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ORIGINAL PAPER

Clinical Symptoms in Hospitalized and Self-Quarantined Patients with SARS-CoV-2 Infection in Northwestern Greece – Association with Olfactory and Gustatory Dysfunction

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ABSTRACT

Backround: *We aimed to assess the relation of chemosensory dysfunction with the reported symptoms in two subgroups of patients in Northwestern Greece: the first one included patients with moderate to severe symptomatology who needed hospitalization and the second one, patients with mild symptoms who recovered at home.*

Methods: *We used a questionnaire to select information about patient demographics, medical history and reported symptoms during infection. Three hundred COVID-19 positive patients who were identified via RT-PCR test in the University Hospital of Ioannina, Greece, were included in the present study, of which 150 recovered at home and the remaining 150 needed hospitalization. Statistical analysis was based on IBM-SPSS Statistics 26.0.*

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Results: *The majority of patients had fever during infection, while o minor percentage of those who needed hospitalization (12.67%) suffered from sore throat. There was a statistically significant difference between the loss of smell and clinical symptoms including fatigue, nose congestion, body aches and headache, and loss of taste and reported symptoms including fatigue, body aches, runny nose, headache and sore throat.*

Conclusion: *Fever was the symptom with the highest percentage rate, while sore throat was the symptom with the lowest percentage rate. There are reported clinical symptoms related with olfactory and gustatory dysfunction during COVID-19 infection.*

Keywords: COVID-19, olfactory dysfunction, gustatory dysfunction, reported symptoms, Northwestern Greece.

INTRODUCTION

Reduction or loss of smell and taste are already recognized as common symptoms during SARS-CoV-2 infection, although they appear to be improving after several days to weeks (1, 2). At first, many treatments have been evaluated for post-viral olfactory dysfunction; however, current research supports the benefit of olfactory training therapy. Previous studies have proved that the quality of life was significantly affected by olfactory dysfunction, while most patients reported difficulties in differentiating the basic taste qualities of salty, bitter, sweet, and sour when asked to evaluate their taste system (3, 4). The major cause of chronic olfactory dysfunction seems to be the acute upper respiratory viral infections that damage the olfactory epithelium (5). It is estimated that the virus can pass from the non-neural olfactory epithelium cells directly to the cerebrospinal fluid near the cribriform plate, close to the olfactory bulb, while the role of the angiotensin converting enzyme 2 (ACE2) receptor is also proven to be important as a pathway for chemosensory dysfunction in COVID-19 infection (6-8). Some of the most common reported symptoms during COVID-19 infection include fever, headache, difficulty in breathing, decrease in taste and smell, runny nose, nose congestion, body aches, sore throat, fatigue, cough and less often diarrhea or vomiting (9, 10).

The aim of the present study was to record the percentage of self-reported symptoms in hospitalized and self-quarantine patients with SARS-CoV-2 infection in Northwestern Greece as well as to evaluate the relation between self-reported symptoms and chemosensory dysfunction in this population. ❑

METHODS

Participants

The present prospective observational cohort study was submitted to and approved by the research ethics committee and scientific council of the University General Hospital of Ioannina, Greece. The total study sample included 300 male and female patients aged 18 to 80 years old with COVID-19 infection, who referred to either the Emergency Department (ED) of Infectious Diseases or the Outpatient Clinic screening for SARS-CoV-2 infection. All participants had a positive reverse transcription-polymerase chain reaction (RT-PCR) test result between November 2020 and May 2021. An informed consent form was completed and obtained from each eligible patient prior to participation in the study.

The study population was divided into two subgroups. The first one consisted of 150 patients who recovered at home because they had mild to moderate disease and did not need hospitalization. The second subgroup comprised the remaining 150 patients who had severe disease and needed hospitalization in the Infectious Diseases Unit (IDU) of the University General Hospital of Ioannina, Greece.

Specific inclusion and exclusion criteria were used in order to determine the sample size of the present research. Taking into account the factors that potentially influence olfactory and taste function, we excluded every participant who had previous sinus surgery, underwent head and neck radiation therapy, was suffering from aller-

gic rhinitis or chronic rhinosinusitis, or had a history of head injury (11-20).

Data collection

Data was collected during the first days of COVID-19 infection by using a questionnaire. One hundred and fifty COVID-19 positive patients who recovered at home were informed in person at the time of diagnosis by either telephone or email, following the safety measures provided by National Organization of Public Health of Greece. Information about the study was given by officially designated investigators. One hundred and fifty patients who required hospitalization were examined in person by one of the study investigators. Patient demographics, including name, age, height, weight, sex and contact details, as well as medical history, reported comorbidities, smoking and alcohol habits were all recorded. Patients also reported their associated symptoms during infection using a questionnaire. They had to choose symptoms from the following list: fever, cough, headache, sore throat, difficulty in breathing, fatigue, body aches, runny nose, nasal congestion, loss of smell and loss of taste. The questionnaire was completed by the examinee after ensuring that every patient had received all needed information about the purpose of the study as well as a written consent form.

