Review

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Anosmia: a missing link in the neuroimmunology of coronavirus disease 2019 (COVID-19)

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Abstract: Just before 2020 began, a novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), brought for humans a potentially fatal disease known as coronavirus disease 2019 (COVID-19). The world has thoroughly been affected by COVID-19, while there has been little progress towards understanding the pathogenesis of COVID-19. Patients with a severe phenotype of disease and those who died from the disease have shown hyperinflammation and were more likely to develop neurological manifestations, linking the clinical disease with neuroimmunological features. Anosmia frequently occurs early in the course of COVID-19. The prevalence of anosmia would be influenced by self-diagnosis as well as self-misdiagnosis in patients with COVID-19. Despite this, the association between anosmia and COVID-19 has been a hope for research, aiming to understand the pathogenesis of COVID-19. Studies have suggested differently probable mechanisms for the development of anosmia in COVID-19, including olfactory cleft syndrome, postviral anosmia syndrome, cytokine storm, direct damage of olfactory sensory neurons, and impairment of the olfactory perception center in the brain. Thus, the observation of anosmia would direct us to find the pathogenesis of COVID-19 in the central nervous system, and this is consistent with numerous neurological manifestations related to COVID-19. Like other neurotropic viruses, SARS-CoV-2 might be able to enter the central nervous system via the olfactory epithelium and induce innate immune responses at the site of entry. Viral replication in the nonneural olfactory cells indirectly causes damage to the olfactory receptor nerves, and as a consequence, anosmia occurs. Further studies are required to investigate the neuroimmunology of COVID-19 in relation to anosmia.

Keywords: anosmia; COVID-19; neuroimmunology; olfactory sensory neurons; SARS-CoV-2.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), an enveloped, positive-sense single-stranded RNA virus belonging to the Coronaviridae family of the Nidovirales order, is the source of the recent outbreak which has started in Wuhan, Hubei Province, China (Brann et al. 2020; Su et al. 2016). The severe acute respiratory syndrome (SARS) epidemic was the first outbreak of the Coronaviridae family that took place in 2003, followed by the second one, the Middle East respiratory syndrome epidemic that occurred in 2012. The current outbreak of novel coronavirus disease 2019, known as COVID-19, has spread at an unprecedented pace making the World Health Organization declare it as a pandemic on March 11, 2020 (Hanaei and Rezaei 2020). As of writing this manuscript, the total number of confirmed cases has exceeded 14 million worldwide, with a total of approximately 600,000 records of deaths. More than 80% of people have shown mild to moderate infection, while the remaining portion would progress to severe and critical conditions. Older people and people with comorbidity, especially cardiovascular disease, diabetes, hypertension, chronic respiratory disease, and cancer,
mostly make up the population of those dying from COVID-19 (Ahmadi et al. 2020; Hessami et al. 2020; Shamshirian and Rezaei 2020; Sahu et al. 2020). However, the observation of severe infection and death from infection in young people and people without a preexisting condition has pointed to the possible role of genetics in susceptibility to COVID-19 (Ahanchian et al. 2020; Darbeheshti and Rezaei 2020; Yousefzadegan and Rezaei 2020).

COVID-19 is considered an immune-mediated disorder that can affect multiple organs/systems. Patients with a severe phenotype of disease and those who died from the disease have shown hyperinflammation and were more likely to develop neurological manifestations, linking the clinical disease with neuroimmunological features (Bahrampi et al. 2020; Lotfi et al. 2020; Lotfi and Rezaei 2020; Sahu et al. 2020; Yazdanpanah et al. 2020). Anosmia and ageusia are neurological manifestations that have recently appeared in several publications from which an exciting field of research about COVID-19 emerged. This attention dates back to debates over the olfactory pathway as a possible route of central nervous system (CNS) involvement by viruses (van Riel et al. 2015). Also, evidence shows the tendency of coronaviruses to involve the CNS (Arbour et al. 2000). Therefore, it is possible to assume the olfactory route as a potential gateway of CNS involvement by coronaviruses, especially the recently emerged one, SARS-CoV-2, which has been associated with anosmia.

Self-diagnosis and self-misdiagnosis of anosmia in COVID-19

As evidenced by the Google trends, there has been a surge in searches about the association between anosmia and COVID-19 (Walker et al. 2020). It provides evidence that there might be a possibility of anosmia approaching the epidemic mass hysteria. Whenever a group of symptoms of illness spread swiftly among members of a group, epidemic mass hysteria should be considered. Epidemic mass hysteria is a social phenomenon where physical complaints as signs or symptoms occur unconsciously with no definite corresponding organic etiology (Bartholomew and Wessely 2002). This phenomenon usually happens when there is extreme stress about an alarming event or newly emerged diseases. Hence, in the stressful condition of the current pandemic, the occurrence of anosmia as such a phenomenon might be possible. More clearly, a considerable number of reported anosmia cases are self-diagnosed because of the fear of COVID-19 transmission that has caused the reference to the clinics and hospitals to get decreased.

By contrast, there might be underestimation in the incidence of anosmia with COVID-19 due to the effect of visual cues on odor assessment (Blackwell 1995). More clearly, individuals who have heard about anosmia tend to test themselves. However, consistent with the lack of access to an approved specific olfactory test, they try smelling different objects to examine their state of sense of smell. Hence, they presume that they can feel the smell, but it is their visual sense helping them remember the smell of the object they are looking at, and this leads to a self-misdiagnosis of anosmia in patients with COVID-19. However, recently published studies, including extensive survey reports that have estimated the prevalence of clinically diagnosed anosmia, highly suggest that anosmia might be a symptom of COVID-19 infection in mild to moderate cases (Bagheri et al. 2020; Gane et al. 2020; Giacomelli et al. 2020; Lechien et al. 2020; Mao et al. 2020; Moein et al. 2020; Parma et al. 2020). It is in line with the previous findings related to anosmia in the context of other coronaviruses (Akerlund et al. 1995; Suzuki et al. 2007), such as SARS-CoV-1 (Hwang 2006).

