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Anosmia in the Era of COVID-19

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Dear Editor,

We read the interesting article of "the neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients" by Li et al. (1) that mentioned a heavy infection of the brainstem in patients with SARS-COV that could be extended to SARS-COV2 (COVID-19) infection due to the high similarity between them. Furthermore, the authors claimed this invasion was responsible for the acute respiratory syndrome caused by this viral infection. They also mentioned that via in vivo models, intranasal entry of low doses of SARS-COV or MERS-COV may be spread through olfactory nerves to other areas of brains such as brainstems and thalamus (1). As you know, here in Iran, we are also struggling with COVID-19 infection. Nevertheless, like any other regions with limited resources around the world, due to the shortage in laboratory tests, and false-negative results or incompatibility of clinical manifestations and laboratory or imaging findings, we may miss some cases of COVID-19 in our area.

There were numbers of patients with respiratory difficulties admitted to our local hospitals or visited as outpatients (with mild to moderate disease), presumed to be infected with respiratory viruses. During this period, our clinicians noticed a significant rise in cases complained of anosmia for more than two weeks, even without fulfilments of typical criteria of flu or COVID-19, compared to the same time of the last year. As these cases have not been tested for coronaviruses or have no respiratory complaints, we have no documents available to prove the infection, but it may bring up possibilities about the infection in a larger population with low doses of viruses.

Previous studies reported that nasal discharge of cases with post-viral olfactory dysfunction (PVOD) contains human rhinoviruses, coronavirus, parainfluenza virus, and Epstein-Barr viruses, which presented as anosmia or dysosmia. Although authors mentioned that "evidence of a specific virus in the nasal cavity is not equal to the persistence of the virus within the olfactory cells", they showed that the reason for olfactory dysfunction could be other than nasal obstruction (2). Further, there has been reported a case with SARS disease presented with persistent anosmia for 2 years after recovery. There has been proposed a role of autoimmune system in its pathogenesis, and it was claimed that the damage could be irreversible (3).

There are some possible explanations for this issue. First, as reported before viruses can escape from the immune system and spread to extra-respiratory sites such as the central nervous system (CNS) by means of the bloodstream. Second, respiratory viruses such as coronaviruses, commonly enter the human body through the airways and the main center of colonization is lungs. In this invasion, the nasal respiratory epithelium could be damaged by the viruses, and the sensory nerve fibers get infected. This peripheral infection can use axonal transport machinery to access to the olfactory bulb through olfactory nerves and affects olfaction (4).

This is not the only way, other cranial nerves that have branches in the respiratory system may prepare other routes for the viral infection to damage CNS such as the ophthalmic branch of the trigeminal nerve that innervates the nose, the nasal mucosa, and the frontal sinuses. The vagus nerve gives rise to a couple of branches in the larynx, the trachea, and the lungs. This cranial nerve stems from the medulla oblongata of the brainstem. On the other hand, some of the COVID-19 cases showed neurologic signs, including nausea and vomiting. Area postrema in the medulla oblongata of the brainstem is the vomit-inducing center. It can be probable that the virus reaches the brainstem by the use of vagus nerve as a retrograde neuronal route (5). In addition, vagus nerve also gives

rise to the cardiac branches, and cardiac manifestations of COVID-19 are common (1). The cardiovascular center is in the medulla oblongata of the brainstem too. According to the anatomic connections, the infection of both the vagus nerve and the brainstem affects the cardiovascular system. Hypothetically there are different possible ways for the SARS-CoV2 to invade the CNS, and the neurologic signs of the COVID-19 cases guide us to look for the neurological pathology of SARS-CoV2. Further experimental investigations are needed to explore this relationship between COVID-19 and the rise of anosmia in this era.

Footnotes

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