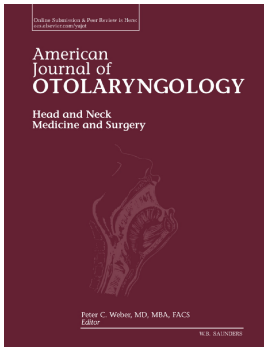

Xerostomia, gustatory and olfactory dysfunctions in patients with COVID-19

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Xerostomia, gustatory and olfactory dysfunctions in patients with COVID-19.

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We declare that this manuscript is original, has not been published before, and is not currently being considered for publication elsewhere.

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Abstract

Background: The novel Coronavirus Disease-19 (COVID-19) continues to have profound effect on global health. Our aim was to evaluate the prevalence and characterize specific symptoms associated with COVID-19.

Methods: This retrospective study included 326 patients with confirmed SARS-CoV-2 infection evaluated at the Emergency Department of the Umberto I Polyclinic Hospital, Rome, Italy between March 6th and April 30th, 2020. In order to assess xerostomia, olfactory and gustatory dysfunctions secondary to COVID-19, a telephone-based a modified survey obtained from the National Health and Nutrition Examination Survey (NHANES) 2013-2014 for taste and smell disorders and the Fox Questionnaire for dry mouth were administered to 111 patients (34%) after discharge between June 4th and June 12th.

Results: Taste dysfunction was the most commonly reported symptom (59.5%; n= 66), followed by xerostomia (45.9%; n=51) and olfactory dysfunctions (41.4%; n=46). The most severe symptom was olfactory dysfunction with a median severity score of 8.5 (range 5-10). Overall 74.5% (n=38) of patients with xerostomia, 78.8% (n=52) of patients with gustatory dysfunctions and 71.1% (n=33) of patients with olfactory dysfunctions reported that all symptoms appeared before COVID-19 diagnosis. Overall, the majority of patients reported one symptom only (45.9%, n=51), 37 (33.3%) reported the association of two symptoms, and 23 (20.7%) patients reported the association of three symptoms at the same time.

Conclusion: Xerostomia, gustatory and olfactory dysfunctions may present as a prodromal or as the sole manifestation of COVID-19. Awareness is fundamental to identify COVID-19 patients at an early stage of the disease and limit the spread of the virus.

Keywords: COVID-19; public health; xerostomia; oral medicine; oral diseases; dysgeusia; anosmia;

Background

The recent Coronavirus Disease-19 (COVID-19) pandemic continues to have profound social and economic effects, with more than twelve millions infections and more than half a million deaths reported globally by July 1st,2020 [1], [2]. Patients affected by COVID-19 may present with a variety of conditions that usually start from two to 14 days after exposure, and range from a mild flu-like condition to a life-threatening multi-organ failure with mortality being significantly higher among those having co-morbidities, older individuals and among those who require hospital admission and ventilation support in intensive care units [3].

Interestingly, a significant number of patients reported taste and smell dysfunction as a prodromal, concomitant or as the sole manifestation of COVID-19 infection [4], [5], [6]. A recent systematic review and meta-analysis showed that 1627 patients had a prevalence of 52.7% of olfactory dysfunction and 1390 patients had a prevalence of 43.9% of gustatory changes, respectively [7]. On the other hand, oral complications secondary to COVID-19 have been poorly described, with one study reporting dry mouth and taste changes in 46.3% and 47.2% of COVID-19 patients (n=108), respectively [8]. While the pathobiology of dysgeusia, hyposmia/anosmia and xerostomia secondary to the COVID-19 is yet to be determined, it is well-reported that angiotensin-converting enzyme II (ACE2) may represent the novel coronavirus (2019-nCoV) cell receptor. In fact, recent studies showed that 2019-nCoV may specifically target ACE2-expressing olfactory/trigeminal and salivary glands cells following inoculation, or induce such manifestations as a consequence of the central nervous system involvement through the invasion of the olfactory/trigeminal bulb [7], [9], [10].

