

A Cross-Sectional Study of Olfactory and Taste Disorders in COVID-19 Patients in China

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Abstract

Objective To determine the prevalence and features of olfactory and taste disorders in coronavirus disease of 2019 (COVID-19) patients in China.

Methods A cross-sectional study was performed from 3 April to 15 April 2020 in Wuhan. A total of 187 patients with confirmed severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection completed face-to-face interviews or telephone follow-up. Patients' information including epidemiological, clinical, imaging, and serological records and treatment and outcomes data. Patients were further evaluated using questionnaires and visual analogue scale. Statistical analysis was performed with SPSS software (version 22.0).

Results The enrolled 187 patients, 23 (12.3%) reported olfactory disorders, 42 (22.46%) reported taste disorders. Females are more prone to olfactory and taste disorders. Among patients that can clearly describe the fluctuation of olfactory and taste dysfunctions, 4 (20.0%) and 7 (18.92%) cases occurred before other symptoms appeared, the average number of days in advance was 3.5 and 3.57, respectively. The majority of patients can return to normal or basic normal, but in 4 (17.39%) and 9 (21.43%) cases olfactory and taste can not fully recover during the research period.

Conclusions Prevalence of olfactory and taste disorders substantially lower in China cohorts compared to abroad COVID-19 cohorts. The prevalence of olfactory and taste disorders in COVID-19 patients was higher in females than in males. In some patients, olfactory and taste disorders precede other symptoms and can be used as a symbol for early screening and warning. The restoration of olfactory and taste function was independent of age; females recover more easily than males; olfactory or taste disorders were not easily recovered for patients with clinically classified as severe; when olfactory or taste disorders themselves were serious, it was not easy to recover; olfactory or taste disorders occurred early in the disease were more likely to be recovered, otherwise they were hard to be recovered.

Introduction

The COVID-19 caused by SARS-CoV-2 was first reported in Wuhan, China in December 2019 [1], but the origin of the virus remains unknown. Since the outbreak of COVID-19 the number of cases continues to rise worldwide, over ten million cases including 502600 deaths have been reported globally as of Jun 30, 2020. Studies have shown that the disease caused by SARS-CoV-2 could induce symptoms including fever, dry cough, dyspnea, fatigue and lymphopenia in infected patients [2]. COVID-19 infection presented few obvious upper respiratory symptoms. The spread of the COVID-19 infection abroad has highlighted a new atypical presentation of the symptom: olfactory and taste disorders. It was not reported by most of the early studies from China and still neglected in Chinese COVID-19 patients [3]. Herein, we present for the first time the prevalence of reduced olfaction and decreased sense of taste in Chinese COVID-19 patients. We conducted a follow-up survey of 187 patients with COVID-19 who were recruited in the

General Hospital of Central Theater Command and indicated the prevalence and features of olfactory and taste disorders in COVID-19 patients in China.

Materials And Methods

A cross-sectional study was performed from 3 April to 15 April 2020 in Wuhan. A total of 187 patients with confirmed SARS-CoV-2 infection admitted in General Hospital of Central Theater Command in Wuhan completed face-to-face interviews or telephone follow-up. Inclusion criteria were laboratory-confirmed COVID-19 infection (reverse transcription polymerase chain reaction, RT-PCR) in a deep throat-swab; patients clinically able to fulfill the questionnaire. Exclusion criteria were patients unable to cooperate independently to complete the questionnaire survey; patients with olfactory or taste disorders before; patients who were currently in the intensive care unit (ICU). In addition, patients were tested for other respiratory tract pathogens (e.g. rhinovirus, parainfluenza, Epstein-Barr virus) and therefore other infections were excluded. We reviewed clinical charts, nursing records, laboratory results and chest CT characteristics for all patients. Epidemiological, clinical, imaging, serological records, treatment and outcomes data were collected from the electronic medical network of the hospital. Otolaryngologist and infectious diseases doctor created the questionnaire, which consisted of 5 general clinical questions (age, sex, date of diagnosis, comorbidities, symptoms associated with COVID-19 infection); 5 questions about olfactory function; 4 questions investigating taste function; one question about the treatment of the COVID-19 infection. The patients' olfactory and taste impairments were scored using a visual analogue scale. The higher of the score, the more severe of the symptoms. Patients in the hospital completed questionnaire in the patient's room. Patients who had been discharged from hospital completed questionnaire over the phone. The data were also collected through an online form for discharged patients. None of the included participants reported medical treatment potentially influencing the sense of smell and taste. Statistical Package for the Social Sciences for Windows (SPSS version 22.0) was used to perform the statistical analyses. The potential associations between epidemiological, clinical and olfactory and taste outcomes have been assessed through cross tab generation between 2 variables (binary or categorical variables) and Chisquare test. The threshold for statistical significance was set at $p < 0.05$. This research is a retrospective study based on clinical data. The Medical Ethics Committee of PLA General Hospital has confirmed that no ethical approval is required.

