

Olfactory and Gustatory Dysfunctions in Patients With COVID-19 in Wuhan, China

Li Zou (✉ zouli1231@whu.edu.cn)

Wuhan University Renmin Hospital

Ting Yu (✉ 1458984897@qq.com)

Wuhan University Renmin Hospital

Yangyang Zhang (✉ 2018283020141@whu.edu.cn)

Wuhan University Renmin Hospital

Lijun Dai

Wuhan University Renmin Hospital

Zhaohui Zhang

Wuhan University Renmin Hospital

Zhentao Zhang

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Abstract

Background: The coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 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.

Objective: To investigate the incidence of olfactory and gustatory dysfunctions in patients with confirmed COVID-19 infection, in Wuhan, China.

Methods: 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.

Results: A total of 81 confirmed COVID-19 patients were enrolled in this study (38 males). The most prevalent symptoms include 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. 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 are positively 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 ($r = 0.275$, $P = 0.013$). In 81.8% of the cases with OD and 28.6% of the cases with GD, the symptoms lasted for at least 1 month after discharge. 3.6% of inpatients without OD developed OD after discharge.

Conclusion: OD and GD are common in COVID-19. These symptoms appear early during the course of disease, and may last for at least 1 month. The incidence of OD and GD is related to neurological manifestations, diabetes, and IgM titers.

Introduction

Coronavirus disease 2019 (COVID-19), an infectious disease caused by the acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has spread globally [1–3]. As of April 24, 2020, there were more than 2.71 million confirmed cases of COVID-19 globally [4]. Early epidemiological investigations show that the basic reproduction number (R_0) of SARS-CoV-2 is estimated to be about 2.2 or higher (from 1.4 to 6.5) [5]. The high spread and low fatality rate of COVID-19 makes its global pandemic. At present, COVID-19 became the largest epidemic 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) [6]. The similarity of the gene sequence and infection route highly 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. Some cases reported gastrointestinal symptoms, such as diarrhea [2, 7, 8]. It is worth noting that SARS-CoV can be detected 60 to 66 h after infection and is most abundant in the olfactory bulb [9]. 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 [10, 11]. Current research mainly focuses on the respiratory and gastrointestinal symptoms of COVID-19, while paying less attention to sensory symptoms such as olfactory and gustatory dysfunctions.

The purpose of this study is 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 as 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 is 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, symptoms, olfactory and gustatory dysfunctions), 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 $\leq 93\%$ at rest; 3) arterial partial oxygen pressure (PaO_2)/oxygen absorption concentration (FiO_2) ≤ 300 mmHg; 4) respiratory failure that needs mechanical ventilation; 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 include blood routine examination (including white blood cells, lymphocytes, and platelets), coagulation function, lactate dehydrogenation, and immune indicators (including lymphocyte differential counts and inflammatory factors). Four weeks after the patients were discharged from the hospital, we conducted a telephone follow-up, asking the patients to record their clinical symptoms, especially the sense of smell and taste. Cases with unsuccessful follow-up 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 nonnormally 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. 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

Demographics and clinical characteristics

The demographic characteristics, clinical manifestations, and comorbidities are shown in **Table 1**. Of the 81 patients, 63 cases were diagnosed as non-severe disease and 18 cases were severe. The median age was 58 years (IQR, 50.0 to 68.5 years). The median age of the severe group is 10.5 years higher than that of the non-severe group. Males accounted for 46.9% (38 of 81) of the total patients. 66.7% (12 of 18) of the patients were males in the severe group, compared with 41.3% (26 of 63) of males in the non-severe group. 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%, 12.3%, 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%). 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%).

Table 1
Demographic Characteristics of 81 Patients with COVID-19

Clinical characteristics and symptoms	All patients (n = 81)		Disease Severity	
			Non-severe	Severe
			(n = 63)	(n = 18)
Age, Median (IQR) - yrs	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.				
[§] Chronic pulmonary disease includes tuberculosis, chronic obstructive pulmonary disease, and bronchiectasis. All cases were stable and no obvious bacterial infections.				

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 altered sense of smell or taste. 13.6% and 25.9% reported OD and GD, respectively. 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, $P < 0.05$).

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, $P > 0.05$.

The factors related to OD and GD are summarized in **Table 3**. We brought general conditions, symptoms, comorbidities, and laboratory tests into consideration and calculate the Pearson correlation coefficient. We found some factors are 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 are also positively correlated to GD (all $r > 0.2$, $P < 0.05$). The IgG titers were neither significantly related to patients with OD ($r = 0.083$, $P = 0.496$) nor with GD ($r = 0.164$, $P = 0.176$). But IgG titers were associated with the incidence of patients with either OD or GD ($r = 0.269$, $P < 0.05$).

