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Olfactory and gustatory dysfunctions in patients with COVID-19 in Wuhan, China

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Abstract

The coronavirus disease 2019 (COVID-19) is spreading all over the world. The main symptoms of COVID-19 include fever, cough, fatigue, and myalgia. However, there are few reports on olfactory and gustatory dysfunctions in patients with COVID-19. Our objective was to investigate the incidence of olfactory and gustatory dysfunctions in patients with COVID-19 infection in Wuhan, China. In this retrospective study, we collected 81 confirmed cases of COVID-19 from the Renmin Hospital of Wuhan University from February 2020 to March 2020, and analyzed the demographic characteristics, clinical manifestations (including olfactory and gustatory dysfunctions), laboratory findings, and comorbidities. In total, 81 confirmed COVID-19 patients were enrolled in this study (38 males and 43 females). The study showed that the most prevalent symptoms included cough, myalgia, and loss of appetite. On admission, 25 (30.9%) of all patients reported either olfactory dysfunction (OD) or gustatory dysfunction (GD), and 7 (8.6%) reported both OD and GD. Overall, 13.6% and 25.9% of all patients reported OD and GD, respectively. OD and GD were not associated with disease severity. Pearson correlation analysis identified some factors that are correlated with OD and GD, including headache or dizziness (r = 0.342, *P* = 0.002), dark urine (r = 0.256, *P* = 0.021), IgM titer (r = 0.305, *P* = 0.01), and diabetes (r = 0.275, *P* = 0.013). Multivariate adjusted logistic analysis showed that patients with headache or dizziness (OR = 7.382, 95%CI: 1.028-53.022) and diabetics (OR = 6.871, 95%CI: 1.096-43.086) were at higher risk of developing OD. In addition, patients with high IgM titers (OR = 1.006, 95%CI: 1.000-1.006) and diabetes (OR = 4.335, 95%CI: 1.098-17.287) were at high risk of developing GD. In 81.8% of the cases with OD and 28.6% of the cases with GD, the symptoms lasted for at least one month after

discharge. In addition, 3.6% of inpatients without OD developed OD after discharge. These findings suggest that OD and GD are common in COVID-19. These symptoms appear early during the course of the disease and may last for one month. The incidence of OD and GD is related to neurological manifestations, diabetics, and IgM titers.

Keywords: COVID-19, SARS-CoV-2, smell, taste, infection

INTRODUCTION

Coronavirus disease 2019 (COVID-19), an infectious disease caused by the acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has spread globally. As of March 20, 2022, there have been more than 464 million confirmed cases of COVID-19 globally[1]. Early epidemiological investigations show that the basic reproduction number (R0) of SARS-CoV-2 is estimated to be about 2.2 (range, 1.4-6.5)[2]. The high spread and low fatality rate of COVID-19 made it a global pandemic. COVID-19 has become the largest pandemic since the H1N1 flu outbreak in 1918. Early genetic tests emphasized that the genome sequence identity of SARS-CoV-2 and SARS-CoV is 79.5%. Both viruses infect cells through angiotensin-converting enzyme 2 (ACE2)[3,4]. The similarity of the gene sequence and infection route suggests that SARS-CoV-2 and SARS-CoV have similar clinical manifestations. Similar to SARS, the most common symptoms of COVID-19 are fever, cough, sputum, fatigue, and myalgia[5-7]. Complications of COVID-19 involve multiple systems, such as the cardiovascular system, digestive system, and nervous system[8-10]. Current research mainly focuses on central nervous system complications such as cerebrovascular diseases and acute encephalopathy[10], while less is known about the peripheral nervous system complications. Symptoms in the head and neck such as dry eyes, tearing, and smell and taste disturbances were reported in COVID-19 patients and believed to be related to the neurophagy of the virus[11-12]. It is worth noting that SARS-CoV can be detected 60-66 h after infection and is most abundant in the olfactory bulb[13]. In addition, the virus may enter the brain through the olfactory bulb. Viral antigens can also be detected in brain areas connected to the olfactory bulb, such as the piriform nucleus and subliminal leather, basal ganglia, and midbrain[14,15].