Statistical analysis

The statistical analysis approach regarding categorical data was performed using the χ^2(chi-square) test or Fisher's exact test in the case where at least one frequency in the contingency table was smaller than 5. As far as the numerical data were concerned (*i.e.*, BMI, weight, height, and age), either the Mann–Whitney test or t-test was applied upon evaluation of the normality of each distribution using the Shapiro-Wilk normality test.

We analyzed the percentages of patients who reported loss of smell and/or taste, cough, headache, sore throat, difficulty in breathing, fatigue, body aches, runny nose, or nasal congestion during infection, in the total sample as well as in hospitalized and self-quarantined patients.

We also investigated whether there was a statistically significant difference between the subgroup of patients with loss of smell and their reported symptoms during infection. This relation was examined in the total sample as well as in both study subgroups. Thus, we investigated if there was a statistically significant difference between the subgroup of patients with loss of taste and the reported symptoms during infection. This relation was examined in both the total sample and the subgroups of patients who recovered at home and needed hospitalization, respectively.

P-values and odds ratio (OR) were calculated for every feature that was statistically analyzed. ❑

RESULTS

The present study had a total number of 300 participants, of which 106 (35.33%) female and 194 (64.67%) male patients.

Analysis of reported symptoms showed that the rate of subjects who had fever during infection was 72% in the total sample, 82.67% in the subgroup of hospitalized patients and 61.33% in self-quarantined patients. Cough during infection occurred in 52.67% of patients in the total sample, 60.67% of those who needed hospitalization and 44.67% of self-quarantined patients. Difficulty in breathing was seen in 25.33% of patients who reported this symptom in the total sample, 38.67% of those requiring hospitalization and 12% of self-quarantined patients. Fatigue during infection was noted in 49% of patients in the total sample, 50% of those in the subgroup who needed hospitalization and 48% of patients who recovered at home. Body aches was a clinical symptom in 47% of patients in the total sample, 49.33% of those who were hospitalized and 44.67% of self-quarantined patients. Runny nose during infection was seen in 25.67% of patients in the total sample, 20% of those requiring hospitalization and 31.33% of subjects who recovered at home. Nose congestion was an annoying symptom for 37.33% of patients in the total sample, 23.33% of hospitalized ones and 51.33% of those who recovered at home. Sore throat was reported by 17.67% of patients in the total sample, 12.67% of those requiring hospitalization and 22.67% of self-quarantined ones. Loss of smell was reported by 57% of subjects in the total sample, 46.67% of hospitalized ones and 67.33% of self-quarantined patients. Loss of taste was noted in 51.67% of patients in the total sample, 46.67% of hospitalized ones and 56.67% of those who recovered at home.

TABLE 1. Percentages of patients with reported clinical symptoms as per the analysis of results for the total sample and the two subgroups of patients who needed hospitalization and self-quarantine

Reported symptoms	Total sample (n=300)%	Hospitalization (n=150)%	Self-quarantined (n=150)%
Fever	72	82.67	61.33
Cough	52.67	60.67	44.67
Difficulty in breathing	25.33	38.67	12
Fatigue	49	50	48
Body aches	47	49.33	44.67
Runny nose	25.67	20	31.33
Nose congestion	37.33	23.33	51.33
Sore throat	17.67	12.67	22.67
Loss of smell	57	46.67	67.33
Loss of taste	51.67	46.67	56.67
Headache	37	31.33	42.67

Finally, the percentage of patients with headache was 37% in the total sample, 31.33% among hospitalized subjects and 42.67% in self-quarantined ones (Table 1).

Data analysis in the total sample showed that there is statistically difference between the subgroup of patients with loss of smell and fatigue (p=0.024), (OR=1.750551335). There is also statistically significant difference between the subgroup of patients with loss of smell and nose congestion, in the total sample (p=0.002), (OR=2.2). Through the statistical analysis between the subgroup of patients with loss of smell and headache in the total sample, we found that there is statistically significant difference between them (p=0.007), (OR=2.018229167) (Table 2).