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
Abbreviations:						
OD: olfactory dysfunction; GD: Gustatory dysfunctions						

Table 4 describes the incidence of OD and GD one month after the patients were discharged from the hospital. 6 patients had residual GD, and 11 patients reported OD. Of patients with OD or GD during hospitalization, 48.0% still complained OD or GD 1 month after discharge. In patients with no OD or GD during hospitalization, 3.6% reported OD or GD after discharge. We also analyzed the relationship between treatment and the incidences of olfactory and urinary dysfunction after discharge (**Supplementary Table 1**), and found that treatment had no effect on the clinical outcomes of OD and GD after patients were discharged.

Table 4
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.

Discussion

This retrospective descriptive study included 81 confirmed cases of COVID-19 with a median age of 58 years. The median age of the severe group was 11.5 years older than that of the non-severe group. The ratio between males and females was about 0.88 (46.9% vs 53.1%). However, males accounted for 66.7% in the severe group, compared with 41.3% in the non-severe group. These results seem to suggest that males and older patients are more likely to develop severe disease, which is consistent with other reports[12]. On admission, fever and respiratory symptoms were the most common clinical manifestations. Compared with the non-severe group, there were more patients with dark urine in the severe group. This might suggest a potential relationship between urinary system dysfunction and disease severity. Among 81 patients, more than half had at least one comorbidity. Patients with cardiovascular and cerebrovascular diseases are more likely to develop severe illness. These above findings are consistent with the previous studies [2, 8, 13]. This study focuses on the OD and GD in COVID-19 patients in Wuhan.

On admission or during hospitalization, patients self-reported 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.

Most of the previous trials focused on the patient's respiratory symptoms, sensory disturbances were largely ignored. There are currently few studies on the incidence of OD and GD in Asia. One study found that 5.6% of COVID-19 patients reported hypogeusia, while 5.1% reported hyposmia[14]. Compared with this study, we found a higher rate of hypogeusia (13.6%) and hyposmia (25.9%). A multicenter European study conducted a quantitative analysis of patients with OD and GD, showing that 66.2%, 13.5%, and 88.8% of patients suffer from anosmia, hyposmia, and gustatory disorders, respectively[15]. These results indicate that compared with Asian patients, olfactory disorders are more common in European patients.

The reasons for the different incidence of OD and OD 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[16]. 2) The different affinity of the virus to different populations may lead to clinical differences between patients in different regions. A study showed that ACE2 mutations can reduce the correlation between human ACE2 and SARS-CoV S-protein, thereby reducing the chance of infection[17]. 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 [18]. 3) Different strains of virus may cause different clinical manifestations.

In addition, 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 had been excluded. Headache or dizziness are the most common symptoms of the nervous system. It has been reported that the incidence of headache and dizziness in COVID-19 patients were 13.1% and 16.8%, respectively[14]. 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[19]. 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, like OD/GD, were signs 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[20]. The infection might exacerbate potential nerve damage in diabetic patients.

One month after discharge, some patients still suffer from OD and GD. A few patients who did not have OD or GD during hospitalization developed these symptoms after discharge. Considering the damage of the virus to the olfactory or gustatory nerve, this may be one of the possible sequelae of COVID-19 patients. Our analysis found that drug treatment is not related to the recovery of OD and GD in patients with COVID-19, suggesting that the OD and GD are most likely to be the primary symptoms caused by SARS-CoV-2, rather than the side effects of drugs. It is worth noting that SARS-CoV can be detected 60 to 66 h after infection and is most abundant in the olfactory bulb[21]. 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 OD 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 course of disease and may last for at least 1 month. 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 small and geographically limited. Third, we only collected data 1 months after discharge. The duration of OD and GD in these patients need to be followed up.

Declaration:

Ethics approval and consent to participate:

This study was approved by the Hospital Ethics Committee of the Renmin Hospital of Wuhan University [WDRY2020-K136]. All patients agreed to participate in this study.

Consent for publication:

All authors read and approved the final manuscript.

Competing interests:

None.

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Authors' Contributions:

Li Zou had 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. Ting Yu and Yangyang Zhang helped in the acquisition of data. Lijun Dai reviewed literature and gave technical support. Zhentao Zhang and Zhaohui Zhang conceived the project, and are responsible for critical revision of the manuscript. All authors had seen, and approved the final, submitted version of the manuscript.

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