The purpose of this study was to investigate the incidence of olfactory and taste disorders in confirmed COVID-19 cases and to analyze the risk factors related to olfactory and gustatory dysfunctions in order to provide clues for the clinical diagnosis and treatment of COVID-19.

METHODS

Patient enrollment and data collection

This descriptive study included 81 inpatients diagnosed with COVID-19 in the Renmin Hospital of Wuhan University, Wuhan, China. The diagnosis of COVID-19 was based on clinical symptoms, computed tomography (CT), real-time RT-PCR, and next-generation sequencing. The patient's admission date was from February 1 to March 3, 2020. All patients participating in this study lived in Wuhan during the COVID-19 outbreak. Two well-trained investigators collected the data including demographic characteristics, clinical characteristics (including medical history, comorbidities, and symptoms), preliminary laboratory findings, treatment, and clinical outcomes.

According to the SARS-CoV-2 diagnosis and treatment guidelines (Versions 3-7) issued by the National Health Commission of China, the severity of COVID-19 patients was defined. Severe cases were designated when the patients fit one of the following criteria: (1) respiratory distress with respiratory rate ≥ 30/min; (2) oxygen saturation ≤ 93% at rest; (3) arterial partial oxygen pressure (PaO_2)/oxygen absorption concentration (FiO_2) ≤ 300 mmHg; (4) respiratory failure that needs mechanical ventilation; or (5) shock or organ failure requiring ICU care.

Procedures

Two investigators collected the information on epidemiology, clinical symptoms, laboratory test results, treatment, and clinical outcomes. Laboratory tests included routine blood examination (including white blood cells, lymphocytes, and platelets), coagulation function, lactate dehydrogenation, and immune indicators (including lymphocyte differential counts and inflammatory factors). Participants were interviewed by telephone and were asked to report their olfactory and gustatory dysfunctions at the time of hospitalization and one month after discharge. Two years after discharge, those with olfactory and gustatory dysfunctions one month after discharge were re-interviewed to report their smell and taste status. Verbal informed consent was obtained from all participants or their legal guardians. The severity of symptoms was graded as totally normal, mild, moderate, and severe. Totally normal means that respondents rated smell and taste as "Good" or "Unaffected", mild dysfunction means the patient hardly noticed a smell and taste reduction, moderate dysfunction means there was a noticeable reduction, and severe dysfunction means the patient reported an almost complete loss of smell and taste. Patients with olfactory and gustatory dysfunctions before contracting COVID-19 were excluded, and so were patients with a diagnosis of chronic rhinitis, Alzheimer's disease (AD), or Parkinson's disease (PD) on admission. We also asked patients during the telephone interview whether they had a history of chronic rhinitis, AD, or PD. These patients might experience olfactory and gustatory dysfunctions, which could affect the study results. Cases with unsuccessful follow-ups were excluded.

Statistical analysis

Continuous variables were described as medians and interquartile range (IQR), and categorical variables were described as frequency rates and percentages. We used the chi-square (χ^2) test or the Fisher's exact test to compare categorical data. Mann-Whitney-Wilcoxon test was applied to compare non-normally continuous variables. Pearson correlation analysis was used to examine the correlations between olfactory/gustatory dysfunctions and all indicators (including epidemiology, clinical symptoms, laboratory test results, treatment, and disease severity). The sample size varied due to missing data, and missing data were not imputed. The analyses regarding different factors were based on non-missing data. Multivariate adjusted logistic regression models were adopted to analyze the factors influencing olfactory and gustatory dysfunction in patients with COVID-19. All statistical analyses were performed using SPSS software (V.23.0). Two-tailed *P* values were considered statistically significant at < 0.05. This study was approved by the Hospital Ethics Committee of the Renmin Hospital of Wuhan University (WDRY2020-K136).

