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A 32-Year-Old Man with Persistent Olfactory Dysfunction Following COVID-19 Whose Recovery Was Evaluated by Retronasal Olfactory Testing

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 32-year-old
Final Diagnosis: Olfactory impairment caused by COVID-19
Symptoms: Olfactory impairment
Medication: —
Clinical Procedure: —
Specialty: Otolaryngology

Objective: Unusual clinical course

Background: Anosmia, which is loss of smell, is a recognized complication of coronavirus disease 2019 (COVID-19) due to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which may persist after recovery from infection. Retronasal olfactory testing includes both subjective questionnaires and physiological tests that can be used to evaluate recovery of smell. This report presents the case of a 32-year-old man with persistent loss of smell following COVID-19 whose recovery was evaluated by retronasal olfactory testing.

Case Report: The patient was a 32-year-old man with confirmed SARS-CoV-2 infection. He was aware of his olfactory dysfunction. Using the orthonasal test, a T&T Olfactometer 2 months after disease onset showed an olfactory threshold score of 2.2 points (mild decrease) and olfactory identification result of 3.4 points (moderate decrease). However, the retronasal intravenous olfactory test showed no response, indicating severe olfactory dysfunction. After 3 months of olfactory training and therapy with steroidal nasal drops (Fluticasone Furoate, 27.5 µg/day) and oral vitamins (Mecobalamin, 1500 µg/day), the patient's orthonasal test olfactory threshold score improved to 0.6 points (normal), and his olfactory identification result improved to 1.2 points (mild decrease). Although the retronasal intravenous olfactory test showed a weak response, a reaction did occur. At this time, the patient did not report any improvement in his symptoms.

Conclusions: This report has shown that in cases of persistent anosmia following COVID-19, retronasal olfactory testing can be used to evaluate recovery of the sense of smell.

Keywords: Anosmia • COVID-19 • Olfaction Disorders

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Background

Case reports on coronavirus disease (COVID-19) have been increasing worldwide. Furthermore, the proportion of cases presenting with COVID-19-associated loss of smell (anosmia) has been reported to be 5-85% among the affected population [1]. It has been reported that 59 (98%) of 60 patients with COVID-19 who underwent the University of Pennsylvania Olfaction Identification Test (UPSIT) presented with some forms of smell dysfunction [2]. Previous work in transgenic animal models showed intracranial entry of severe acute respiratory syndrome coronavirus (SARS-CoV) via the olfactory bulb [3]. This has led to speculation that SARS-CoV-(2) (SARS-CoV-2) can pass to the brain, with potential downstream effects on the olfactory regions, resulting in reduced olfactory function [4]. Severity of olfactory disturbances, associated or not with gustatory disturbances, can vary according to various factors, including patient age, immune system status, and pre-infection vaccination [5]. For patients with sudden and severe olfactory dysfunction, at-home isolation or social distancing is recommended whenever possible. In addition, these patients should undergo diagnostic tests for SARS-CoV-2.

The perception of odor comprises orthonasal olfaction via sniffing and retronasal olfaction, processed within the oropharynx. It is caused by airflow to the olfactory clefts via the nasopharynx during swallowing or nasal exhalation [6] (**Figure 1**). Although there are various tests to assess olfactory ability, most of them are subjective olfactory tests. Most previous reports on olfactory dysfunction caused by COVID-19 were based on orthonasal tests (five odorants test [1], UPSIT [1], Le Nez du Vin [1], Importance of Smell (IOS) Questionnaire [7], and Questionnaire of Olfactory Disorders (QOD) [8]). However, it has been previously reported that the retronasal olfactory tests – intravenous olfactory test [9], taste powder test [10], 7-item Candy Smell Test [11], Suprathreshold Taste Strips Test (STST) [12] – are correlated with prognosis of post-infectious olfactory disorders. The intravenous olfactory test is performed by injecting prosultiamine (10 mg, 2 ml) into the median vein of the arm at a constant rate over 20 s. Latency is measured as the time from start of injection until a garlic-like odor is detected. Moreover, duration is measured as the time from odor onset to its disappearance. The intravenous olfactory test is the most widely used olfaction test in Japan. After intravenous injection, it is thought that the mixed gas with the degradation products of prosultiamine diffuses into the lungs and is excreted in the exhaled air. Thereafter, it reaches the olfactory epithelium via the posterior nares and stimulates olfactory cells to signal an odor [13]. However, patients who have lost their ability to breathe via the posterior nostril after total laryngectomy may also smell a garlic-like odor in this test. This suggests that olfactory elements may stimulate olfactory cells directly via the hematogenous process that reaches the olfactory mucosa and stimulates olfactory cells via secretions from Bowman's glands [13].

