Anosmia, trigeminal nerve dysfunction, and COVID-19: A personal account

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ABSTRACT
I contracted coronavirus disease 2019 (COVID-19) and suffered not only from sudden anosmia, but also from a strange stinging and burning sensation inside my nose with some pain complicated by desensitization to spicy foods and fizziness of carbonated drinks. As a possible mechanism involving these symptoms, I theorize that not only is the olfactory epithelium within the olfactory nerve damaged, but the trigeminal nerve might also be affected, leading to olfactory dysfunction and strange nasal sensations.

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Introduction
Olfactory dysfunction causing anosmia or hyposmia is a common manifestation of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 infection. More than 60% of COVID-19 patients experience anosmia or hyposmia, although there have been no specific findings in the nasal cavity or olfactory bulb on radiological evaluation [1–4]. It has been suggested that the angiotensin-converting enzyme 2 (ACE2) receptor, a key molecule for the entry of the virus into human cells, is localized on the olfactory epithelium. In contrast, ACE2 is has not been observed in olfactory sensory neurons or olfactory bulb neurons themselves [5,6]. Despite emerging evidence, the underlying mechanisms involving olfactory dysfunction remain unclear.

I contracted COVID-19 and suffered from unexpectedly severe anosmia, which was different from the anosmia I had previously experienced with influenza or the common cold. I present my clinical course as well as the results of survey regarding the loss of smell conducted on a small group of hospital colleagues. The results suggest the involvement of the trigeminal nerve in olfactory dysfunction.

Case presentation
I am a 47-year-old otolaryngologist with no chronic disease history. I work at Aizawa Hospital. The number of COVID-19 patients requiring hospitalization increased after December 2020, and resulted in the spread of infections among health care workers. On 16 January 2021, I developed a sudden fever of 37.8°C with mild malaise. A COVID-19 quantitative antigen test was positive (5,000-fold). I was quarantined at a hotel hired by the prefectural government to isolate COVID-19 patients in accordance with the regulations imposed.

On day 2, the fever subsided without any medications, and I exhibited no symptoms. On day 3 in the morning, I made strong instant coffee. Although I could sense the bitter taste, it was strange and weak and I had no sense of smell. I felt a strange sensation of stinging and burning inside my nose with a little pain during breathing. I had no rhinorrhea or nasal congestion. From days 4 to 7, I had modest malaise, a non-productive cough, and anosmia with strange nasal sensations. After day 8, my symptoms gradually improved except for the anosmia and nasal sensations. On day 11, my quarantine ended, and I returned home to continue isolation. I had only nasal symptoms. I experimented with various foods, drinks, and other materials to evaluate my sense of smell and taste. When I smelled my cologne, it seemed faint. I presumed the smell was affected by the strange sensation of stinging and burning inside my nose. I could recognize the sweetness of Coca-Cola, but the carbonated fizzy sensation was weak. I could not taste the...
wasabi’ that normally stimulates a stinging sensation going through the nose and has a very sharp taste.

On day 18, I returned to work. I underwent head computed tomography scan and magnetic resonance imaging. These revealed no abnormalities. An intravenous olfactory test (prosultiamine injection) produced a normal result for latency and duration of smell; however, I continued having persistent hyposmia and the on-going strange nasal sensation. On day 30, I subjectively deduced that my nasal symptoms had recovered to approximately 80%.

**Subjects and methods**

A total of 18 health care workers at my institution, myself included, contracted COVID-19 between 3 and 20 January 2021. Among the 17 health care workers identified, 9 participated and were interviewed. The University of Pennsylvania Smell Identification Test (UPSIT) was performed. This study was approved by my hospital’s Ethics Committee (IRB approval number: 2020-069).

**Results**

The case demographics are presented in Table 1. The onset of anosmia or hyposmia during the course of the disease varied. Of the 10 cases (including myself), 4 cases developed unusual smell and taste sensations whereas 2 experienced frontal headaches; however, their UPSIT results were normal.