Results

We reviewed 187 patients diagnosed with COVID-19 who were hospitalized in General Hospital of Central Theater Command in Wuhan. Among participants, 95 were males and 92 were females with a mean age of 53.58 years (range from 17-90 years; Table 1).

Reduced olfaction occurred in 23(12.3%) COVID-19 patients with a mean age of 50.17 years, 16 (8.56%) were females, 7 were males (3.74%; Table 1). The females would be more likely to suffer from olfactory disorders compared with males ($p < 0.001$). 7 (30.43%) cases were complete loss, 13 (50.52%) cases were moderate to severe decline, 3 (13.04%) cases were mild decline. While in patients with olfactory

disfunctions, 19 (82.61%) cases have completely recovered or obtained a substantial improvement, 4 (17.39%) cases have partially recovered. The mean duration of olfactory disorders was 15.57 days (Table 2).

There were 42 (22.46%) cases of taste disorders with a mean age of 52.55 years, 25 (13.37%) were females, 17 were males (9.1%; Table 1). The females would be more likely to suffer from taste disorders compared with males ($p < 0.001$). 2 (4.76%) cases were complete loss, 33 (78.57%) cases were moderate to severe decline, 7 (16.67%) cases were mild decline. In patients with taste disorders, 33 (78.57%) cases recovered or almost recovered, 5 (11.9%) cases have partially recovered, 4 (9.52%) cases didn't recover. The mean duration of taste disorders was 11.09 days (Table 2).

20 of 23 patients with olfactory disfunctions can clearly describe the fluctuation of symptoms. 4 (20.0%) cases occurred before other symptoms (e.g. fever, dry cough, dyspnea, fatigue) appeared, the average number of days in advance was 3.5, which was negative value; 2 (10.0%) cases occurred at the same time as other symptoms; 14 (70.0%) cases occurred after other symptoms appeared, the average number of days delayed was 7.5, which was positive value. In general, 20 patients develop olfactory disfunctions at an average of 4.55 days after other symptoms (Table 3).

37 of 42 patients with taste disfunctions can clearly describe the fluctuation of symptoms. 7 (18.92%) cases occurred before other symptoms appeared, the average number of days in advance was 3.57, which was negative value; 4 (10.81%) cases occurred at the same time as other symptoms; 26 (70.27%) cases occurred after other symptoms appeared, the average number of days delayed was 9.65, which was positive value. In general, 37 patients develop olfactory disfunctions at an average of 6.38 days after other symptoms (Table 3).

Of the 42 patients with olfactory or taste disorders, 9 cases did not recover their sense of olfactory or taste. We compared these patients with 33 patients who had restored olfactory or taste function (Table 4). There was no significant difference in mean age between the functional recovery group and the non-recovery group with 54.2 and 54.23 years, respectively. In functional recovery group, there were 20 (60.61%) females and 13 (39.39%) males; in functional non-recovery group, there were 5 (55.56%) females and 4 (44.44%) males, the proportion of female was lower than in functional recovery group ($p < 0.001$). Among the patients with functional recovery, 8 (24.24%) were clinically classified as severe patients; among the patients with functional non-recovery, 4 (44.44%) were clinically classified as severe patients, significantly higher than the functional recovery group ($p < 0.001$). In functional recovery group, there were 5 (15.15%) patients with moderate to severe decline of olfactory or taste; in functional non-recovery group, there were 3 (33.33%) patients with moderate to severe decline of olfactory or taste; there were significant differences between the two groups ($p < 0.001$). Patients in functional recovery group had olfactory or tasting disorders on average 2.73 days after occurrence of disease, patients in functional non-recovery group had olfactory or tasting disorders on average 27.4 days after occurrence of disease. Olfactory or taste disorders occurred early in the disease were more likely to be recovered ($p < 0.001$).

Conclusions

Through the analysis of the data we draw the following conclusions. Prevalence of olfactory and taste disorders substantially lower in China cohorts compared to abroad COVID-19 cohorts. The prevalence of olfactory and taste disorders in COVID-19 patients was higher in females than in males. In some patients, olfactory and taste disorders precede other symptoms and can be used as a symbol for early screening and warning. The restoration of olfactory and taste function was independent of age; females recover more easily than males; olfactory or taste disorders was not easily recovered for patients with clinically classified as severe; when olfactory or taste disorders itself was serious, it was not easy to recover; olfactory or taste disorders occurred early in the disease were more likely to be recovered, otherwise they were hard to be recovered.

