CoV-2 infection in detail, there is a paucity of data, though, in relation to the oral manifestations of this infectious disease with oral mucosa being a possible source of infection acting as a reservoir for the virus in clinically occult cases. Fewer studies, though, 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 is based on a systematic search of the available medical database on similar lines until 29th of the June 2020.

Materials and Methods

The present review was based on a systematic search of PubMed, Google Scholar and Elsevier data base up till 29th of the June 2020 with key words oral manifestations/signs/symptoms of and olfactory and gustatory dysfunction in SARS-CoV-2 infection. Quick readings of abstract were conducted, and significant articles were kept for review. In addition, we, also, accessed and retrieved the cross references which seemed to be clinically relevant. Articles written exclusively in Chinese were excluded while all the original articles, letters to the editor, case reports and reviews in English literature were included for the review.

Discussion

SARS-CoV-2 virus is a single-stranded, positive-sense ribonucleic acid wrapped in a nucleoprotein (N). The viral envelop (E) surrounds this helical nucleocapsid while the 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 infectious disease process. Several of beta corona viruses, also, possess hemagglutinin esterase protein [9]. Also, RNA genomes code for 4 structural protein (E, N, S, M) and one protein for viral replication/transcription (RNA dependent RNA polymerase, RdRp) [9]. The virus S glycoprotein attaches to the enzyme angiotensin-converting enzyme-2 (ACE-2) expressed in the various host cell types including various organs such as lungs, kidney, heart, gastrointestinal tract and oral mucosa with this facilitating the entry of virus into the host body [9]. The entry and binding processes are, then, followed by fusion of the viral membrane and host cell membrane [10]. After fusion occurs, the Type 2 transmembrane serine protease (TMPRSS2) that is present on the surface of the host cell membrane clears the enzyme ACE2 and activates the receptor-attached spike-like, S protein [11]. Once the virus enters the host cell, the viral genome (mRNA) is ready for translation and uses the RNA dependent RNA polymerase for its synthesis [11]. Since the oral mucosa could, also, express enzyme ACE2, 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 the saliva of the infected host even before lung lesions appear [12]. Vinayachandran D, et al. (2020) [13], also, reported possible oral symptoms including hypogeusia, xerostomia and chemosensory alterations in the infected hosts. An experiment in Rhesus Macaques has, also, demonstrated that the initial target of SARS virus is the epithelial lining of the salivary glands [14]. Mucosal involvement includes viral exanthems composed of diffuse erythema, petechiae and pustule formations [15]. In accordance with the said findings, Seo MY, et al. (2020) [16], also, reported olfactory and gustatory dysfunction in around 24.2% of the patients presenting with mild SARS-CoV-2 infection. Evidence has, also, suggested that 95.8% of the infected hosts of SARS-CoV-2 infection present with the symptom of anosmia. In addition to anosmia, the 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, to the local tissues effecting olfaction with the exact phenomenon behind this, still, being unclear.

Another possibility behind the olfactory and gustatory dysfunction seen as manifestations of SARS-CoV-2 infection is due to the SARS-CoV-2 virus entering via the olfactory nerve or, peripheral trigeminal nerve carrying the infection to the CNS, thus, potentially damaging the trigeminal nerve into 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 diseases. In addition, upper respiratory tract infections due to the virus can induce a permanent disorder leading to a partial or, complete loss of the olfactory senses. Fewer studies have, also, suggested that post-infections, anosmia can be stabilised [8,17, and 18].

The oral manifestations have already been seen as an indicator of several systemic diseases. Oral cavity may exhibit manifestations in the form of oral ulcerations, gingival bleeding, stomatitis and glossitis. Viral infections usually manifest either as superficial or, deep oral ulcerations or, vesicle formations in relation to the various parts of the oral mucosa depending upon the severity of the infection and area of involvement [19-21]. In a case series published by Martín Carreras-Presas C, et al. (2020) [22], out of 3 patients including 2 suspects and one confirmed case of SARS-CoV-2 infection, case 1 presented with multiple with an erythematous halo and symmetric distribution on the right side of hard palate in the affected patient. Furthermore, case 2 presented with multiple pinpoint yellowish ulcers with an erythematous halo on the left side of hard palate of the patient while case 3 reported that the lesions were more pruritic than painful. The said patient presented with 3 vesicles on the inner lip mucosa with the vesicular lesion located closer to the right commissure being intact and tense suggesting oral vesiculo-bullous lesions to be one of the marked features in SARS-CoV-2 infection.

