

Characteristic Features of Olfactory and Gustatory Dysfunctions of COVID-19 in Japanese Population

Katsuhisa Ikeda*, Kumiko Tanaka, Shinpei Arai, Nanae Yoshii and Ayako Inoshita

Department of Otorhinolaryngology, Juntendo University, Faculty of Medicine, Tokyo, Japan

*Corresponding Author: Katsuhisa Ikeda, Department of Otorhinolaryngology, Juntendo University, Faculty of Medicine, Tokyo, Japan.

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Abstract

Purpose: Chemosensory dysfunctions have been widely known as frequent and early symptoms of COVID-19. However, the underlying mechanisms of gustatory dysfunction associated with COVID-19 remain controversial. We aimed to reveal the dependency of taste impairment on smell function.

Materials and Methods: Olfactory and gustatory functions were subjectively and objectively examined in 54 COVID-19 patients.

Results: There were 5 patients with isolated subjective gustatory dysfunction and 4 patients with continuing smell dysfunction but resumed taste function, implying smell-independent gustatory dysfunction. Two patients with combined subjective dysfunctions showed objective smell dysfunction and normal objective taste function, suggesting a smell-dependent gustatory event. Olfactory and gustatory dysfunctions were subjectively found in 37.0 and 40.7%, respectively. Smell loss was objectively observed in 64.3% over 65 years, which was significantly greater than those (25.6%) of below 65 years. There was a significant difference in the mean open essence score between those under and those over 65 years.

Conclusion: Gustatory dysfunction is induced by both mechanisms of smell-independent and -dependent fashions in COVID-19 infection. The prevalence of olfactory and gustatory dysfunctions in Japanese corresponded to those of the countries with Caucasians rather than East Asians. A significant increase of objective olfactory dysfunction was recognized in the aged patients older than 65 years.

Keywords: COVID-19, olfactory dysfunction, gustatory function, objective test, smell-dependency

Introduction

There have been a variety of clinicopathological reports related to chemosensory deficits associated with coronavirus disease 2019 (COVID-19) regarding the effects of ethnicity, age, and gender, with discrepancies among self-reporting and examination results, etc. Chemosensory dysfunctions have been widely known as frequent and early symptoms of COVID-19 in Europe and America [1]. However, the prevalence of smell and taste dysfunctions in East Asians was significantly lower than that in Caucasians [2]. All the

studies on East Asians were based on anamnestic-observational evaluation, suggesting limitations in accuracy and reliable characteristics. Objective evaluations of olfactory and gustatory functions of Japanese populations have not yet been reported.

The underlying mechanisms of gustatory dysfunction associated with COVID-19 are still controversial, namely i) smell-dependent events secondary to the retronasal olfactory loss [3] and ii) smell-independent isolated gustatory disorders [4,5]. An objective assessment is essential for quantifying the extent of gustatory as well as olfactory dysfunction.

Correlations between chemosensory dysfunctions and the age of the patients are also controversial. Several investigations noted that smell and taste dysfunctions appeared to be more frequent in younger aged patients infected with COVID-19 [2,6]. On the other hand, no significant correlation was found between the olfactory and gustatory function and age [3,7].

In the present study, we report and analyze the results of subjective and objective evaluations of the olfactory and gustatory functions in COVID-19 Japanese patients with special reference to the dependency of taste impairment on smell function, prevalence and age difference.

Materials and Methods

The study was conducted in patients treated for severe acute respiratory syndrome coronavirus 2 SARS-CoV-2 hospitalized in departments of the Juntendo University Hospital between May 1, 2020 and June 30, 2021. The study inclusion criteria were adults over 18 years of age, rhino-pharyngeal swab positive for SARS-CoV-2 infection, and patient acceptance for participation in the study. Whole genome sequencing to detect mutant variants was not performed. Patients with previous nasal surgery, allergic rhinitis, or chronic rhinosinusitis were excluded. The study was approved by the ethics committee of the Juntendo University Faculty of Medicine. All subjects entered the study after signing an informed consent form.

Demographic and clinical characteristics such as age, gender, smoking history, the date of onset of smell and taste dysfunction, and presence/absence of other symptoms related to COVID-19 were obtained by questionnaire.