Despite different studies reporting taste and olfactory changes being common in patients with COVID-19, there remain important gaps in the recognition of the onset, characterization of such symptoms and association with COVID-19 outcome. With this work we aimed to assess the prevalence and the characterize xerostomia, gustatory and olfactory dysfunctions in COVID-19 patients.

Materials and Methods

Study Design

This was a retrospective cohort study of adult patients (≥ 18 years) who were evaluated at the Emergency Department (ED) of the Umberto I Polyclinic Hospital, Rome, Italy between March 6th and April 30th, 2020 with confirmed SARS-CoV-2 infection. SARS-CoV-2 testing was obtained by sampling both the nasal and oropharyngeal mucosa and analyzed with real-time polymerase chain reaction (rtPCR) according to the WHO interim guidance [11]. Demographic data, co-morbidities, SARS-CoV-2 Polymerase Chain Reaction (PCR) results, additional laboratory tests (including Complete Blood Count (CBC), Lactate Dehydrogenase (LDH), Creatinine, C-Reactive Protein (CRP), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), D-dimer, fibrinogen, and International Normalized Ration (INR)), home medications, and outcomes data of patients with a diagnosis of COVID-19 were abstracted from electronic medical records and entered into a de-identified electronic spreadsheet. This study was reviewed and approved by the Sapienza University/Umberto I Polyclinic Hospital Institutional Review Board.

Survey

All patients were queried on xerostomia, dysgeusia and hyposmia/anosmia, using a modified survey obtained from the National Health and Nutrition Examination Survey (NHANES) 2013-2014 for taste and smell disorders [12] and the Fox Questionnaire for dry mouth [13]. The survey consisted of a total of ten questions divided into five sections; the first section assessed the patients' demographic information (gender and age) and date when the survey was administered. The second, third and fourth sections focused on the onset, duration and characterization of xerostomia, dysgeusia and hyposmia/anosmia. Patients rated their level of xerostomia, dysgeusia and hyposmia/anosmia on a 11-point scale (from 0=absent to 10=severe). The last section of the survey assessed the patients' tobacco and alcohol consumption (appendix 1). The survey was administered by phone by five investigators (DDV, EP, SM, EP, PJF) after discharge between June 4th and June 12th. Informed consent was obtained verbally as per protocol.

Statistical Analysis

Responses to the survey were recorded in an electronic spreadsheet for statistical analysis. The intensity of xerostomia, taste and smell dysfunctions was registered using a numeric rating scale (NRS) which ranged from 0 (absent) to 10 (maximum intensity). After assessing the normal distribution, median values and interquartile ranges (IQRs) were calculated for the NRS scores. Qualitative variables were assessed using chi-square test, while quantitative variables were firstly assessed for normal distribution and then compared through the Mann-Whitney U test.

In order to describe the presence of multiple oral symptoms and their different intensity levels in our study population, a k-means clusters analysis was performed [14]. The clustering process was determined considering xerostomia, gustatory and olfactory dysfunction scores, which were graded as absent (0), very low (1-2), low (3-4), intermediate (5-6), high (7-8) and very high (9-10). To determine the optimal number of clusters we used the Calinski and Harabasz stopping method; specifically, larger pseudo-F index values indicated a more distinct clustering [15] (Supplementary Table 2). The interpretation of clustering in the clinical context was assessed by an Oral Medicine specialist (AV) and expert oral health providers (EP, PJF, UR). Finally, clusters were compared according to the same variables previously considered for xerostomia, gustatory and olfactory dysfunction. All P values were considered statistically significant at $P < .05$. Data were analyzed using STATA 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX, USA: StataCorp LLC).