Discussion

The continued rise in COVID-19 cases and deaths poses an unprecedented global health threat, and asymptomatic infection may contribute to delays in identifying and managing outbreaks. Luers et al. described from a retrospective adult cohort of confirmed COVID-19 from Germany that 74% of patients reported anosmia [4]. Spinato et al. described from a retrospective cohort study of COVID-19 patients that 64.4% reported alternations in taste or smell [5]. According to our results the incidence of olfactory and taste disorders in Chinese COVID-19 patients is 12.3% and 22.46%. Which is remarkable lower than the results reported in abroad COVID-19 cohorts. The first possible reason is that there are differences in angiotensin-converting enzyme 2 (ACE2) receptor expression in the nasopharynx between East Asians and European [6]. The infection of SARSCoV-2 is primarily through ACE2 receptor, which serves as a gateway for the virus's entry into tissues [7]. Increased expression of ACE2 in nasopharynx may contribute to a higher risk of olfactory and taste symptoms. The other possible reason is that this emerging symptom among European populations is actually related to mutations in the virus itself, mutations that may be resulting in a clinical difference. New genomic analysis shows that the Spike mutation (D614G; a G-to-A base change at position 23 403 in the Wuhan reference strain) is found almost exclusively in Europe [8].

Among patients with olfactory disfunctions, females accounted for 8.56%, significantly higher than males. The ACE2 gene is located on the X chromosome, therefore female individuals should have higher ACE2 levels [9], which might be the reason for more susceptible to SARS-CoV-2 infection in comparison to males. The olfactory epithelium is one of the target organs of estrogen. The primary olfactory sensory cells contain estrogen metabolic enzymes, which affect the effect of estrogen on the olfactory epithelium [10]. Due to the effect of estrogen, women have a more sensitive sense of smell than men, and women's sense of smell fluctuations are more obvious than men's. In addition, Sex-dependent production of steroid hormones may contribute to gender specific disease outcomes after virus infections [11, 12].

There was 4 (20.0%) and 7 (18.92%) cases showing olfactory or taste dysfunction before other symptoms appeared, the average number of days in advance was 3.5 and 3.57, respectively. As the

number of diagnosed cases have increased, so has our understanding of clinical manifestations of COVID-19. Some previously neglected symptoms such as olfactory or taste dysfunction may provide new clues for early detection of the disease [13]. The SARS-CoV-2 virus first enters the upper respiratory tract, causing smell and taste impairment, before arriving in the lower respiratory tract and causing lung infection. In the early stage of disease there is usually no fever, cough and other symptoms. However smell and taste disorder are often ignored by patients and doctors. These can lead to delayed diagnosis and treatment, which can lead to further spread of the infection. We would regard olfactory or taste dysfunction as a possible early-warning symptom, especially if it comes along without rhinitis. Compared with nucleic acid testing and Chest CT, olfactory or taste disorder is a unique screening indicator for its simplicity and low cost. Early identification of suspected patients, isolation monitoring and early diagnosis and treatment of COVID-19 patients, which is of great significance for more precise prevention and more efficient surveillance of COVID-19 in China as well as in other affected countries.

The olfactory and taste were restored in 82.61% and 78.57% of patients, respectively which is similar to other survies [14]. Nevertheless, The olfactory and taste were not fully recovered in 4 (17.39%) and 9 (21.43%) cases, respectively. The pathophysiology through which SARS-CoV-2 affects the olfactory and taste system is unclear. It is postulated to be the impairment of the olfactory neuroepithelium and olfactory bulb, because of the high expression of ACE present in the respiratory system[15]. We divided 42 patients with impaired sense of olfactory or taste into functional recovery and non-recovery groups and made analysis to find out the relevant factors affecting functional recovery. We find that the restoration of olfactory and taste function was independent of age; females recover more easily than males; olfactory or taste disorders was not easily recovered for patients with clinically classified as severe; when olfactory or taste disorders itself was serious, it was not easy to recover; olfactory or taste disorders occurred early in the disease were more likely to be recovered, otherwise they were hard to be recovered. Female individuals generally have stronger innate and adaptive immune responses than males, because the X-chromosome contains more copy numbers of immune-related genes [16]. A recent observation that the female patients have higher level of IgG antibody against SARS-CoV-2 compared with male patients [17], provides direct evidence for sex differences in immune responses. Severity of COVID-19 was defined according to the diagnostic and treatment guideline for SARS-CoV-2 issued by Chinese National Health Committee (version 3-5). Severe COVID-19 was designated when the patients had one of the following criteria: respiratory distress with respiratory frequency ≥ 30 /min; pulse oximeter oxygen saturation $\leq 93\%$ at rest; oxygenation index (artery partial pressure of oxygen/ inspired oxygen fraction, P_{aO_2}/F_{iO_2}) ≤ 300 mm Hg. In patients with clinically classified as severe, impaired olfactory sensory neuron was difficult to recover due to decreased blood oxygen content. Olfactory or taste disorders occurred early in the disease may trigger a series of early warning mechanisms to quickly mobilize the body's immune system to combat the virus attack, thus preventing causing the virus from further attacking other important tissues and organs. University of California San Diego health researchers published online research results in the International Forum of Allergy and Rhinology on April 24, 2020, and pointed out that loss of olfaction may predict a milder clinical course of COVID-19. Olfactory or taste disorders occurred early in the disease