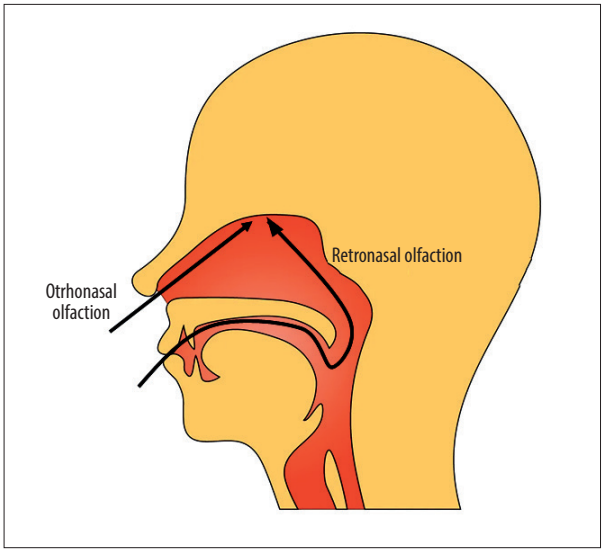

Figure 1. A diagram of orthonasal and retronasal olfaction. Orthonasal olfaction is airflow from anterior nares and retronasal olfaction is airflow from the choanae.

The mean latency and duration times of the test in healthy volunteers are 8 s and 70 s, respectively. However, latency is prolonged and duration is shortened when the sense of smell is impaired. If there is no response to the test, the patient is considered to have anosmia. Non-responders to the intravenous olfactory test have been previously shown to have a poor prognosis for recovery of olfactory acuity [14].

In a report of retronasal olfactory testing for olfactory dysfunction due to SARS-CoV-2, Prem et al performed the 7-item Candy Smell Test 10 times over 7 weeks. They reported that subjective evaluation improved without improvements in the 7-item Candy Smell Test results [15]. To date, olfactory damage caused by SARS-CoV-2 has been evaluated by orthonasal tests and less frequently by retronasal tests. Therefore, we present the case of a 32-year-old man with persistent anosmia following COVID-19, whose recovery was evaluated by retronasal olfactory testing.

Case Report

The patient was a 32-year-old Japanese man with no health problems or co-existing diseases. He had no history of smoking, drinking, or drug abuse. He experienced fever and cough since July 2, 2020. On July 4, 2020, he visited an internist and was diagnosed with COVID-19 based on a positive polymerase chain reaction (PCR) test for SARS-CoV-2. Viral ribonucleic acid (RNA) extraction was performed using the QIAamp Viral RNA

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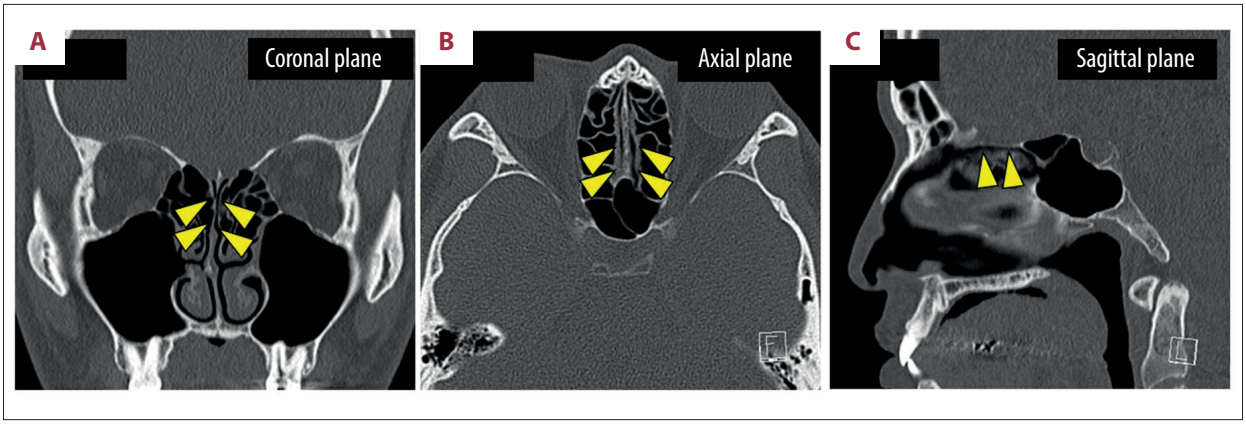