Respectively in the total sample, we found that there is statistically significant difference between the subgroup of patients with loss of taste and fatigue (p=0), (OR=2.527777778). Statistically significant difference also was found for the subgroup of patient with loss of taste and the reported symptoms; body aches (p=0.002), (OR=2.156045752), runny nose (p=0.005), (OR=2.244452663), headache (p=0.002), (OR=2.21875) (Table 2).

Data analysis in self-quarantined patients showed that there is statistically difference between the subgroup of patients with loss of smell and nose congestion (p=0.02), (OR=2.419312169) (Table 3).

Through the analysis in the group of patients that recovered at home, we found that there is statistically significant difference between the group of patients with loss of taste and the reported symptoms; fatigue (p=0.027), (OR=2.216216216), body aches (p=0.013), (OR=2.471306471), runny nose (p=0.015),

TABLE 2. Statistically significant difference between the subgroup of patients with loss of smell/loss of taste and the reported symptoms in the total sample (*p <0.050, **p <0.005, ***p <0.001, OR >1 means greater odds of association with exposure and outcome, OR=1 means no association between exposure and outcome, OR <1 means lower odds of association between exposure and outcome)

Reported symptoms	Loss of smell p-value	Loss of smell Odds ratio	Loss of taste p-value	Loss of taste Odds ratio
Fever	0.144	0.656565657	0.456	1.252475248
Cough	0.918	0.996732026	0.666	1.135135135
Difficulty in breathing	0.306	0.734643735	0.639	0.852238157
Fatigue	**0.024**	1.750551335	**0**	2.527777778
Body aches	0.057	1.60717636	**0.002**	2.156045752
Runny nose	0.078	1.683653846	**0.005**	2.244452663
Nose congestion	**0.002**	2.2	0.068	1.595994138
Sore throat	0.19	1.587009804	0.064	1.863418878
Headache	**0.007**	2.018229167	**0.002**	2.21875

TABLE 3. Statistically significant difference between the subgroup of patients with loss of smell/loss of taste and the reported symptoms in self-quarantined patients (*p <0.050, **p <0.005, ***p <0.001; OR >1 means greater odds of association with exposure and outcome, OR=1 means no association between exposure and outcome, and OR <1 means lower odds of association between exposure and outcome)

Reported symptoms	Loss of smell p-value	Loss of smell Odds ratio	Loss of taste p-value	Loss of taste Odds ratio
Fever	0.605	0.777439024	0.423	1.387387387
Cough	0.892	0.986201299	0.611	1.251028807
Difficulty on breathing	0.74	0.733333333	0.389	0.571428571
Fatigue	0.722	1.203208556	**0.027**	2.216216216
Body aches	0.892	1.115151515	**0.013**	2.471306471
Runny nose	0.148	1.913286713	**0.015**	2.666666667
Nose congestion	**0.02**	2.419312169	0.202	1.610438024
Sore throat	0.278	1.776666667	**0.014**	3.139830508
Headache	0.62	1.268796992	0.158	1.701581028

(OR=2.666666667), sore throat (p=0.014), (OR=3.139830508) (Table 3).

Data analysis in hospitalized patients showed that there is statistically difference between the subgroup of patients with loss of smell and fatigue (p=0.05), (OR=2.674937965). There is also statistically significant difference between the subgroup of patients with loss of smell and body aches, in hospitalized patients (p=0.009), (OR=2.517323775). Through the statistical analysis between the subgroup of patients with loss of smell and headache in hospitalized patients, we found that there is statistically significant difference between them (p=0.008), (OR=2.779411765) (Table 4).

Respectively in hospitalized patients, we found that there is statistically significant difference between the subgroup of patients with loss of taste and fatigue (p=0.02), (OR=3). Statistically significant difference also was found for the subgroup of patient with loss of taste and headache (p=0.008), (OR=2.779411765) (Table 4). ❑

DISCUSSION

Many studies have already proved that fever was estimated to be the most commonly reported symptom during COVID-19 infection. It is important to mention that the absence of

TABLE 4. TABLE 4. Statistically significant difference between the subgroup of patients with loss of smell/loss of taste and the reported symptoms in hospitalized patients (*p <0.050, **p <0.005, ***p <0.001; OR >1 means greater odds of association with exposure and outcome, OR=1 means no association between exposure and outcome, and OR <1 means odds of association between exposure and outcome)

