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Letter to the Editor

Olfactory and gustatory dysfunction caused by SARS-CoV-2: Comparison with cases of infection with influenza and other viruses

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To the Editor—Among the symptoms of SARS-CoV-2 infection (or COVID-19), olfactory or gustatory dysfunction may possibly present first or may be the only symptom.[1] Three Japanese professional baseball players complained of smell and taste dysfunction. Although 2 of them had neither fever nor cough, a viral polymerase chain reaction (PCR) test revealed that all 3 were SARS-CoV-2 positive (*The Chunichi Newspaper*, March 27, 2020). Two nurses working in the National Cancer Center Hospital underwent the viral PCR test because they had similar symptoms, and they were both SARS-CoV-2 positive, although they had neither fever nor cough (*Asahi Shimbun* newspaper [digital], March 28, 2020).

Olfactory dysfunction is caused by blockage of the nasal airways or disturbance of the sensory system, including olfactory receptor cells, and the nervous system. As the olfactory receptor cells adjoin the upper part of the nasal cavity, the receptor cells are vulnerable. Viral infection was the most common cause of loss of olfactory function. With this viewpoint, we reviewed the available literature on olfactory and gustatory dysfunction caused by influenza and other viruses. Postviral infection olfactory dysfunction was more common in women and elderly people.[2-4] The influenza and parainfluenza type 3 viruses were reported to be causative of olfactory loss most frequently. Seasonal changes in the incidence of olfactory loss have been reported with respect to influenza and parainfluenza type 3 infections, occurring most frequently in winter and spring, respectively.[2,5] Flanagan et al[6] reported that the proportion of persons who received influenza vaccination was significantly lower among those with olfactory dysfunction than that in a control group. However, the adverse effect of olfactory dysfunction due to influenza vaccination was also reported. Dotty et al[7] attributed 9 of 4,554 patients (0.19%) with olfactory dysfunction to influenza vaccination. Suzuki et al[8] confirmed the presence of various viruses in the nasal discharge of patients with postviral infection olfactory dysfunction, such as rhinovirus, parainfluenza virus, Epstein-Barr virus, and coronavirus. Significant recovery was not observed after 24 weeks in almost all of the patients.[8] In contrast, olfactory dysfunction due to hepatitis virus was recovered within 6 weeks in almost all cases.[9] In acute viral hepatitis, hyposmia, dysosmia, and dysgeusia are common symptoms. As smell and taste are closely associated; persons with olfactory dysfunction and normal gustatory function often complain that they "cannot taste coffee."[9]

Some recent reports described early improvement of olfactory and gustatory dysfunction in many COVID-19patients. According to the newspaper, olfactory and gustatory function in the professional baseball players also returned to normal relatively soon. However, only short-term follow-up investigation has been conducted regarding the effect of SARS-CoV-2 infection on the chemosensory function. Hwang[10] reported that anosmia induced by SARS-CoV continued for >2 years in a 27-year-old woman. We believe that epidemiological investigation is required regarding the effect of SARS-CoV-2 on the olfactory and gustatory functions in terms of the frequency, time course, and relationship with other symptoms.

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Asymptomatic SARS-CoV-2 infections: What do we need to know?

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To the Editor—The global outbreak of coronavirus disease 2019 (COVID-19) was officially declared as a pandemic by World Health Organization (WHO) on March 11, 2020,[1] and it has imposed unprecedented, far-reaching impacts upon public health and the global ecomony. As of April 30, 2020, >3 million cases of COVID-19 have been confirmed, including >210,000 deaths.[2] Meanwhile, a growing body of are reporting that many COVID-19 infections might present no or only mild symptoms, with a much higher proportion of asymptomatic infections than previously expected.[3–5] Asymptomatic COVID-19 includes asymptomatic infected persons and presymptomatic infected persons. Those with positive reverse transcription-polymerase chain reaction (RT-PCR) results who never develop any signs or clinically symptoms of COVID-19 are considered asymptomatic infected persons. Those with positive reverse transcription-polymerase chain reaction (RT-PCR) results who fail to show any signs or clinically symptoms of COVID-19 at testing but eventually developed symptoms are considered presymptomatic infected persons. Approximately 60% of COVID-19 cases may have no symptoms or mild symptoms, according to an article published online in *Nature* on March 20.[6] In fact, as of April 14, 2020, some 6,764 asymptomatic infections have been recognized in mainland China, including 588 imported infections and 1,297 cases that had been recategorized as confirmed cases.[7] Also, SARS-CoV-2 can not only damage human lungs but can also attack many other organs, including the gut and blood vessels, kidneys, etc, thus presenting different symptoms and signs.[8] So, why do some infected persons still show no symptoms or only mild symptoms?

The virus is transmitted by exhaled virus-laden droplets that are inhaled by susceptible individuals; these droplets enter the nose and throat, and the virus attacks the cell-surface receptor called angiotensin-converting enzyme 2 (ACE2).[9] Because SARS-CoV-2 is a new pathogen to this individual, the immune cells do not recognize it and it escapes the defense system of the body and replicates itself to invade new host cells. These host cells are destroyed in this process, and these pathological changes alert the immune system to begin fighting the diseased cells as well as the virus. A recent study indicated that the genes involved in innate immunity are coexpressed in nasal epithelial cells with viral-entry–associated genes.[9] Thus, if the early immune response can suppress enough viral replication to prevent it from continuing into the lungs, the infected individual could have no or only mild symptoms. Another ex vivo study has shown that SARS-CoV-2 induced significantly less host interferon and proinflammatory response than SARS-CoV, and the low degree of innate immune activation could account for the mild or even lack of symptoms in many COVID-19 patients.[10] To date, the exact reasons for no or only mild symptoms in many COVID-19 patients remain unclear, and further research is urgently needed to explore the causes and transmission of asymptomatic infections.

The SARS-CoV-2 viral load in upper respiratory specimens is almost as high in asymptomatic infections as symptomatic infections.[11] Several studies have indicated that asymptomatic and presymptomatic patients can transmit virus to others.[12–14] A study published in *Nature Medicine* reported that patients with laboratory-confirmed COVID-19 began to shed virus 2–3 days before the onset of symptoms and that their infectivity peaked before symptom onset.[15] Another study conducted by the Department of Statistics and Actuarial Science of the University of Hong Kong concluded that there was no difference in the transmission rates of coronavirus between symptomatic patients and asymptomatic cases.[16] Overall, these studies provided evidence that the risk of transmission by asymptomatic patients might be not lower than that by symptomatic patients. Moreover, some individuals infected with the virus experience no or only mild symptoms, and they might be unaware of their disease and thus not isolate themselves or seek treatment. They might be overlooked by healthcare works (HCWs) and possibly trigger a "butterfly effect." Finally, although many detection methods are available, individuals in the "window period" of COVID-19 infection can be missed, and up to 29% of patients could have an initial RT-PCR false-negative result,[17] a paper prepublished on the *medRxiv* website suggests, so it is possible that a large portion of asymptomatic infections are going undetected.

All of this evidence indicates that the spread of pandemic of COVID-19 will be difficult to curb by focusing on symptomatic infections alone. Therefore, how can we detect as many asymptomatic infections as possible and hopefully prevent a new wave? First, to achieve universal participation during the pandemic, authorities should fully use mainstream media and the internet to provide timely release of relevant information about the pandemic in an open and responsible manner. Then citizens can correctly understand the severity of the outbreak and act accordingly. Mass media need to disseminate health promotion messages such as indications for wearing a mask and handwashing routine and the importance of maintaining 2-m (6 feet) social distancing. Also, considering that medical supplies are in short

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