Results

Patients Characteristics

A total of 326 patients tested positive for SARS-CoV-2 in the ED. Among these, 40 (12.2%) deceased before discharge, and were therefore ineligible to participate to the survey. A total of 157 patients were contacted via phone; 111 agreed to participate and completed the questionnaire (34.0%). Most patients were males (52.3%) with a median age of 57 (range: 48-67) (Table 1); 38 patients reported being former (34.2%) and 7 patients current (6.3%) tobacco smokers, while 44.1% (n=49) of patients reported to be social alcohol consumers. Common signs and symptoms at ED presentation included fever (n=101, 90.9%), cough (n=52,46.8%), and dyspnea (n=38, 34.3%). Hypertension (n=29; 26.1%) and chronic pulmonary disease (n=11; 9.9%) were the most common co-morbidities. Of all queried patients (n=111), 5.4% (n=6) were admitted in the ICU, spending a median number of days of 12.5 (range: 5-22) (Supplementary table 1). All of them were males and had a median age of 60 (range: 54-82).

Patients Reported Oral Symptoms

Xerostomia was reported by 51 (45.9%) patients with a median dryness score of five (range: 3-8) and with 39/51 (76.5%) patients mentioning that it was their first-time experiencing xerostomia in their lifetime (Table 2). Ten (19.6%) patients reported xerostomia as one of the first symptoms associated with SARS-CoV-2 infection with a median onset time of seven days (range: 4-7.8) before the COVID-19 diagnosis. Among xerostomia patients (n=51), 20 (39.2%) had also swallowing difficulties, 14 (27.5%) reported difficulties only when swallowing dry foods, and 19 (37.3%) needed to sip liquids to help the swallowing process.

Dysgeusia was the most common oral symptoms with 66 (59.5%) patients reporting taste changes as a prodromal, or concomitant symptom of COVID-19, with a median dysgeusia score of eight (range: 5.8-9). Overall, 58 out of 66 (87.9%) reported that it was their first time experiencing dysgeusia, whereas 18 (27.3%) patients reported that dysgeusia was one of the first onset symptoms of COVID-19. Fifty-two (78.8%) patients

reported experiencing dysgeusia with a median of six days (range: 4-7) before the diagnosis of COVID-19 and 14 (21.2%) patients reported that dysgeusia started a median of three days (range: 2-4) after the COVID-19 diagnosis. Of all dysgeusia patients (n=66), 47 (71.2%) reported that dysgeusia reduced their appetite, with 40 (60.6%) patients reporting a change in their daily diet because of dysgeusia.

Olfactory dysfunctions were reported by 46/111 (41.4%) patients, with a median severity score of 8.5 (range: 5-10) and with 10/46 patients reporting anosmia (21.7%). Of all patients with altered smell functions (n=46), 40 (87.0%) reported that it was their first time having hyposmia/anosmia, with 17 (37.0%) patients reporting smell alterations as one of the first COVID-19 associated symptoms. Thirty-three (71.1%) patients reported experiencing smell dysfunctions with a median of six days (range: 4-8) before the COVID-19 diagnosis, whereas 12 (26.1%) patients experienced smell dysfunctions with a median of two days (range: 2-3.5) after the COVID-19 diagnosis.

Cluster Analysis

In order to evaluate the distribution between xerostomia, taste and smell dysfunction, a K-means cluster analysis was performed (table 3), with three-cluster solution selection (cluster 1, cluster 2, cluster 3) to show the largest pseudo-F statistics. (Supplementary Table 2).

Cluster 1, which was mostly characterized by xerostomia, included 47/111 (42.3%) patients, 46 of which (97.9%) reported one symptom, with one (2.1%) patient only that reported two symptoms. Of the 47 patients, 37 (78.7%) had their symptoms (xerostomia, dysgeusia, hyposmia) scored below five (on a scale 0-10). Nine (19.1%) patients had xerostomia with a score above five (on a scale 0-10), and one (2.1%) patient had smell dysfunctions with a score above five (on a scale 0-10).