On elicitation of the case history, the first patient was a 56 years old, healthy male patient and he had, also, reported pain, dysgeusia and enlargement of lymph nodes before the onset of intra-oral lesions. The 2nd patient among these three was 58 years old, male with a positive history of diabetes mellitus (DM) with hypertension (HT). He, also, reported the oral lesions to be painful. Interestingly, in last case of confirmed SARS-CoV-2 infection, initially, the female patient, a sufferer of co-morbidities in the form of obesity with HT, pain on tongue was reported while cutaneous manifestations were, also, observed followed by vesicles in her inner lip mucosa as well as desquamative gingivitis. In the 3rd patient, co-morbidities were considered to have triggered ulcerative/herpetic-like lesions in relation to the hard plate. Not to forget, all the three patients were in a period of lock down that might have contributed to a psychological breakdown, too, with stress and anxiety arising due to the recent pandemic leading to such characteristic oral manifestations. Furthermore, in the last case of confirmed SARS-CoV-2 infection, lesions appeared a week post discharge, thereby, making the clinicians conclude that oral manifestations associated with SARS-CoV-2 might have nothing to do with the active SARS-CoV-2 infection per se (Table 1).

Table 1: Oral manifestations of SARS-CoV-2 infection.

Author/Reference	Sample size & Diagnostic status of SARS-CoV-2 infection	Past History	Days of onset of oral and related symptoms	Common oral manifestations
Martín Carreras-Presas C, et al. (2020) [22]	Total 3 patients; 2 of them were suspects while one confirmed SARS-CoV-2 patient.	Case 1: Healthy; Case 2: Diabetic with hypertension; Case 3: Obese with hypertension.	--	Case 1: Multiple orange-colored ulcers with an erythematous halo and symmetric distribution on the right hard palate of the patient; Case 2: Multiple pinpoint yellowish ulcers with an erythematous halo on the left hard palate of the patient; Case 3: The patient reported that the lesions were more pruritic than painful. The patient presented with 3 vesicles on the inner lip mucosa with the vesicular lesion located closer to the right commissure intact and tense.
Ciccarese G, et al. (2020) [23]	One confirmed SARS-CoV-2 patient.	None.	2 days before being admitted in hospital.	Sudden onset of anosmia, asymptomatic cutaneous and oro-pharyngeal lesions. Oral findings included oral erosions and ulcerative lesions with encrustations on the inner surface of the lips, palatal and gingival tissues and petechiae.
Soares CD, et al. (2020) [24]	One confirmed SARS-CoV-2 patient.	Diabetes with hypertension.	--	Painful ulceration in the buccal mucosa. Oral examination revealed that besides the ulcerated lesions, multiple reddish macules of different sizes were scattered along the hard palate, tongue and lips.
Cebeci Kahraman F, et al. (2020) [15]	One confirmed SARS-CoV-2 patient.	None.	10th day of onset.	Sore throat symptoms worsened 10 days after the onset of symptoms. Oral examination revealed a large erythematous surface in the oropharynx and on the hard palate, few petechiae in the midline and numerous pustular exanthems near the soft palate which were more prominent on the left side and ranged from 1-3 mm in diameter.
Ansari R, et al. (2020) [25]	Two confirmed SARS-CoV-2 patients.	None.	5th day of onset. 7th day of onset.	Ulcers on hard palate. Ulcers with an erythematous background on the anterior aspect of dorsal surface of tongue.
Amorim Dos Santos J, et al. (2020) [26]	One confirmed SARS-CoV-2 patient.	Coronary artery disease (CAD); Autosomal polycystic kidney disease; Systemic hypertension; Kidney transplant; On immunosuppressants and pharmacological prophylaxis for venous pulmonary thrombo-embolism).	--	A persistent white plaque on the dorsal aspect of tongue. Other oral findings included multiple pinpoint yellowish ulcers on the dorsal surface of tongue resembling ulcers seen in the late stage of recurrent intra-oral herpes. A nodule located in the lower lip measuring approximately 1 cm in its largest diameter.
Chaux-Bodard A-G, et al. (2020) [27]	One confirmed SARS-CoV-2 patient.	None.	4th day of onset.	Painful inflammation of tongue papilla followed by erythematous macules which further evolved into irregular ulcers.
Jimenez-Cauhe J, et al. (2020) [46]	21 confirmed SARS-CoV-2 patients. Evidence of skin rashes. Out of these, 6 developed viral exanthems. Data of six patients with oral cavity rashes. Age range 40-69 years.	None.	Case 1: 12th day; Case 2: 2nd day; Case 3: 19th day; Case 4: 24th day; Case 5: 2nd day; and Case 6: 19th day of onset.	Types of viral exanthems observed: Case 1: Macules; Case 2: Petechiae; Case 3: Macules with petechiae; Case 4: Macules with petechiae; Case 5: Petechiae; and Case 6: Macules with petechiae.
Chen J, et al. (2020) [29]	Total of 108 validated questionnaire participants. No. of males and females being 52 and 55 respectively.	None.	--	Oral manifestations with their respective % of involvement in patients: Amblygeustia: 51 (47.2%); Dry mouth: 50 (46.3%); Dryness and inflammation of mouth: 12 (11.1%); and Enlargement of lymph nodes in the submandibular region: 1 (0.9%).