Olfaction was assessed by smell identification test cards, Open EssenceOR (OE, Wako Pure Chemical Industries, Tokyo, Japan) according to our previous report [8]. The OE is comprised of 12 kinds of card-type materials embedded with a microencapsulated odorant. For a given item, the patient releases an odor by opening the card and smelling the label and, if there is no smell, by scratching the microencapsulated surface and opposite surface and smelling the label, again. Then, the patient indicates the odor quality from a four-plus alternative method, in which a modified force-choice paradigm is added by the choices: "detectable but not recognized" and "no smell detected". Participants were instructed to try to choose the correct odor name from four alternatives; they were,

however, allowed to choose "detectable but not recognized" or "no smell detected" if they could not identify the odor. The number of correct answers was defined as the OE score. Patients with OD scores >7 were considered normosmia.

The taste test to perceive four primary tastes (sweet, salty, sour and bitter) included a description of four solutions in water. The four solutions were prepared as follows: i) 10% sucrose solution for sweet taste, 5% saline solution for salty taste, 2% tartaric acid solutions for sour taste and 0.1% quinine hydrochloride solution for bitter taste. De-ionized water was used as the control. Each solution was prepared in a small bottle. During the trial, a couple of drops of each solution were placed on the center of the tongue. The answers were recorded as either correct or incorrect. The taste score ranged from 0 to 4: score 4 was considered as normal.

The data were expressed as the mean±S.D. Statistical analyses were made by IBM SPSS Statistics (SPSS Inc, Chicago IL). For comparison of the numeric variables such as sex and age, Pearson's chi-square test was used. For analysis of the prevalence of subjective and objective chemosensory dysfunctions, McNemar test was applied. For the comparison of the OE score, Mann-Whitney U test was made. Differences were considered to be significant if $P < 0.05$.

Results

A total of 54 patients with olfactory and gustatory dysfunctions were recruited. Average age was 49.4 ± 16.8 years and ranged from 19 to 79 years. Thirty-two were male and 22 female. Twenty-three were active smokers and 31 nonsmokers. The mean time after the onset of COVID-19 for the objective examination was 11.1 ± 5.1 days.

The most common general symptoms that developed during the clinical course were fever (83.3%) followed by fatigue (70.4%), headache (59.3%), sore throat (50.0%), arthralgia (50.0%), cough (42.6%), dyspnea (37.0%), hoarseness (35.2%), and diarrhea (31.5%). Olfactory and gustatory dysfunctions were subjectively found in 37.0 and 40.7%, respectively. Table 1 shows the results of subjective olfactory and gustatory dysfunctions. No significant differences were found between the sex of the patients in the prevalence of self-reported smell ($P = 0.095$) and taste loss ($P = 0.918$). The ages of the patients were divided into 3 groups, under 40 years ($n = 17$), 40 to 65 years ($n = 22$) and over 65 years ($n =$

15). There were no significant differences in the prevalence of smell (P = 0.225) or taste loss (P = 0.260) among these 3 age groups. Subjective olfactory and gustatory dysfunctions at the time point of the objective examination were found in 15% and 4%, respectively.

Gender	Presence of olfactory dysfunction	Presence of gustatory dysfunction
Male	50%	47%
Female	73%	46%
Pearson’s chi-square test	P = 0.095	P = 0.918
Age	Presence of olfactory dysfunction	Presence of gustatory dysfunction
<40 years	71%	53%
40-65 years	46%	50%
>65 years	67%	27%
Pearson’s chi-square test	P = 0.225	P = 0.260

Table 1: Demographic results of subjective olfactory and gustatory dysfunctions.

Fifty-three patients took the olfactory function assessment using OE. Abnormal results of OE were obtained in 35.8% of patients. Figure 1 shows the distribution of OE scores. At the time of the OE examination, complete or severe anosmia was detected in 6 patients (11.3%), 13 patients showed variable degrees of hyposmia (24.5%) while in 34 patients (64.2%) the olfactory function was normal. On the other hand, subjective smell dysfunction at the time of OE examination was observed in 14.8% of patients. The difference in the prevalence between subjective and objective smell loss was significant (P = 0.007).

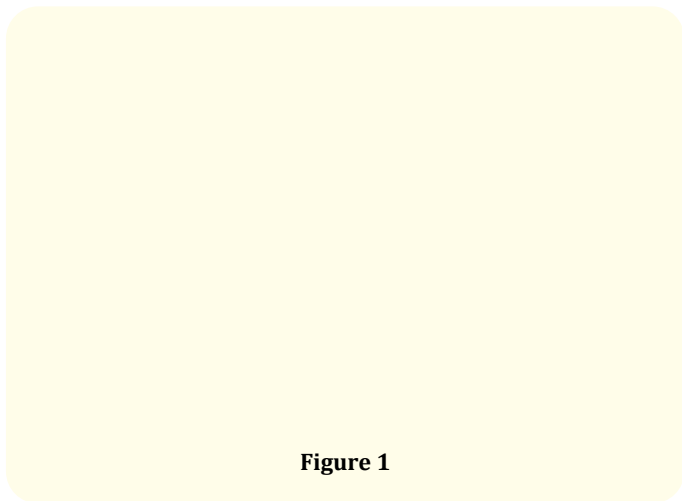


Figure 1

The effect of age on the objective olfactory assessment was evaluated by two methods. First, smell loss was observed in 9 of the 14 patients (64.3%) over 65 years, which was significantly