Figure 2. CT image shows no sinusitis or inflammation in the olfactory cleft. (**A, B**) There is no inflammatory obstruction in the bilateral olfactory clefts (arrowheads). (**C**) There is no inflammatory obstruction in the right olfactory clefts (arrowheads). CT – computed tomography.

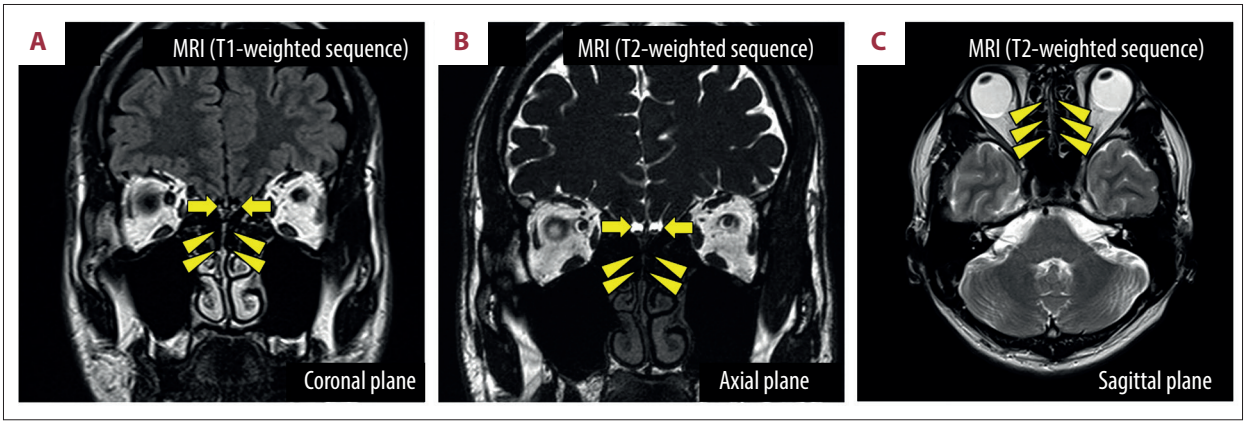

Figure 3. MRI image. (**A-C**) MRI; the olfactory bulbs (arrow) appear normal, and there is no inflammatory obstruction in the bilateral olfactory clefts (arrowheads). MRI – magnetic resonance imaging.

Mini Kit (QIAGEN®, Hilden, Germany) from nasopharyngeal swabs. qPCR was performed using TaqMan Fast Virus 1-Step Master Mix (Applied Biosystems® Thermo Fisher Scientific, Waltham, USA) and the StepOnePlus Real Time PCR System (Applied Biosystems®). At the time, the patient was aware of his olfactory and gustatory dysfunction. On July 9, 2020, the patient's gustatory dysfunction resolved. Although it was improving slowly, his olfactory dysfunction persisted. Therefore, the patient was referred to our department on September 16, 2020 for further evaluation and management.