may also mean a strong and effectiveness of the host's immune response, thus more conducive to the recovery of the function.

This study has some limitations. First, due to the limitation of availability of testing, olfactory and taste function evaluation did not use more objective electrophysiological tests, but were obtained through on-site inquiries or telephone follow-up questionnaires and visual analogue scale [18,19]. Second, due to the retrospective study, it is difficult for some patients to give a clear answer to the exact time and duration of the occurrence of olfactory and taste disorders. And will resulted in an overestimate of asymptoms and underestimate of persons who developed symptoms. Larger prospective population studies are required to validate these findings. Finally, this study is a cross-sectional study. We did not perform follow-up testing for patients who developed symptoms; therefore, we cannot determine the patients who have not recovered their sense of olfactory and taste function will regain their functions in the future, and whether the patients who currently recover will have recurrent symptoms. Further epidemiological and biological investigations are required to better understand the pathogenic mechanism for effective interventions.

Declarations

Ethics approval and consent to participate

This research study was conducted retrospectively from data obtained for clinical purposes. The Medical Ethics Committee of PLA General Hospital has confirmed that no ethical approval is required.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due to individual privacy, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to the study conception and design. S-MY, X-BF and C-LY supervised the overall study. YS, C-CH, F-JZ, R-YC, L-BZ collected clinical data. J-HL and M-RL made the table. HY, QL, J-JH and X-JZ searched the literature. J-HL and M-RL wrote the manuscript. HY and NY revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Demographic Characteristics according to Olfactory and Taste dysfunction

	Total	Olfactory	Taste	Olfactory and
		disfunction	disfunction	Taste disfunction
Number of patients-no.(%)	187(100%)	23(12.3%)	42(22.46%)	22(11.76%)
Mean age-years	53.58	50.17	52.55	49.59
Gender-no.(%)				
Male-no.(%)	95(50.8%)	7(3.74%)	17(9.1%)	7(3.74%)
Female-no.(%)	92(49.2%)	16(8.56%)	25(13.37%)	15(8.02%)

Table 2 Clinical Characteristics of Olfactory and Taste dysfunction		
	Olfactory	Taste
	dysfunction	dysfunction
Number of patients-no.(%)	23(100%)	42(100%)
Total loss-no.(%)	7(30.43%)	2(4.76%)
Moderate-severe-no.(%)	13(50.52%)	33(78.57%)
Mild-no.(%)	3(13.04%)	7(16.67%)
Recovery-no.(%)	19(82.61%)	33(78.57%)
Part recovery-no.(%)	4(17.39%)	5(11.9%)
Not recovered-no.(%)	0	4(9.52%)
Mean duration of symptoms-days	15.57	11.09

Table 3 The occurrence time and the corresponding proportion of personnel about olfactory and taste disorders

The time of disorder	Olfactory disorders		Taste disorders	
	The number of people	Average number of days	The number of people	Average number of days
Before other symptom	4(20.0%)	-3.5	7(18.92%)	-3.57
At the same time	2(10.0%)	0	4(10.81%)	0
After other symptom	14(70.0%)	7.5	26(70.27%)	9.65
Total number	20	4.55	37	6.38

Table 4 Functional recovery versus non-recovery in patients with olfactory or taste impairments

	Recovery	Non-recovery	
Number of patients		33	9
Mean age-years		54.2	54.23
Gender-no.(%)			
Male-no.(%)	13(39.39%)	4(44.44%)	
Female-no.(%)	20(60.61%)	5(55.56%)	
Clinical severe		8(24.24%)	4(44.44%)
Moderate or severe impairment of olfactory or taste		5(15.15%)	3(33.33%)
The time of disorder after other symptom-days		2.73	27.4