greater than 10 of the 39 patients (25.6%) below 65 years (P = 0.003). Second, the OE scores was calculated and evaluated by the age group. The mean OE score below 50 years was not significantly different from that over 50 years (P = 0.061). There was a significant difference in the mean OE score between those under and those over 65 years (P = 0.003, Figure 2).

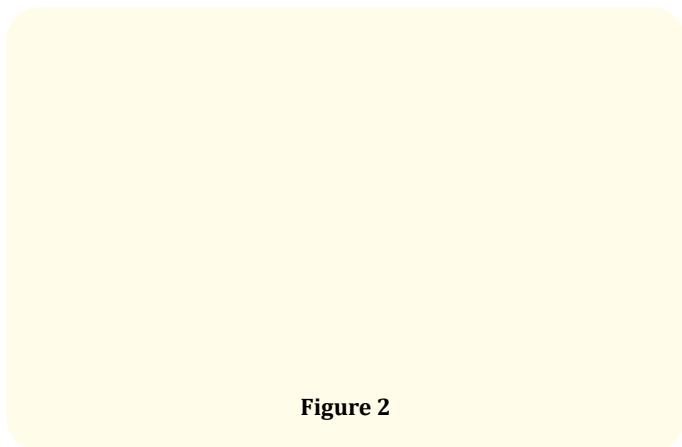


Figure 2

Objective assessment of the gustatory function was performed in all of the 54 patients. Objective taste disturbance was found in 7.4% of the patients, whereas 3.7% of patients complained of subjective taste dysfunction at the time of testing. There was no significant difference in the prevalence of taste dysfunction between subjective and objective methods (P = 0.668).

At the time of COVID-19 onset, isolated subjective olfactory dysfunction was found in 1 patient (1.9%) alone and isolated

subjective gustatory dysfunction in 5 patients (9.3%), whereas 15 patients (27.8%) showed combined subjective dysfunctions. These 15 patients with combined dysfunctions resulted in 11 patients with normal smell and taste functions and 4 patients with smell dysfunction and normal taste function at the time point of the testing. At the time point of the testing, isolated subjective olfactory dysfunction was found in 6 patients (11.1%) of which all except one patient showed objective olfactory dysfunction. There was no isolated subjective taste dysfunction at the testing. Two patients (3.7%), who showed objective smell dysfunction (zero OE score) and normal objective taste function, revealed combined subjective smell and taste dysfunctions at the examination, suggesting smell-dependent subjective gustatory dysfunction. These 2 patients showing smell-dependent subjective gustatory events reported prolonged and persistent olfactory dysfunction a few months after discharge.

In the fifteen patients (27.8%) with combined subjective olfactory and gustatory dysfunctions at the COVID-19 onset, 4 patients (7.4%) continued to have smell dysfunction but recovered taste function, suggesting that the gustatory event was smell-independent, and 11 patients (20.4%) recovered both normal smell and taste functions at the time of the testing.

Discussion

The most important findings in the present study are i) that COVID-19 independently caused olfactory and gustatory dysfunctions in the early stage of infection and ii) that gustatory symptoms resulted from smell-dependent events as prolonged symptoms or the sequelae of infection. At the early stage of COVID-19 onset, at least 9 patients, corresponding to 45.0% of the patients with subjective taste dysfunction, appeared to have smell-independent gustatory dysfunction, while 4 patients showed isolated taste dysfunction at the onset and 5 patients with combined dysfunctions at the onset recovered their normal taste function but continued to have smell dysfunction. Smell-dependent subjective taste dysfunction evidenced by normal objective taste function with objective smell dysfunction was recognized in 2 patients. Interestingly, smell-dependent taste events may be related to the late-onset, prolonged and persistent symptoms or the sequelae of post-COVID-19, since no olfactory or gustatory dysfunction at the early stage was seen in these 2 patients. Another possibility is that the true gustatory dysfunction observed in the early stage

of COVID-19 infection is replaced by smell-dependent gustatory dysfunction in the late stage, which may be influenced by severe olfactory dysfunction.