At presentation, olfactory dysfunction was observed without any other subjective symptoms. During this first visit, the patient underwent nasal endoscopy, sinus computed tomography (CT), orthonasal testing using a T&T Olfactometer (Daiichi Yakuhin Sangyo Co.) [16], and retronasal intravenous olfactory test [9]. However, nasal endoscopy and sinus CT revealed no significant findings (**Figure 2A-2C**). The T&T Olfactometer could measure the olfaction threshold and olfactory identification (0-1.0: normal, 1.1-2.5: mild decrease, 2.6-4.0: moderate decrease, 4.1-5.5: severe decrease, 5.6 and higher: anosmia). The patient had scores of 2.2 points in the olfaction threshold (mild decrease) and 3.4 points in the olfactory identification results (moderate decrease). However, the retronasal intravenous olfactory test showed no response, indicating severe olfactory dysfunction. On August 25, 2020, magnetic resonance imaging (MRI) performed at the patient's insistence indicated no significant findings (**Figure 3A-3C**).

After 3 months (December 16, 2020) of olfactory training and therapy with steroidal nasal drops (Fluticasone Furoate, 27.5 µg/day) and oral vitamins (Mecobalamin, 1500 µg/day), using a T&T Olfactometer, the olfaction threshold test result improved to 0.6 points (normal) and olfactory identification result improved to 1.2 points (mild decrease). However, the retronasal test using the intravenous olfactory test resulted in a faint uncomfortable feeling at 40 s (severe decrease [anosmia]) [9]. The patient did not report any improvement in his symptoms.

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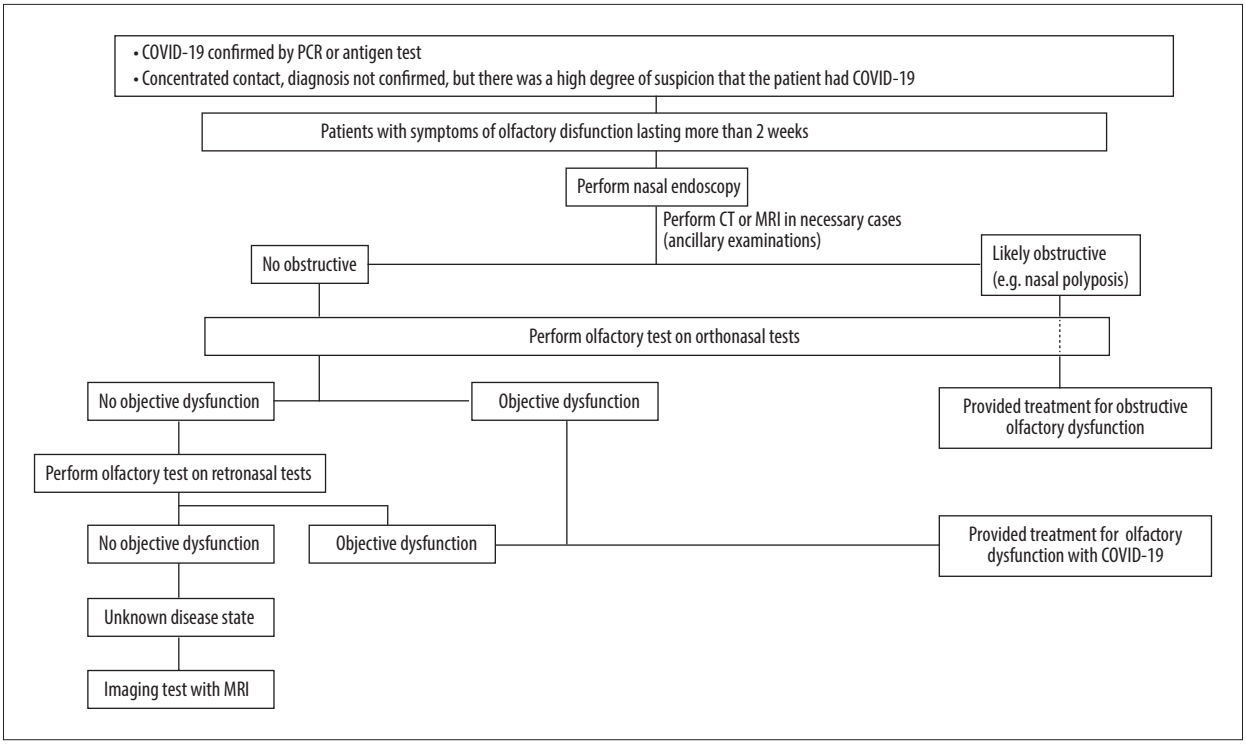

Figure 4. Flow chart of diagnostic management.

