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Taste and Smell Disorders in COVID-19 Patients at a Local Healthcare Trust in Northern Italy: a Cross-Sectional Study

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Key words: Covid-19, Loss of smell, Loss of taste, Severity of disease
Parole chiave: Covid-19, Anosmia, Ageusia, Decorso clinico grave

Abstract

Background. *In Italy, since the beginning of the COVID-19 pandemic, patients testing positive for SARS-CoV-2 through nasopharyngeal swab have reported taste and smell alterations. As these symptoms are quite uncommon in other respiratory infections, their specificity and prevalence are useful features for the differential diagnosis of COVID-19.*
The objective was to describe taste and smell alterations in patients diagnosed with SARS-CoV-2 infection and to define the onset of those disorders during the clinical course of the disease.
Study design. *Cross-sectional study.*
Methods. *This study was conducted on adult patients testing positive for SARS-CoV-2 infection through nasopharyngeal swab at a Local Healthcare Trust in Northern Italy between April 27th and May 27th, 2020. In order to investigate the clinical course, the onset of the first symptoms, smell and/or taste alterations, a phone-based questionnaire was administered during the programming of the second nasopharyngeal swab.*
Results. *We recruited 168 patients; the mean age was 52 years old, and 94 (56.0%) were female. Among the 135 symptomatic patients, 87 (64.4%) reported taste and smell alterations. Patients with a mild clinical course showed the highest prevalence for taste and smell disorders (76.6%), which were also associated with a more benign clinical course of the disease (P = 0.0166). Furthermore, in 33 (37.9%) of these patients, changes in smell and taste perception appeared before the acute phase of the disease. Among the 14 patients with a severe clinical course of SARS-CoV-2 infection, 8 reported a variation of taste and smell perception before the hospitalization, with a median of 4 days (IQR 2-7)*
Conclusions. *Smell and taste disorders can be listed among the first symptoms of SARS-CoV-2 infection and may anticipate the acute phase of the disease. Noteworthy, they seem to be associated with a more benign clinical course.*

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Background

In Italy, since the beginning of the COVID-19 pandemic, there have been numerous reports of patients testing positive for SARS-CoV-2 infection through nasopharyngeal swab, recounting taste and smell alterations (1). Moreover, taste and smell alterations, which are not frequently found in other respiratory infections, are among the most frequent and specific symptoms of infection, making their specificity and prevalence particularly useful for the differential diagnosis of COVID-19, especially during the upcoming flu season.

The most frequent symptoms of the disease are fever (83.3%), cough (60.3%), and asthenia (38%), which are often accompanied by chest pain, myalgia, sore throat and dyspnea. Rhinorrhea (3.5%) and nasal congestion (2%), probably due to ageusia and anosmia, are less frequent (2).

Smell and taste alterations (65%) are amongst the earliest and more frequent symptoms of COVID-19 to appear (3). In patients tested positive for SARS-CoV-2, taste and smell alterations are the first symptoms to manifest in 10% and 11% of cases, respectively (4). A study also described their specificity (90.3%) due to estimation of the positive predictive value (5).

The purpose of this study was to describe and ascertain the association between smell and taste disorders and the clinical course of SARS-CoV-2 infection, and to define the temporal association of those symptoms with the acute phase of the disease. In particular, we sought to determine whether they might be associated with a more benign clinical course of the disease.

Methods

Population

Our study population consisted of COVID-19 patients followed by the Local Healthcare Trust of Vercelli, which consists of all persons residing and healthcare workers (HCWs) in the care homes in this area. Enrolled participants were identified using the current Administrative Health Database (AHDs) of Piedmont Region. For this reason, the HCWs in the care homes, although not resident in this area, were enrolled in the study. On the contrary, the HCWs from the Regional Health Service, whose healing process was followed by the occupational health services of the same Local Healthcare Trust, were not included.

Study design

This was a cross-sectional study conducted between April 27th and May 27th, 2020. A random sample of subjects were included. The phone calls were assigned randomly to four operators by the administrative manager of the contact tracing force working at the Local Healthcare Trust in Vercelli. Only two of them (NP, AI) were involved in the study, and contacted 168 patients out of 351 subjects. At the time of the second nasopharyngeal swab, they were submitted to a phone-based questionnaire.

The survey was structured in order to investigate the clinical course, the time of onset of the first symptoms, smell and/or taste alterations onset, and association of those disorders with the severity of the disease. During this phonr interviews, patients were asked whether they had experienced symptoms and when they had begun to exhibit symptoms before diagnosis. On the basis of symptoms and of the severity of the disease, we stratified patients in “asymptomatic, “mild, “moderate”, or “severe” according to the WHO severity classification (6). Participants were also asked to evaluate their sense of smell and sense of taste as normal, decreased or lacking. For participants reporting ‘‘decreased’’ or ‘‘lacking’’, a follow-up question was provided asking how many days before or after the onset of COVID-

Table 1 - Age and sex for different clinical course.