A variety of studies have demonstrated that smell testing increases odor detection thresholds in a subset of COVID-19 patients who subjectively report a normal sense of smell [9-14]. A recent meta-analysis [15,16] revealed that objective measures are a more sensitive method for identifying smell loss that results from infection with SARS-CoV-2; a higher overall prevalence of olfactory loss was reported in studies using objective methods (77%) compared to those using subjective methods (44%). In the present study, the prevalence of olfactory dysfunction in COVID-19 patients evaluated by objective smell examination using OE was significantly higher than that detected by questionnaires. On the other hand, according to findings from the objective test, gustatory disorder showed no significant difference with the subjective assessment, which may have resulted from small numbers of patients with gustatory dysfunction at the time of testing. In other words, the small numbers of patients with taste dysfunction observed at the time of the testing may be explained by the rapid recovery of gustatory function after the onset. In most patients, it was suggested that the gustatory dysfunction tends to regress completely within 10 days, while recovery of the olfactory disorder is slower [7].

It is well known that the prevalence of smell, taste and any chemosensory dysfunction is higher in countries where Caucasians are the majority than in those where East Asians are predominant [2,17,18]. The estimated random prevalence of smell loss was 43.2%, ranging from 31.9 to 53.3% for Caucasians, and 15.1% ranging from 8.3 to 25.7% for East Asians. The estimated random prevalence of taste loss was 38.3%, ranging from 27.0 to 51.0% among Caucasians and 6.4%, ranging from 5.7 to 51.0% among East Asians. In the present study, the prevalence of olfactory and gustatory dysfunctions in Japanese was 37.0% and 40.7%, respectively, both of which corresponded to those of the countries with Caucasians, but not with East Asians. The difference in the prevalence between Caucasians and East Asians is believed to result from ethnic differences in the frequency of variants of the ACE2 virus entry protein [1]. However, there have not yet been studies that compared the expression of ACE2 variants among Caucasians, Japanese and the other East Asians.

Previous investigators have noted that smell and taste dysfunctions appeared to be more frequent in younger age groups of COVID-19 patients [2,6]. On the other hand, no effect of age on olfactory phenotypes was found [3,7]. The present study revealed a novel finding regarding the effect of age on objective olfactory function in COVID-19 patients, namely a significant disturbance of olfactory function in those above 65 years as compared with those younger than 65 years. The reduction of the sense of smell with age, especially above 65 years, is a well-known phenomenon [19]. Although the present finding of a significant disturbance of olfactory function above 65 years can be explained by the age-related decline of olfactory function, the age-dependent manner of olfactory dysfunction would be specific for COVID-19 infection. Recent researches of mouse models [20,21] demonstrated an age-dependent increase in the expression of SARS-CoV 2 entry sites, both ACE2 and TMPRSS2, which may explain why animals and humans are more susceptible to COVID-19 infection when they reach old age.

The results of our study have some limitations to be considered. First, the heterogeneity among patients during the time that the objective testing was carried out. It is also difficult to recruit patients at an early stage of the chemosensory disorder since many patients focus on other troublesome symptoms such as fever, fatigue, myalgia, etc., which may limit the reliability of the tests. A uniform time point of testing after the COVID-19 onset is also difficult due to the daily hospital routine. Second, the small sample size of patients, especially those with smell-dependent subjective taste dysfunction, can be attributed to the rapid recovery of taste function after the COVID-19 onset, and reduces our ability to generalize findings. Nine of 15 patients with combined dysfunctions were identified as smell-independent gustatory dysfunction. The remaining 6 patients simultaneously recovered both chemosensory functions, which makes it difficult to judge the independency of olfactory and gustatory dysfunctions.

Conclusion

The present study revealed that gustatory dysfunction is induced by both mechanisms of smell-independent and -dependent fashions in COVID-19 infection. The prevalence of olfactory and gustatory dysfunctions in Japanese corresponded to those of the countries with Caucasians rather than East Asians. A significant increase of objective olfactory dysfunction was recognized in the aged patients older than 65 years.

Authorship Contribution Statement

Katsuhisa Ikeda conceived, designed and performed the study, wrote and revised the manuscript and approved the final manuscript. Kumiko Tanaka performed the study and approved the final manuscript. Shinpei Arai performed the study and approved the final manuscript. Nanae Yoshii performed the study and approved the final manuscript. Ayako Inoshita performed statistical analysis and approved the final manuscript.

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