Discussion

Olfactory dysfunction due to COVID-19 is often rapid and mild and sometimes persists for a long time [1]. It has been reported that fever and other symptoms may be preceded by dysfunction of the sense of smell and taste. However, in this case, fever was the initial symptom [17]. Although orthonasal tests are used to evaluate olfactory dysfunction, they may deviate from patient's subjective symptoms. This case shows the possibility that retronasal olfactory tests could be used to correctly assess the patient's olfactory dysfunction. In many cases, the orthonasal test may be better utilized to assess patient's subjective symptoms. However, depending on lesion location, the retronasal olfactory test may be better to assess subjective symptoms [9].

Of note, a metanalysis on anosmia and hyposmia reported that a total of 2065 unique titles were returned upon the initial search. Out of these, 226 abstracts were examined, yielding 27 full-text articles meeting the inclusion criteria (level of evidence ranging from 1 to 4; mostly level 2). These studies included a total of 13 577 patients. The most utilized diagnostic tools were orthonasal smell tests (such as the Sniffin' Sticks, the UPSIT, and validated abridged smell test). Although various imaging modalities (including MRI and CT) were frequently mentioned in the workup of olfactory dysfunction, routine imaging was not used to primarily diagnose smell loss [18].

The human olfactory nerve epithelium occupies 1.25% of the nasal mucosa, covering an area of 8-10 cm^2. It is composed of the cribriform plate, upper nasal septum, and middle and superior turbinates [19]. Approximately 10 million dendrites of the olfactory receptor neurons located in the olfactory bulb protrude into the nasal mucosa [19]. Once odorant molecules reach the olfactory epithelium, they dissolve into the mucus layer and bind to/activate the olfactory receptors through complex interactions [19]. A single odorant molecule can activate multiple receptor types to varying degrees [19].

The olfactory nerves in the olfactory mucosa do not express genes for angiotensin-converting enzyme 2 (*ACE2*) or transmembrane serine protease 2 (*TMPRSS2*), whose translation products are important for binding of the SARS-CoV-2 outer membrane with infected cell membranes. However, these genes are expressed by the supporting and basal cells in the olfactory epithelium [20]. It has been reported that widespread olfactory epithelial shedding occurs in hamsters in the early stages of SARS-CoV-2 infection regardless of viral load. Moreover, the degree of damage and rate of regeneration of the olfactory epithelial lining vary depending on the site of olfactory epithelium [21]. One possibility is that there may be individual differences in location of olfactory epithelial shedding caused by SARS-CoV-2 infection.

Prem et al reported that a cross-sectional observation group of retronasal olfactory performance showed that the 7-item

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Candy Smell Test results were outside the normal range in 58 of 78 patients (74%). Additionally, this probability was higher than that reported on orthonasal smell tests [15]. Considering the report of Prem et al, it is possible that olfactory dysfunction due to SARS-CoV-2 might have been exacerbated by retronasal tests even when orthonasal test results were normal. There was a difference between the study by Prem et al and the present case report. According to Prem et al, the patient's subjective symptoms improved without improvements in retronasal tests. However, in the present case neither the patient's subjective symptoms nor results of retronasal tests improved. Retronasal tests are not totally reliable and should be used in combination with orthonasal tests. The literature on olfactory tests suggests differential processing and neural recruitment for the orthonasal versus retronasal pathways [22]. Therefore, the differences in findings between the 2 tests cannot be reliably attributed to correlation with symptoms. Conducting both tests rather than replacing one with the other might be an efficient strategy. We recommend that retronasal tests be considered when the patient is aware of olfactory dysfunction, even if orthonasal tests show normal results (**Figure 4**).

Conclusions

This report has shown that in cases of persistent anosmia following COVID-19, retronasal olfactory testing can be used to evaluate recovery of the sense of smell.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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