RESULTS

Demographic characteristics in COVID-19

The demographic characteristics, clinical manifestations, and comorbidities are shown in Table 1. Of the 81 patients, 63 cases were diagnosed as non-severe and 18 cases were severe. The median age was 58 years (IQR, 50.0-68.5 years). The median age of the severe group was 11.5 years older than that of the non-severe group. Males accounted for 46.9% (38 of 81) of the total patients. However, males accounted for 66.7% (12 of 18) of patients in the severe group compared with 41.3% (26 of 63) of the non-severe group. These results suggest that males and older patients are more likely to develop into severe cases, which is consistent with other reports[16]. On admission, the most common clinical manifestations were fever (72.8%) and respiratory symptoms (70.4%), while chest pain, fatigue, gastrointestinal symptoms, dark urine, and headache or dizziness accounted for 27.2%, 37%, 27.2%, 19.8%, and 14.8% of the patients, respectively. Compared with the non-severe group, the severe group had a higher proportion of dark urine (17.5% *vs.* 27.8%), suggesting a potential relationship between urinary system dysfunction and disease severity. Among the 81 cases, 51.9% had at least one comorbidity, including hypertension, diabetes, coronary heart disease, stroke, cancers, and chronic pulmonary diseases. Compared with the non-severe group, more patients in the severe group had a history of stroke (0% *vs.* 5.6%) and coronary heart disease (1.6% *vs.* 11.1%), suggesting that patients with

Table 1. Demographic characteristics of the 81 patients with COVID-19

Clinical characteristics and symptoms	All patients (*n* = 81)	Disease severity	
		Non-severe (*n* = 63)	Severe (*n* = 18)
Age, median (IQR) - years	58 (50.00-68.50)	57 (49.00-67.00)	68.5 (56.25-77.25)
Age groups - No., %			
< 65	51 (63.0)	45 (71.4)	6 (33.3)
≥ 65	30 (37.0)	18 (28.6)	12 (66.7)
Gender - No., %			
Male	38 (46.9)	26 (41.3)	12 (66.7)
Female	43 (53.1)	37 (58.7)	6 (33.3)
Symptoms or signs - No., %			
Fever on admission	59 (72.8)	46 (73.0)	12 (72.2)
Chest distress	22 (27.2)	19 (30.2)	3 (16.7)
Fatigue	30 (37.0)	23 (36.5)	7 (38.9)
Headache or dizziness	12 (14.8)	9 (14.3)	3 (16.7)
Respiratory symptoms	57 (70.4)	45 (71.4)	12 (66.7)
Gastrointestinal symptoms	22 (27.2)	17 (27.0)	5 (27.8)
Dark urine	16 (19.8)	11 (17.5)	5 (27.8)
Coexisting disorders - No., %			
Any	42 (51.9)	30 (47.6)	12 (66.7)
Hypertension	23 (28.4)	17 (27.0)	6 (33.3)
Diabetes	15 (18.5)	12 (19.0)	3 (16.7)
Coronary heart disease	3 (3.7)	1 (1.6)	2 (11.1)
Stroke	1 (1.2)	0 (0.0)	1 (5.6)
Cancer*	6 (7.4)	4 (6.3)	2 (11.1)
Chronic pulmonary disease#	7 (8.6)	5 (7.9)	2 (11.1)

Data are presented as medians [interquartile ranges (IQR)] and n/N (%). *Cancers referred to any malignancy. All cases had stable disease. #Chronic pulmonary disease includes tuberculosis, chronic obstructive pulmonary disease, and bronchiectasis. All cases were stable and no obvious bacterial infections.

cardiovascular and cerebrovascular diseases are more likely to develop severe illness. The above findings are consistent with previous studies[17-19].

Olfactory and gustatory dysfunctions in COVID-19

Table 2 summarizes the incidence of olfactory dysfunction (OD) and gustatory dysfunction (GD) when the patients were admitted to the hospital. On admission, 30.9% of all patients reported an altered sense of smell or taste. Overall, 13.6% and 25.9% reported OD and GD, respectively, while 8.6% reported both OD and GD. The incidence of OD in the severe group (11.1%) was not significantly different from that in the non-severe group (14.3%). Compared with the non-severe group, the incidence of GD was lower in the severe group (28.6% *vs.* 16.7%). However, OD and GD do not seem to be related to the severity of the disease (Fisher's exact test, $P < 0.05$).