Clinical course	Age	Males	Females	Total
Asymptomatic	52.3±14.4	9(12.2%)	24(25.5%)	33 (19.6%)
Mild	45.9±14.9	19(25.7%)	28 (29.8%)	47 (28.0%)
Moderate	52.5±13.2	27(36.5%)	33(35.1%)	60 (35.7%)
Severe	63.7±9.7	19(25.6%)	9 (9.6%)	28 (16.7%)
Total	**52.5±14.5**	**74**	**94**	**168**

19 symptoms any sense of smell and taste decreased perception had begun.

Statistical Analysis

Descriptive analysis reporting absolute frequencies and percentages for categorical variables was performed. In addition, mean and standard deviation or median and interquartile range was carried out for numerical ones.

The analysis was conducted jointly on all subjects, but also disjointedly for severity level. To evaluate the association between clinical severity and smell and taste alterations, a chi-square test was performed. In addition, Cochran-Armitage trend test was conducted to take the trend into account.

A logistic model was implemented using, as outcome variable, the alteration of taste and smell, and as covariate the clinical course severity. Odds ratio (OR) and the respective confidence intervals (IC 95%) has been reported. *P*-values lower than 0.05% were considered significant. The analysis was performed using the software STATA (version 14.0).

Results

We enrolled 168 patients. The mean age was 52.5 (SD 14.5) years old, and 94 (56.0%) were female. Of them, 33 (19.6%) were asymptomatic, 47 (28.0%) reported mild symptoms, 60 (35.7%) reported moderate symptoms and 28 (16.7%) had a severe clinical course (oxygen therapy in hospital setting). Demographic characteristics, separated according to disease severity, are described in Table 1.

We found a statistically significant positive association between gender and severity of the disease ($P = 0.02$); males seemed to report a more severe clinical course than females.

Among 135 symptomatic patients, 87 (64.4%) reported taste and smell alterations. Patients with a mild clinical course showed the highest prevalence for taste and smell disorders (76.6%). In addition, an inverse association between the severity of the disease and the presence of smell and taste alterations was found: smell and taste alterations were associated with a more

Table 2 - Distribution of taste/smell alterations in the symptomatic population.

Clinical course	Smell/taste disorder	Total
Mild	36 (76.6%)	47
Moderate	37 (61.7%)	60
Severe	14 (50.0%)	28
Total	**87 (64.4%)**	**135**

The *P*-value was computed by Cochran-Armitage ($P = 0.02$)

Table 3 - Taste and smell alteration onset time compared to general symptoms onset.

Clinical course	Before	At the same time	After	Total
Mild	17	12	7	36
Moderate	8	18	11	37
Severe	8	3	3	14
Onset %	37.9%	37.9%	24.1%	100%
Total	33	33	21	87

benign clinical course of the disease (P = 0.0166) (Table 2).

In 57.1% (n=8) of participants with a severe course of disease and smell and taste disorder, the onset of those symptoms was established before the hospitalization, with a median of 4 days (IQR 2-7) (Table 3). In addition, it is to consider that, for patients who did not show smell and taste alterations before, oxygen-therapy might be the cause itself.

Discussion

The onset of smell and taste alterations (e.g anosmia, disgeusia, hyposmia, hypogeusia, etc.), considered as one of the most suggestive symptoms related to COVID-19, is used by clinicians as a screening symptom useful to identify suspected cases. Indeed, it has been largely observed and reported a more significant prevalence of anosmia in COVID-19 patients than in patients suffering from different respiratory infections (7).

The primary aim of this cross-sectional study was to ascertain the potential association between smell and taste disorders and the clinical course of SARS-CoV-2 infection, in order to determine whether they might be associated with a more benign clinical course of the disease.

Incidence of these dysfunctions in COVID-19 patients was higher in European countries, including Italy (34 to 86%), North America (19 to 71%) and the Middle East (36 to 98%), lower in Asian populations (8).

Our study confirmed a consistent prevalence (51.7%) of smell and taste disorders in the enrolled participants. Those results are in line with a previous systematic review and meta-analysis that reported a prevalence for olfactory dysfunction of 52.73% (95% CI: 29.64% - 75.23%) among COVID-19 patients, 36.64% (95% CI: 18.31% - 57.24%), using non-validated instruments *vs* 86.60% (95% CI: 72.95% - 95.95%), using validated instruments (9). Similarly, the prevalence for gustatory dysfunction was 43.9% (95% CI: 20.46% - 68.95%).

Specifically, some cross-sectional studies reported a prevalence of anosmia ranging between 33.9% and 35.7% (21% for patients who have been hospitalized and 64.4% - 68% for patients treated at home) (10).