In another case reported by Ciccarese G, et al. (2020) [23], where a 19 year old female was a confirmed case of SARS-CoV-2 infection, the patient reported cutaneous and oral manifestations including hyposmia and oro-pharyngeal lesions on the 7th day of onset of symptoms. The characteristic findings in the said patient included sudden onset of anosmia with asymptomatic cutaneous and oro-pharyngeal lesions which later evolved into frank oral erosions and ulcerative lesions with encrustations on the inner surface of the lips, palatal and gingival tissues and petechiae (Table 1). Interestingly, Soares CD, et al. (2020) [24] reported not only the oral clinical manifestations in a confirmed SARS-CoV-2 patient with a known history of DM and HT but, also, stated the histopathology of oral lesions in a 42 years old male patient. The said patient had reported painful ulceration in the buccal mucosa while further examination revealed that besides the ulcerated lesions, multiple reddish macules of different sizes were scattered along the hard palate, tongue and lips (Table 1).

In a similar case study of another 51 years old male patient published by Cebeci Kahraman F, et al. (2020) [15] who was, also, a confirmed SARS-CoV-2 patient, the patient presented oral symptoms on the 10th day after onset of symptoms when the sore throat symptoms worsened 10 days after the onset of symptoms. Also, in the same patient, oral examination revealed a large erythematous surface in the oropharynx and on the hard palate, while few petechiae in the midline and numerous pustular exanthems near the soft palate which were more prominent on the left side and ranged from 1-3 mm in diameter (Table 1). Another interesting finding in the said patient was that the patient had reported altered olfactory and gustatory functions before the onset of oral lesions (Table 1). Ansari R, et al. (2020) [25], in his literature review of two confirmed SARS-CoV-2 patients including a 56 years old female and 75 years old male patients, also, described ulcers on hard palate while ulcers with an erythematous background on the anterior aspect of dorsal surface of tongue on 5th and 7th day of onset of active SARS-CoV-2 infection. A histo-pathological examination, also, confirmed the findings observed clinically in the said patients (Table 1).

In a Brazilian case reported by Amorim Dos Santos J, et al. (2020) [26], of a 67 years old Caucasian male patient with a known history of coronary artery disease (CAD), autosomal polycystic kidney disease, systemic hypertension and kidney transplant, the patient presented with being on immunosuppressants and pharmacological prophylaxis for venous pulmonary thrombo-embolism. On clinical examination, the said patient presented with a persistent white plaque on the dorsal aspect of tongue with multiple pinpoint yellowish ulcers on the dorsal surface of tongue resembling ulcers seen in the late stage of recurrent intra-oral herpes. A nodule was, also, observed in the lower lip suggesting a reactive fibroma measuring approximately 1 cm in its largest diameter. The said authors, though, failed to mention regarding the onset of the said manifestations as there was a high probability of the lesions being reactive in nature to the drugs taken rather than being associated with the active SARS-CoV-2 infection per se (Table 1). In another case reported by Chaux-Bodard A-G, et al. (2020) [27], painful inflammation of tongue papilla followed by erythematous macules which further evolved into irregular ulcers were observed in a 45-year-old female patient confirmed as SARS-CoV-2 infected on the 4th day of onset of the infection (Table 1).