Reported symptoms	Loss of smell P-value	Loss of smell Odds ratio	Loss of taste p-value	Loss of taste Odds ratio
Fever	0.874	0.850746269	0.48	1.5
Cough	0.496	1.330434783	0.729	1.188216039
Difficulty in breathing	0.884	1.111111111	0.63	1.243902439
Fatigue	**0.005**	2.674937965	**0.002**	3
Body aches	**0.009**	2.517323775	0.051	2.013584117
Runny nose	0.838	1.181818182	0.306	1.653120464
Nose congestion	0.652	1.28280543	0.652	1.28280543
Sore throat	0.857	1.032786885	0.857	0.809384164
Headache	**0.008**	2.779411765	**0.008**	2.779411765

fever at the time of initial screening in a patient with suspicious symptoms does not exclude COVID-19 infection (21-24). Our data confirm these findings in the selected Northwestern Greek population of patients with COVID-19, among which fever was the symptom with the highest incidence rate in the total sample. This percentage of patients with fever was also higher in hospitalized ones compared with the subgroup of subjects who recovered at home. Although this may indicate that fever is a risk factor in poor prognosis of infection, we have to clarify that our study has not been geared towards identifying the impact of fever on COVID-19 prognosis.

Subsequently, loss of smell occurred in 57% of patients in the total sample and had the highest rate in self-quarantined subjects. Olfactory dysfunction was frequently reported in COVID-19 patients in more recent studies (2, 5, 25-29). Systemic corticosteroids could constitute a treatment option in cases with anosmia and signs of nasal inflammation (30, 31). We supposed that this was probably a reason of the loss of smell improvement in hospitalized patients. Yan *et al* found that patients with COVID-19 and anosmia were less likely to be hospitalized than their normosmic counterparts. Such observations suggest that severe chemosensory dysfunction is unrelated to measures which are typically related to hospitalization and that anosmia or severe hyposmia reflects milder forms of the disease (25).

In this study, cough turned to be the third most commonly encountered clinical symptom in the total sample of 300 COVID-19 positive patients and the second commonest symptom in the subgroup of hospitalized subjects, which was in accordance with many other researchers who described it as a common symptom in COVID-19 infection (23, 24).

Loss of taste, fatigue and body aches follow the sequence of symptoms, while sore throat was the less commonly reported symptom.

The statistical analysis of symptoms including olfactory and gustatory dysfunction showed that loss of smell was related to fatigue, nose congestion and headache in the total sample, to nose congestion in self-quarantined patients, and in a statistically significant manner to fatigue, body aches and headache in hospitalized subjects. Loss of taste was related to fatigue, body aches, runny nose and headache in the total sample, and to about the same symptoms, excepting headache, which was replaced by sore throat, in self-quarantined patients, while gustatory dysfunction was significantly correlated to fatigue and headache in the subgroup of hospitalized patients.

Our results suggest that anosmia is associated with nasal obstruction but not with runny nose. Previous studies support that nasal inflammation and obstruction is not the only reason for olfaction dysfunction in COVID-19 infection, analyzing other probable pathways such as invasion of the olfactory bulb and central nervous system (32). Our observations did not come to an agreement with other studies showing that COVID-19-related olfactory dysfunction was not associated with rhinorrhea and nose inflammation (33-38). Although the underlying mechanisms require further elucidation, the association between loss of smell compared with common sinonasal symptoms such as runny nose or nasal obstruction probably suggest a greater affectation of the olfactory neuroepithelium due to COVID-19 (39). Our observations that loss of smell also relates to fatigue, body aches and headache are supported by those from previous studies. Menni C. *et al* performed a real-time tracking of self-reported symptoms in order to predict potential COVID-19 and identified a combination of symptoms, including loss of smell, fatigue and cough (10). Sakali *et al* showed that the rates of symptoms including "the need to blow nasal obstruction", rhinorrhea, fatigue, myalgia, fever, facial pain, and headache were significantly higher in the group of subjects with loss of smell group than that without loss of smell (40). A systematic review about the onset and duration of symptoms in patients with COVID-19 showed that changes in smell and/or taste may occur concomitantly with other symptoms, of which the most commonly reported included fever, cough, headache and fatigue (25, 32, 33, 41-51).

There were several study limitations. In the context of a global pandemic during which millions of patients have been infected, our study included a relatively low sample size of 300 patients, who were examined while the COVID-19 outbreak was rapidly spreading. A major limitation of the current study was the self-report nature of included data, which cannot replace ob-

jective assessments of the olfactory and gustatory function. ❑

CONCLUSIONS

The present study concluded that fever was the most commonly reported clinical symptom among both hospitalized patients with moderate to severe disease and those with mild symptoms who recovered at home. By contrast, sore throat was the less commonly reported symptom. We proved that there was a relationship between olfactory dysfunction and symptoms including nose congestion, fatigue, body aches and headache, on one hand, and between gustatory dysfunction and symptoms including fatigue, body aches, runny nose, sore throat and headache, on the other hand. Our observations were in accordance with those from previous studies. ❑

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