The factors related to OD and GD are summarized in Table 3. We considered general conditions, symptoms, comorbidities, and laboratory tests and calculated the Pearson correlation coefficient. Some factors were positively correlated with OD, including headache or dizziness ($r = 0.342$, $P = 0.002$), dark urine ($r = 0.256$, $P = 0.021$), IgM titer ($r = 0.305$, $P = 0.01$), and diabetes ($r = 0.275$, $P = 0.013$). These factors were also positively correlated to GD (all $r > 0.2$, $P < 0.05$). The IgG titers were not significantly related to patients with OD ($r = 0.083$, $P = 0.496$) or GD ($r = 0.164$, $P = 0.176$). However, IgG titers were associated with the

Table 2. The incidence of olfactory and gustatory dysfunctions in patients with different disease severity

Disease severity	Olfactory dysfunction				Gustatory dysfunction				OD and GD	Any
	Total	Mild	Moderate	Severe	Total	Mild	Moderate	Severe		
Non-severe - *n*/%	9 (14.3)*	5 (7.9)	1 (1.6)	3 (4.8)	18 (28.6)*	8 (12.7)	7 (11.1)	3 (4.8)	5 (7.9)*	22 (34.9)*
Severe	2 (11.1)	0 (0.0)	1 (5.6)	1 (5.6)	3 (16.7)	1 (5.6)	1 (5.6)	1 (5.6)	2 (11.1)	3 (16.7)
All patients	11 (13.6)	5 (6.2)	2 (2.5)	4 (4.9)	21 (25.9)	9 (11.1)	8 (9.9)	4 (4.9)	7 (8.6)	25 (30.9)

*Compared with the severe group, $P > 0.05$. OD: Olfactory dysfunction; GD: gustatory dysfunction.

Table 3. Factors associated with olfactory and gustatory dysfunctions in COVID-19

Factors	OD		GD		OD or GD	
	r	*P* value	r	*P* value	r	*P* value
Headache or dizziness	0.342	0.002	0.308	0.005	0.248	0.026
Dark urine	0.256	0.021	0.273	0.014	0.273	0.014
IgM	0.305	0.01	0.238	0.046	0.251	0.035
IgG	0.083	0.496	0.164	0.176	0.269	0.024
Diabetes	0.275	0.013	0.298	0.007	0.301	0.006

OD: Olfactory dysfunction; GD: gustatory dysfunction.

incidence of patients with either OD or GD (r = 0.269, $P < 0.05$).

The association between various factors and the risk of olfactory and gustatory dysfunction in patients with COVID-19 is shown in Table 4. In the multivariate adjusted logistic regression model, patients with headache and dizziness (adjusted OR = 7.382, 95%CI: 1.028-53.022) were more likely to have olfactory dysfunction than those without headache and dizziness. Patients with diabetes had a higher risk of olfactory dysfunction compared to those without diabetes (adjusted OR = 6.871, 95%CI: 1.096-43.086). In the logistic regression analysis of gustatory dysfunctions, patients with high IgM titers had a higher risk of developing gustatory dysfunctions compared to those with low IgM titers (adjusted OR = 1.003, 95%CI: 1.000-1.006). In addition, patients with diabetes had a higher risk of developing GD compared to patients without diabetes (adjusted OR = 4.335, 95%CI: 1.098-17.287). Similarly, when OD and GD were treated as one symptom, patients with diabetes (adjusted OR = 7.963, 95%CI: 1.557-37.515) and patients with higher IgM titers (adjusted OR = 1.006, 95%CI: 1.001-1.010) had a higher probability of developing this symptom.

Table 5 describes the incidence of OD and GD one month after the patients were discharged from the hospital. Six patients had residual GD, and eleven patients reported OD. Of patients with OD or GD during hospitalization, 48.0% still complained of OD or GD one month after discharge. In patients with no OD or GD during hospitalization, 3.6% developed OD or GD after discharge. Continued follow-up of these patients with OD or GD showed that, in 60% (6 of 10) of the cases with OD and 20% (1 of 5) of the cases with GD, the symptoms lasted for at least two years; in 20% (2 of 10) of the cases with OD, symptoms aggravated. One OD patient and one GD patient lost in follow-up were excluded. We also analyzed the relationship between treatment and the incidences of olfactory and urinary dysfunction after discharge [Supplementary Table 1] and found that treatments had no effect on the clinical outcomes of OD and GD after patients were discharged, suggesting that the OD and GD are most likely primary symptoms caused by SARS-CoV-2, rather than the side effects of drugs.