Likewise, both olfactory and gustatory dysfunction have been one of the recently reported symptoms seen in increasing numbers in patients infected with SARS-CoV-2 virus. In a recent report by Gane SB, et al. (2020) [28], it was mentioned that a 48-year-old male patient experienced sudden onset anosmia without significant co-morbidities when only two days later, he was diagnosed SARS-CoV-2 positive. In another recent meta-analysis study by Chen J, et al. (2020) [29], including a total of 108 participants with 52 males and 55 females, 47.2% of the participants reported amblygeustia while 46.3% reported xerostomia, 11.1% of the patients reported stomatitis and enlargement of lymph nodes was reported in 0.9% of the patients in submandibular region (Table 1). In a similarly analysis of 131 SARS-CoV-2 patients by Abalo-Lojo JM, et al. (2020) [30], 55% of the patients reported both olfactory and gustatory dysfunction while 3.8% only olfactory and 1.5% only gustatory dysfunction. Also, 39.7% of the patients reported none of above symptoms while the other common SARS-CoV-2 infection-associated symptoms included dry cough, asthenia, myalgia, headache, and diarrhoea. Another notable finding in the said study was that 13.9% of the cases had developed symptoms on day one, 70.9% on day 3 while the remaining 15.2% after day 4 of the onset of infection. In the same study, 13 patients were found positive for the oro-pharyngeal swab nucleic acid detection while 4 of them were, also, tested positive for pure salivary gland secretion (i.e., saliva) highlighting the role oro-pharyngeal secretions and saliva might have in an early detection as well as being a potential source of infection transmission in confirmed SARS-CoV-2 infection (Table 2).

A validated controlled trial conducted in the University of Pennsylvania on 60 confirmed SARS-CoV-2 infected patients by Moein ST, et al. (2020) [31], also, confirmed olfactory dysfunction in 98% of the patients including complete anosmia in 58%, severe microsmia in 33%, moderate microsmia in 27% while mild microsmia in 8% of the patients. Furthermore, 23% of the patients reported gustatory dysfunction as an early symptom of SARS-CoV-2 infection (Table 2). In another larger-scale research from Europe by Lechien JR, et al. (2020) [32], on 417 confirmed SARS-CoV-2 infected 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 the cases while females were found to be affected more as compared to males for olfactory and gustatory dysfunction. Also, phantosmia and parosmia were reported in 12.6% and 32.4% of the patients respectively while among the patients who did not complain of nasal stuffiness and rhinorrhoea, the rates of anosmia and hyposmia reported were found to be 66.2% and 13.5% respectively (Table 2).

Interestingly, in a web-based questionnaire study on 140 quarantined patients, 38.3% and 32.8% of the patients reported impaired sense of smell and taste respectively as their initial symptoms while a total of 25.8% of the patients reported with olfactory and gustatory dysfunction in absence of any other symptoms. Moreover, more than 50% of the patients, also, reported xerostomia and dysgeusia both as the prominent oral manifestations of SARS-CoV-2 infection. In addition to the above-mentioned findings, 22 patients, also, reported paraesthesia in relation to the tongue while 9 patients reported of having plaque-like changes in tongue. Furthermore, 4 patients reported with swelling in relation to palate while the other 4 in relation to tongue and 2 with swelling of the gingival tissues [33]. The findings of xerostomia and dysgeusia in confirmed cases of SARS-CoV-2 infection can be explained by the fact that olfactory and gustatory senses are necessary for stimulation of saliva secretion. Thus, any grade of olfactory and gustatory dysfunction leads to impairment of neurological stimulation that might have led to xerostomia and secondary, dysgeusia in the affected patients [34,35].

Melley LE, et al. (2020) [36], in their report of a 59-year-old female patient, also, suggested hypogeusia and hyposmia as the early symptoms of infection in the patient with hyposmia later turning-out

Table 2: Olfactory and gustatory dysfunction in SARS-CoV-2 infection.

Author/Reference	Patient's Mean Age/ Gender Distribution/ Sample size	Co-morbidities/Severity of SARS-CoV-2 infection	Olfactory and gustatory dysfunction. Clinical outcomes/Early onset of olfactory and gustatory dysfunction (before other symptoms or, hospitalization)	SARS-CoV-2 infection-associated other symptoms
Abalo-Lojo JM, et al. (2020) [30]	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, diarrhoea, odynophagia, fever (>38°c), anorexia, dyspnea, expectoration, chest tightness, dizziness, nausea, abdominal pain, vomiting and conjunctivitis.
Moein ST, et al. (2020) [31]	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 JR, et al. (2020) [32]	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.	Cough, myalgia, loss of appetite, diarrhoea, fever, headache and asthenia.
Klopfenstein T, et al. (2020) [42]	Mean age 47±16 years; Males 33%; Females 67%. Sample size: 114	Hypertension, cardiovascular disease, asthma. Not mentioned.	47% reported olfactory dysfunction (anosmia) while 85% reported dysgeusia.	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 diarrhoea (52%, n = 28).
Beltrán-Corbellini A, et al. (2020) [41]	Mean age 61.6±17.4 years; Males 60.8%; Females 39.2%. Sample size: 79	--	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.	Not mentioned.
Giacomelli A, et al. (2020) [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.