Cluster 2, with most of the patients having taste changes and xerostomia, included 28/111 (25.2%) patients, with the majority of them (n=18/28; 64.3%) reporting the association of two symptoms. When the severity of the symptom was considered, more than 80% of the patients reported dysgeusia with a score

higher than five (on a scale 0-10) (n=23/28; 82.1%), while 50% of them reported xerostomia with a score higher than 5/10 (n=14/28; 50%). Overall a combination of 'dysgeusia + xerostomia', both scored more than five was reported by the 46.4% (n=13) of patients.

Cluster 3, mostly characterized by patients with taste and smell dysfunctions, included 36/111 (32.4%) patients, with 50% of them with two combined symptoms, and the other half (n=18, 50%) with three combined symptoms (i.e. 'xerostomia + dysgeusia + hyposmia'). The majority of these patients (n=22; 61.1%) reported 'dysgeusia + hyposmia', 12 (33.3%) reported 'xerostomia + dysgeusia + hyposmia', and two (5.6%) reported hyposmia only; all of them with a score higher than five (on a scale 0-10).

Discussion

This study reported on the prevalence and clinical characteristics of xerostomia, gustatory, and olfactory dysfunction COVID-19 patients (n=111) presenting to a large Emergency Department (ED) in Italy. Taste alterations were the most common finding reported by approximately 60% of patients, followed by xerostomia and smell dysfunctions (45.9% and 41.4%, respectively). Overall, olfactory alterations were the most severe finding with a median score of 8.5 (5-10), followed by dysgeusia (median score: 8; range: 5.8-9) and xerostomia (median score: 5; range: 3-8). More than 70% of the patients reported that all symptoms occurred before COVID-19 diagnosis, with xerostomia presenting with a median of seven days (range: 4-7.8) prior to the COVID-19 diagnosis, and taste and smell alterations presenting with a median of six days (range: 4-7 and 4-8, respectively) before COVID-19 diagnosis.

While gustatory and olfactory dysfunctions secondary to COVID-19 are well-documented, only few studies report oral complications from SARS-CoV-2 infection. In a large case-series study the olfactory and oral disorders of 140 COVID-19 patients were evaluated through a web-based questionnaire. Overall, olfactory dysfunction was the most common finding reported by 67% (n=86) patients (with 19.5% of them reporting anosmia) and with symptoms mainly starting on the third, fourth, and fifth day of the disease. This was followed by dysgeusia which was reported by 54.3% (n=76) of patients, and xerostomia reported by 51.4% (n=72) patients. The onset time for dysgeusia and xerostomia was not recorded [16]. Another study investigated ear, nose and throat symptoms in a cohort of 50 patients affected by COVID-19 using a standardized questionnaire that assessed olfactory, gustatory, and auditory data, as well as xerostomia and eye dryness. Overall, olfactory disorders were the most prevalent (46/50, 92%), followed by dry eyes (72%) and gustatory disorders (70%); xerostomia was reported in 32% of patients. When the time of onset of the disease was considered, approximately 40% of patients reported developing smell dysfunction before the other COVID-19 symptoms, 46% together with other symptoms, and 14% of patients after the other COVID-19 symptoms. Dysgeusia and xerostomia persisted in 8% and 2% of cases after COVID-19 resolution, respectively [17]. A large systematic review aimed to describe the clinical presentation and assess the