Smell and taste alterations may appear before, concomitantly, or immediately after the onset of the usual symptoms. Based on that, we tried also to better define the temporal onset of those symptoms.

The majority of our study population reported the onset of olfactory and gustatory alterations before the usual symptoms.

In contrast with our results, a study conducted by Lechien et al. found that olfactory dysfunctions appeared mostly after (65.4%) the appearance of general or ENT (ear, nose, throat) symptoms (22.8%) (11). Discrepancies with our results may be due to different methodological approaches, study design, and the fact that we have considered the onset of olfactory and gustatory dysfunction in relation with

symptoms inherent to the ENT, but also with general symptoms.

This cross-sectional study also came with another very interesting finding: a less severe COVID-19 disease is related to a greater prevalence of those dysfunctions.

In an already mentioned systematic review of 18 cohort studies (8), self-reported olfactory and gustatory alteration is considered a favorable prognostic factor in COVID-19 patients, and our results are in line with their ones.

Similarly, another study, not included in the above-mentioned review, reported that loss of smell was also significantly associated with decreased hospitalizations, intensive care unit admissions, intubations, and acute respiratory distress syndrome (12).

This finding may be due to the clinical importance of other symptoms of the disease; patients with severe clinical course, may have not noticed smell or taste alterations.

This work presents some weaknesses that must be taken into account. First, this study was carried out only on Italian population, thus not allowing extension of current finding to non-Italian populations and those results are maybe not completely applicable and generalizable to general populations.

Other limits of the study are represented by the small size of the sub-population with a severe clinical course and the subjective nature of changes in smell and taste perception.

In addition, limitations include the non-utilization of objective olfactory and gustatory testing; therefore, self-reported taste and smell disorders should be validated in future studies with quantitative tests.

Nevertheless, among the strengths of this work, it is possible to cite the use of administrative health data, robust and valid statistical analyses and the "survey approach" that provides information about diagnosis and disease status that deeply mitigates the limitations typical of using claims data (e.g. lack of clinical data).

Conclusions

Our results support previous findings relating to the favorable prognostic nature of taste and smell dysfunctions in COVID-19 patients, providing new insights.

Those symptoms seem to be suggestive in COVID-19 patients and therefore they should be taken into consideration by physicians for COVID-19 clinical diagnosis. Indeed, those alterations act as a worthy biomarker to predict COVID 19 and may anticipate the acute phase of the disease. Although those dysfunctions seem to be associated with a more benign clinical course, further and larger longitudinal studies, with good methodological quality and larger sample size, are warranted in order to confirm this association.

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Conflict of interest: The authors declare to have no conflicts of interest.

Riassunto

Disturbi del Gusto e dell'Olfatto in pazienti COVID-19 in un'Azienda Sanitaria Locale del Nord Italia: uno studio trasversale

Introduzione. Sin dall'inizio della pandemia di COVID-19 in Italia, i pazienti che risultavano positivi a SARS-CoV-2 tramite tampone nasofaringeo, hanno riportato alterazioni di gusto ed olfatto. Questi sintomi non sono comuni in altre infezioni dell'apparato respiratorio quindi la loro specificità e prevalenza sono utili per la diagnosi differenziale di COVID-19.

L'obiettivo dello studio è stato quello di descrivere ageusia e anosmia in pazienti con infezione da SARS-CoV-2 e identificare l'insorgenza di questo i disordini durante il decorso clinico della malattia.

Disegno dello studio. Studio trasversale.

Metodi. Lo studio è stato condotto su pazienti risultati positivi a SARS-CoV-2 tramite tampone nasofaringeo presso un dipartimento sanitario locale del nord d'Italia, tra il 27/04/2020 e il 27/05/2020. Per indagare il decorso clinico, l'insorgenza dei primi sintomi e la presenza di alterazioni di gusto e olfatto, è stato somministrato un questionario telefonico durante la prenotazione del secondo tampone.

Risultati. Sono stati reclutati 168 pazienti, di questi 94 (56.0%) sono donne e l'età media è di 52 anni. Tra i 135 pazienti sintomatici, 87 (64.4%) hanno riportato alterazioni di gusto e olfatto. Pazienti con una sintomatologia lieve hanno mostrato una prevalenza più alta per alterazioni di gusto e olfatto (P=0.0166). Inoltre, in 33 (37.9%) pazienti, le alterazioni di gusto e olfatto sono apparse prima della fase acuta della malattia. Tra i 14 pazienti con decorso clinico grave da SARS-CoV-2, 8 hanno riportato alterazioni di gusto e olfatto prima dell'ospedalizzazione, con una mediana di 4 giorni (IQR 2-7).

Conclusioni. Alterazioni di gusto e olfatto possono essere considerati tra i primi sintomi di infezione da SARS-CoV-2, e potrebbero anticipare la malattia. Inoltre sembrano essere associati con un decorso clinico più benigno.

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