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 80 years old female patient, reportedly presented with a history of sudden anosmia and fatigue in the asymptomatic stage of infection with a concomitant history of ageusia actually preceding complete anosmia in the patients [37]. A letter to editor in Spain, also, suggested similar finding that 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 [38]. Walker A, et al. (2020) [39], in their study using google trends in 8 different countries, hypothesized that increase in searches for anosmia and onset of SARS-CoV-2 infection could be correlated with a surge in the cases reported for anosmia in the current pandemic. Evidence, also, suggests that isolated anosmia could be one of the initial symptoms of SARS-CoV-2 infection without manifestation of other SARS-CoV-2-related symptoms [40].

In another questionnaire-based study in Spain by Beltrán-Corbellini A, et al. (2020) [41], 31.65% of the patients reported olfactory dysfunction including 45.7%, complete anosmia, 29%, hyposmia and

6.5%, dysosmia among the 31 SARS-CoV-2 patients with olfactory and gustatory dysfunction while 35.44% patients reported gustatory dysfunction including 45.2%, complete ageusia, 22.6%, hypogeusia and 25.8%, dysgeusia among the patients included in the study. Furthermore, early onset disease was seen in 35.5% of the patients presenting with olfactory and gustatory dysfunction (Table 2). The numbers of patients affected with olfactory and gustatory dysfunction, though, were found to be even more in another retrospective analysis done by Klopfenstein T, et al. (2020) [42] in France who reviewed 114 medical files of confirmed COVID-19 patients and reported olfactory dysfunction in 47% of the patients while 85% of the patients reported with dysgeusia (Table 2).

Infections of influenza and para-influenza viruses, rhinoviruses and other endemic corona viruses including common cold and flu viruses have all been associated with a characteristic olfactory dysfunction in the past [43,44]. Recent anecdotal and scientific reports have, also, provided evidence that SARS-CoV-2 infection-associated chemosensory impairment is not limited only to olfactory but a gustatory dysfunction as well in addition to chemesthesis [45]. While the final drafting of this literature review, we came across a published article in JAMA Dermatology that correlated viral-induced exanthems along with skin rashes as a confirmed diagnosis of SARS-CoV-2 infection. Out of the 21 confirmed SARS-CoV-2 patients in an age range of 40-69 years in the said study conducted by Jimenez-Cauhe J, et al. (2020) [46], evidence of skin rashes was reported in most of the patients while 6 had developed viral exanthems with a data of 6 patients with oral cavity rashes. The said lesions were, further, classed as being macular in 1 case to petechiae in 2 cases and macules with petechiae in 3 of the cases reported (Table 1). Oral ulceration and erosions in confirmed SARS-CoV-2 cases can be explained by the fact that the named virus uses enzyme ACE-2 to facilitate its entry into the specific host cells which might result in a direct vascular and mucosal damage seen. Martín Carreras-Presas C, et al. (2020) [22], have stated that SARS-CoV-2 patients reported with pain in tongue which can be explained based on the presence of high expression of ACE-2 on tongue as compared to the other sites in oral cavity including buccal and gingival mucosa.

Not to forget, all the recent anecdotal data and research is based on a limited sample size while the case reports published are merely based on suspected SARS-CoV-2 infection without a confirmed laboratory diagnosis. There is always a probability of oral symptoms arising due to the combined effect of psychological changes in the affected patients due to the stress and anxiety related to the virus, an imbalance in the microbiota as well as due to the drugs being used by the patient due to a concomitant co-morbidity. In this line, immunomodulatory drugs used to prevent the infection might, also, be held responsible for the triggering of the manifestations reported commonly. Evidence has, also, suggested that olfactory dysfunction in SARS-CoV-2 patients results in anosmia/hyposmia which can be an initial symptom before the actual onset of other significant SARS-CoV-2 infection-associated symptoms. Also, olfactory dysfunction can be seen alone or, in associated with gustatory dysfunction and vice versa. It is very likely that in millions of SARS-CoV-2 patients seen so far, evidence precisely on oral manifestations is still limited which might be due to a lack of proper facilities to rule-out the oral findings present or, due to a lack of effective screening protocols with another possibility of saliva and other oral and oro-pharyngeal secretions being the potential sources of infection and carriers of the virus in patients suffering from this deadly corona virus disease [47].

Conclusion

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

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