prevalence of olfactory, and taste disorders in 1457 patients coming from China, Europe, UK, and USA. Overall, 60.7% of the patients had olfactory disorders, whereas 56.4% of the patients had gustatory disfunctions. Among the included studies, 2/6 reported on the time of onset of olfactory and gustatory disorders [18]; specifically, Moein et al. showed that smell dysfunctions and taste dysfunctions were present in 59/60 (98.3%) and 14/60 (24%) patients, respectively. Of note, patients with olfactory changes, reported that such disorders started at the same time, or immediately after the other COVID-19 symptoms [19]. Lechien et al. in a large multicenter European study assessed olfactory and gustatory dysfunction in 417 COVID-19 patients through a questionnaire. Taste changes were the most prevalent symptom reported by 82% patients (n=342), whereas olfactory changes were reported by 85.6% of patients (n=357), 79.6% (n=284) of which had anosmia. The onset time was only considered for olfactory changes, which began before (11.8%), after (65.4%) or at the same time as the general or ENT symptoms associated with COVID-19 (22.8%). No onset presentation time was reported for gustatory changes [5]. In terms of prevalence and distribution, our work showed similar results with the studies mentioned above; however, we also described in detail the clinical characterization and onset time of such complications, which in several cases were the first symptoms of SARS-CoV-2 infection

Our study had some limitations. First, the sample size was relatively small and therefore the findings may not be generalizable to all COVID-19 patients. Second, the survey was administered a few days after the diagnosis of COVID-19 and some responses may not be as accurate. Nonetheless, the information provided on xerostomia, olfactory and gustatory dysfunctions were obtained using validated scales and questionnaires in a standardized manner, which may have improved the accuracy of the results. Finally, only 34% of all COVID-19 patients included in the initial cohort (n=326) responded and participated to the survey, which mostly consisted of patients with mild to moderate COVID-19, with few co-morbidities and good prognosis, therefore not representative of the entire COVID-19 population.

In summary, we showed that xerostomia, olfactory and gustatory dysfunctions are common symptoms reported as concomitant, and in some cases the sole manifestation of COVID-19. Oral health and

medical providers should consider the evaluation of such symptoms during the initial work up and screening which may help identifying COVID-19 patients at an early stage.

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Table 1 - Patients characteristics

	N=111 n (%)
Age	
Median age (range)	57 (48-67)
Gender	
Male	58 (52.3)
Female	53 (47.7)
Tobacco use	
Never	66 (59.4)
Current	7 (6.3)
Former	38 (34.2)
Alcohol consumption*	
Never	61 (54.8)
Social consumer	49 (44.1)
Frequent consumer	1 (0.9)
Primary presentation at ED Admission	
Fever	101 (90.9)
Cough	52 (46.8)
Dyspnea	38 (34.2)
Diarrhea	5 (4.5)
Sore throat	4 (3.6)
Fatigue	4 (3.6)
Myalgia/arthralgia	3 (2.7)
Vomit	3 (2.7)
Comorbidities	
Hypertension	29 (26.1)
COPD**	11 (9.9)
Diabetes Mellitus II	10 (9.0)
CVD**	9 (8.1)
Cancer	5 (4.5)
Antihypertensive therapy	29 (26.1)
Ace-Inhibitors	7 (24.1)
Angiotensin II Receptor antagonists	10 (34.5)
Other	12 (41.4)

* Alcohol consumption was determined according to the *National Institute on Alcoholic Abuse and Alcoholism – NIAAA*.

** COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease

Table 2 - Patients' reported oral symptoms

	N=111 n (%)
Xerostomia	51 (45.9)
Median dryness score (range)*	5 (3-8)
Xerostomia questions, "yes" response	
Is it the first time you experience xerostomia?	39 (76.5)
Was xerostomia one of the first COVID-19 symptoms?	10 (19.6)
The symptom occurred before/after COVID-19 diagnosis?	
Before	38 (74.5)
Median number of days (range)	7 (4-7.8)
After	10 (19.6)
Median number of days (range)	*Not available***
Did you have swallowing difficulties because of xerostomia?	20 (39.2)
Hardly ever	4 (7.8)
Occasionally	5 (9.8)
Fairly Often	7 (13.7)
Often	2 (3.9)
Very Often	2 (3.9)
Did you have difficulties swallow dry foods?	14 (27.5)
Hardly ever	2 (3.9)
Occasionally	2 (3.9)
Fairly Often	7 (13.7)
Often	2 (3.9)
Very Often	1 (2.0)
Do you sip liquids to help you swallow dry foods?	19 (37.3)
Hardly ever	1 (2.0)
Occasionally	6 (11.8)
Fairly Often	6 (11.8)
Often	5 (9.8)
Very Often	1 (2.0)