**Discussion**

I had not expected severe COVID-19–related olfactory dysfunction with acute onset. The tingling and strange burning nasal sensation and the weak sensing of carbonated drinks and *wasabi* stimulus seemed to have a different pathogenesis from olfactory nerve dysfunction. Similar symptoms were observed among SARS-CoV-2–infected co-workers with milder manifestations, as summarized in Table 1. Indeed, the normal UPSIT results indicate that the ability to identify odors had been recovered or maintained since SARS-CoV-2 infection. However, individual patients who experienced reduced ability in detecting spicy flavors or frontal headaches still subjectively experienced strange sensations and hyposmia in daily life at the time of testing. This divergence between olfactory test results and subjective olfactory sensations is difficult to explain as just a result of olfactory nerve damage. As a possible mechanism, I theorize that the trigeminal nerve might be affected in addition to damage to the olfactory epithelium or neurons. This could lead to olfactory dysfunction and the strange nasal sensations experienced. Headache is also a common neurological symptom, occurring in approximately 10%–20% of COVID-19 patients [7]. Several potential mechanisms have been suggested. The direct invasion of the trigeminal nerve in the nasal cavity by SARS-CoV-2 may cause frontal and periorbital headaches [8–10]. In contrast, hypothetically, an indirect pathway of neurogenic insult caused by SARS-CoV-2, immune responses to inflammatory mediators, such as IL-1β or TNF-α, may contribute to neuropathies and chronic pain [11,12]. A recent autopsy investigation revealed SARS-CoV-2 RNA and proteins in the olfactory mucosa and within the central nervous system, concluding that neuroinvasion can occur by transmucosal entry through nervous structures at the neural–mucosal interface [13]. Although different studies have proposed different underlying mechanisms of neural damage regarding anosmia and headaches, pathogenic mechanisms and pathways have not been elucidated. Therefore, I suggest that both the olfactory and trigeminal systems may either be directly or indirectly damaged by the aforementioned

| Age/Sex | Severity | COVID-19 medication | Onset of smell loss | UPSIT (4–8 weeks after onset) | Note |
|---------|----------|---------------------|--------------------|-----------------------------|------|
| C1 59y/F | Moderate | Steroids | None | 4/4 | Weak spicy taste |
| C2 22y/F | Mild | Acetaminophen | Day −3 | 4/4 | Weak spicy taste and fizzy feeling |
| C3 30y/F | Mild | None | Day −1 | 4/4 | |
| C4 32y/M | Moderate | Steroids | None | 4/4 | |
| C5 46y/F | Mild | None | Day 4 | 4/4 | Weak spicy taste |
| C6 49y/F | Mild | None | Day 1 | 4/4 | |
| C7 27y/F | Mild | None | Day −3 | 3/4 | Frontal headache |
| C8 58y/F | Mild | Acetaminophen | Day −5 | 4/4 | Frontal headache |
| C9 47y/M | Mild | None | Day 3 | 4/4 | Presented case |
| C10 42y/M | Mild | Acetaminophen | None | 3/4 | |

Case numbers are in chronological order of COVID-19 onset, from 3 to 20 January 2021. Onset of smell loss: — (minus) indicates before the day of diagnosis. UPSIT: University of Pennsylvania Smell Identification Test (4 questions, 4/4 represents all correct).
presumptive mechanism, which could give rise to olfactory dysfunction, frontal headaches, and unusual nasal sensations. A potential concern was raised regarding trigeminal nerve damage, but whether neurogenic insult can cause trigeminal sensitivity increasing with irritation or decreasing with neural damage is unclear. Hypoguesia for spicy flavors and fizzy sensation due to decreased sensitivity of the trigeminal system is plausible. However, neuralgic headaches were likely caused by increased sensitivity, possibly nociceptive hypersensitivity [10,11]. The intranasal trigeminal and olfactory systems have a close relationship; therefore, olfactory dysfunction could reduce trigeminal sensitivity, resulting in strange nasal sensations [14]. The absence of ACE2 in the olfactory sensory neurons could indicate that damage by SARS-CoV-2 to olfactory epithelium cells, including trigeminal nerve endings, was the cause of anosmia, rather than direct injury to olfactory sensory neurons [10]. However, the reasons for these above-mentioned discrepancies remain unclear.

Understanding of anosmia or hyposmia varied among the subjects, suggesting that some of the findings might be overlooked, and the observations might be due to the missing interaction between the trigeminal system and the olfactory system, resulting in a decreased trigeminal sensitivity. If COVID-19 olfactory dysfunction is a disease-specific manifestation, a more specific questionnaire or interview is required. This preliminary survey included only a small number of cases. Further studies of the peripheral and central nervous systems are required to further elucidate the mechanisms.

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Informed consent statement

We confirmed a patient’s anonymity. We obtained informed consent from the participants discussed in the study.

Author contributions

Hideaki Moteki: conception, manuscript preparation, data collection

Disclosure statement

No potential conflict of interest was reported by the author(s).

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