DISCUSSION

This retrospective descriptive study included 81 confirmed cases of COVID-19 and focused on the OD and

Table 4. Multivariate adjusted logistic regression of olfactory and gustatory dysfunctions

Variables	β	SE	Wald	Adjusted OR	95%CI	*P*
OD						
Headache or dizziness	1.999	1.006	3.949	7.382	1.028-53.022	0.047
Dark urine	0.656	1.040	0.397	1.927	0.251-14.796	0.528
IgM	0.002	0.002	1.867	1.002	0.999-1.006	0.172
IgG	-0.001	0.898	3.671	5.591	0.961-32.515	0.055
Diabetes	1.927	0.937	4.234	6.871	1.096-43.086	0.040
Constant	-3.258	0.759	18.412			
GD						
Headache or dizziness	1.358	0.789	2.963	3.890	0.828-18.263	0.085
Dark urine	0.432	0.806	0.287	1.540	0.317-7.472	0.592
IgM	0.003	0.002	4.058	1.003	1.000-1.006	0.044
IgG	0.001	0.002	0.480	1.001	0.998-1.004	0.488
Diabetes	1.471	0.703	4.387	4.335	1.098-17.287	0.036
Constant	-2.098	0.531	15.591			
OD or GD						
Headache or dizziness	1.297	0.841	2.387	3.659	0.704-19.026	0.123
Dark urine	0.338	0.868	0.151	1.402	0.256-7.684	0.697
IgM	0.006	0.002	6.961	1.006	1.001-1.010	0.008
IgG	0.003	0.002	2.526	1.003	0.999-1.007	0.112
Diabetes	2.040	0.714	6.369	7.963	1.557-37.515	0.012
Constant	-2.479	0.589	17.727			

OD: Olfactory dysfunction; GD: gustatory dysfunction.

Table 5. The clinical outcomes of olfactory and gustatory dysfunctions in COVID-19 patients

During hospitalization	After discharged*			
	OD (*n* = 11)	GD (*n* = 6)	OD and GD (*n* = 3)	OD or GD (*n* = 14)
None - *n*/%	2 (3.6)	0 (0.0)	0 (0.0)	2 (3.6)
OD	9 (81.8)	3 (27.3)	3 (27.3)	9 (81.8)
GD	6 (28.6)	6 (28.6)	3 (14.3)	9 (42.9)
OD and GD	6 (85.7)	3 (42.9)	3 (42.9)	6 (85.7)
Any	9 (36.0)	6 (24.0)	3 (12.0)	12 (48.0)

*All enrolled patients' chest CT scanning signs disappeared and permitted discharge. OD: Olfactory dysfunction; GD: gustatory dysfunction.

GD in COVID-19 patients in Wuhan. On admission or during hospitalization, patients self-reporting OD, GD, and both accounted for 13.6%, 25.9%, and 8.6% of all subjects, respectively. The incidence of OD and GD in the severe cases was not significantly different from the non-severe cases, suggesting OD and GD are not related to the severity of the disease. In addition, 48.0% of patients had persistent OD or GD after the other clinical manifestations of COVID-19 disappeared. Continued follow-up showed that, in 20% of the cases with OD, symptoms even aggravated two years after infection.

There are currently few studies on the incidence of OD and GD in patients with COVID-19[20]. One study found that 5.1% of COVID-19 patients reported hyposmia[21]. Compared with this study, we found a higher rate of hyposmia (13.6%). A multicenter European study reported that 85.6% and 88.0% of patients suffer from olfactory and gustatory dysfunctions, respectively[22]; this result indicates that, compared with Asian

patients, gustatory dysfunctions are more common in European patients. Notably, a recent study found that the prevalence of smell and taste dysfunction in COVID-19 patients has dropped significantly with the advent of the Omicron variant[23]. Thus, the different strains of the virus may have distinct effects on olfactory and gustatory dysfunction.