	N=111 n (%)
Dysgeusia	66 (59.5)
Median dysgeusia score (range)*	8 (5.8-9)
Dysgeusia questions, "yes" response	
Is it the first time you experience dysgeusia?	58 (87.9)
Was dysgeusia one of the first COVID-19 symptoms?	18 (27.3)
The symptom occurred before/after COVID-19 diagnosis?	
Before	52 (78.8)
Median number of days (range)	6 (4-7)
After	14 (21.2)
Median number of days (range)	3 (2-4)
Did you experience less appetite following dysgeusia?	47 (71.2)
Hardly ever	2 (3.0)
Occasionally	8 (12.1)
Fairly Often	15 (22.7)
Often	14 (21.2)

Very Often	8 (12.1)
Did your diet change because of dysgeusia?	40 (60.6)
Hardly ever	7 (10.6)
Occasionally	8 (12.1)
Fairly Often	9 (13.6)
Often	11 (16.7)
Very Often	5 (7.6)
	N=111 n (%)
Olfactory Alterations	
Median 0-10 score (range)*	46 (41.4)
Olfactory alteration questions, "yes" response	8.5 (5-10)
Is it the first time you experience olfactory alterations?	40 (87.0)
Were olfactory alterations one of the first COVID-19 symptoms?	17 (37.0)
The symptom occurred before/after COVID-19 diagnosis?	
Before	33 (71.1)
Median number of days (range)	6 (4-8)
After	12 (26.1)
Median number of days (range)	2 (2-3.5)

***** This was assessed using a 0-10-point scale.

****** Patients who reported xerostomia occurring after the COVID-19 diagnosis were not able to determine how many days after the diagnosis the symptoms occurred. Thus, it was not possible to evaluate this data.

Table 3 – Cluster Analysis of xerostomia, gustatory and olfactory symptoms

Variable	Cluster 1[1] N=47 n (%)	Cluster 2[2] N=28 n (%)	Cluster 3[3] N=36 n (%)
Mainly prevalent symptoms			
None or any oral symptom <5*	37 (78.7)	4 (14.3)	0 (0.0)
Xerostomia ≥5*	9 (19.1)	1 (3.6)	0 (0.0)
Dysgeusia ≥5*	0 (0.0)	10 (35.7)	0 (0.0)
Hyposmia ≥5*	1 (2.1)	0 (0.0)	2 (5.6)
Dysgeusia ≥5* + Xerostomia ≥ 5*	0 (0.0)	13 (46.4)	0 (0.0)
Dysgeusia ≥5* + Hyposmia ≥5*	0 (0.0)	0 (0.0)	22 (61.1)
Dysgeusia ≥5* + Xerostomia ≥5*+ Hyposmia ≥5*	0 (0.0)	0 (0.0)	12 (33.3)
Number of symptoms			
One symptom	46 (97.9)	5 (17.9)	0 (0.0)
Two symptoms	1 (2.1)	18 (64.3)	18 (50.0)
Three symptoms	0 (0.0)	5 (17.9)	18 (50.0)

*This was assessed using a 0-10-point scale.

[1] ***Mainly prevalent xerostomia cluster***: 97.9% of the patients had one symptom, all of them with a severity score < than 5 (0-10)

[2] ***Mainly prevalent dysgeusia cluster with or without xerostomia cluster***: more than 60% of the patients had two symptoms, most of them with a severity score > 5 (0-10)

[3] ***Oral symptoms with or without olfactory alteration cluster***: 50% of the patients had two symptoms, 50% had three symptoms, all of them with a severity score > than 5 (0-10)