The reasons for the different incidences of OD and GD may be as follows: (1) Quantitative measurement is more sensitive than self-report. Studies have shown that only 35% of patients are aware of their olfactory deficits[24]. (2) The different affinity of the virus to different populations may lead to clinical differences among patients in different regions. A study showed that ACE2 mutations reduce the correlation between human ACE2 and SARS-CoV S-protein, thereby reducing the chance of infection[25]. ACE2 polymorphisms and the differences in expression levels between Asian and European populations may explain the difference in olfactory dysfunction between Asian and European populations[26]. (3) Different strains of the virus may cause different clinical manifestations.

Pearson correlation coefficient showed that headache or dizziness, dark urine, IgM, and diabetes all showed a positive correlation with OD and GD (all $P < 0.05$). We noted that chronic rhinitis and certain neurodegenerative diseases may directly lead to taste or smell disorders. In this study, such patients were excluded. Headache or dizziness are the most common symptoms of the nervous system. In a previous report, the incidence of headache and dizziness in COVID-19 patients were 13.1% and 16.8%, respectively[21]. OD and GD are positively related to dizziness and headache. It has been reported that ACE2 is highly expressed in the nasal goblet and ciliated cells[27]. The virus may infect the olfactory nerve early and cause OD before other neurological manifestations. OD and GD were also significantly related to dark urine. This may suggest that dark urine, similar to OD/GD, is a sign of early infection and damage to the urinary system. IgM is an early antibody produced by the immune system after infection. The interaction of infectivity, virulence, and immune response may explain the positive correlation between IgM and OD/GD. Consistent with other results, diabetes was significantly correlated with smell dysfunction[28]. The infection might exacerbate potential nerve damage in diabetic patients. In addition, multivariate adjusted logistic analysis showed that patients with headache or dizziness and diabetics were at higher risk of developing olfactory dysfunction, while patients with high IgM titers and diabetes were at high risk of developing gustatory dysfunction, which is consistent with the results of the above Pearson correlation coefficient.

One month or more after discharge, some patients still suffered from OD and GD. A few patients who did not have OD or GD during hospitalization developed these symptoms after discharge. Considering the damage caused by the virus to the olfactory or gustatory nerve, this may be one of the possible sequelae of COVID-19 patients. It is worth noting that SARS-CoV can be detected 60-66 h after infection and is most abundant in the olfactory bulb[29]. While the infection routes of SARS-CoV-2 and SARS-CoV are similar, OD may be an early symptom of COVID-19. Early screening of people with OG and GD, early detection of virus infections, and early isolation of COVID-19 patients can help prevent the spread of COVID-19.

In conclusion, we found that OD and GD are common symptoms of COVID-19. They appear early during the disease and may last from one month to even two years. Headache or dizziness, IgM titers, and diabetes are correlated with the occurrence of OD and GD. This retrospective study has some limitations. First, we collected self-reported data, which may lead to information bias. Second, the sample size was relatively small and geographically limited. We only recruited 81 confirmed cases of COVID-19 in our database since COVID-19 infectious was effectively controlled in Wuhan in early 2020. The cases reported here represent what happened to the first batch of patients in China. Third, grading bias might exist since we did not perform objective smell and taste tests. Fourth, as patients with other infectious diseases were not included

in the control group, it could not be determined whether COVID-19 had a more severe and longer-lasting impact on taste and smell than other infectious diseases.

DECLARATIONS

Authors' contributions

Full access to all of the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis, and wrote the manuscript: Zou L
The acquisition of data: Yu T, Zhang Y
Reviewed literature and gave technical support: Dai L
Conceived and supervised the project: Zhang Z, Zhang Z
All authors read and approved the submission of the manuscript.

Availability of data and materials

All analyzed data of this study are included within the article.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

This study was approved by the Hospital Ethics Committee of the Renmin Hospital of Wuhan University [WDRY2020-K136].

Consent for publication

All patients agreed to participate in this study.

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