From anosmia to the neuropathogenesis of COVID-19 and vice versa

Studies have suggested different probable mechanisms for the development of anosmia in COVID-19, including olfactory cleft syndrome with mucosal obstruction, postviral anosmia syndrome (Gane et al. 2020) cytokine storm, direct damage of olfactory sensory neurons (OSNs) (Butowt and Bilinska 2020), and impairment of the olfactory perception center in the brain. Thus, the observation of anosmia would lead us to find the pathogenesis of COVID-19 in the CNS. COVID-19 might act on the CNS (Jahanshahlu and Rezaei 2020a; Saleki et al. 2020), either directly or indirectly (Butowt and Bilinska 2020). COVID-19 can directly route the CNS through the axons of OSNs, which are claimed to be the only olfactory epithelium neurons connected to the brain. Besides, the olfactory nerve bundles are positioned next to the cribiform plate and are surrounded by the cerebrospinal fluid (CSF). SARS-CoV-2 might be able to infect nonneuronal cells in the olfactory
epithelium but indirectly reaches many parts of the brain through the CSF (Harberts et al. 2011).

Expression of the proteins essential for viral entry in olfactory cells

The angiotensin-converting enzyme 2 (ACE2) receptor is identified as a cell surface receptor for SARS-CoV-2. It has been shown to mediate the entry of the virus into host cells with the aid of transmembrane protease, serine 2 (TMPRSS2), a cell surface enzyme that undertakes the cleavage of the SARS-CoV-2 spike protein (Jahanshahlu and Rezaei 2020b; Saghazadeh and Rezaei 2020b; Yazdanpanah et al. 2020). Hence, as SARS-CoV-2 can involve the CNS, there might be some cells in the CNS with high expression of ACE2. Then, SARS-CoV-2 can bind these cells and thereby transmit the infection to OSNs, which express low levels of ACE2. The olfactory ensheathing cells (OECs) seem to be a potential target for COVID-19 (Butowt and Bilinska 2020). This type of glia is capable of transferring the virus to OSN axons via an ACE2-independent route (Butowt and Bilinska 2020).

Many groups of researchers have performed bulk and single-cell RNA-sequencing surveys to investigate the expression of ACE2 and TMPRSS2 in barrier surfaces such as the olfactory mucosa and nasal epithelium (Bilinska et al. 2020; Brann et al. 2020; Durrant et al. 2016; Durante et al. 2020; Hamming et al. 2004; Kanageswaran et al. 2015; Saraiva et al. 2015 2019; Sungnak et al. 2020). Sungank et al. (Sungnak et al. 2020) reported that TMPRSS2 had a high expression and broader distribution than ACE2 in all data sets they had used. They also found the highest expression of ACE2 and TMPRSS2 in ciliated cells and goblet cells. Brann et al. (Brann et al. 2020) concluded that both ACE and TMPRSS2 exist in mouse whole olfactory mucosa, especially in Bowman's gland cells and horizontal basal cells (HBCs). However, ACE2 was not present in purified OSNs. Notably, the authors stated that sustentacular cells in the human olfactory epithelium express ACE2 and TMPRSS2 at the same level as in lung cells. These results are in line with several studies in humans or animals (Bilinska et al. 2020; Colquitt et al. 2014; Durante et al. 2020; Kanageswaran et al. 2015; Saraiva et al. 2019; Ziegler et al. 2020). However, one study (Nickell et al. 2012) failed to find ACE2 expression in the olfactory epithelium. Moreover, a further study (Krolewski et al. 2013) could not replicate the observation of high expression of ACE2 in nonneuronal cells in the olfactory epithelium, as previously reported. Also, among studies that have investigated TMPRSS2 expression in nonneuronal olfactory epithelium cells, only the study by Olender et al. (Olender et al. 2016) reported a lack of TMPRSS2 in these cells. Technical factors might be the reason for these discrepancies, and hence, the result of these types of studies needs validation (Hughes 2009).

Although the mentioned studies represent different results about the state of ACE2 and TMPRSS2 gene expression, the genes related to the proteins that participate in the cell entry of other coronaviruses are expressed by all cell types in the olfactory epithelium including OSNs (Brann et al. 2020). In the olfactory epithelium, ACE2 expression is highest in sustentacular cells (2.90% of cells), though lower than that is in respiratory ciliated and secretory cells (3.65 and 3.96%, respectively). All horizontal basal cells express ACE2 at a level higher than that of respiratory HBCs (1.78 vs. 0.84%). Besides, the expression of ACE2 and TMPRSS2 is higher in all other respiratory epithelial cells compared to that in olfactory epithelial cells. In contrast, Bilinska et al. reported the higher accumulation of ACE2 protein in the murine olfactory epithelium than in the respiratory epithelium. The authors proposed that if such a pattern of expression exists in humans, then the olfactory epithelium, especially sustentacular cells, offers a useful source of specimens for detection of the SARS-CoV-2 in earlier stages of the disease (Bilinska et al. 2020).

Histopathology findings in the olfactory epithelium

Sustentacular cells in the olfactory epithelium support OSNs and contribute to the odor perception process by releasing odor-binding protein and endocytosing the complex of olfactory binding protein and odorant (Strotmann and Breer 2011). Pericytes are present in the olfactory bulb and play roles in the maintenance of the blood-brain barrier, as well as regulation of the blood pressure and inflammatory responses (Brown et al. 2019).

ACE2 expression in the olfactory pathway is still controversial (Bilinska et al. 2020; Brann et al. 2020; Chen et al. 2020b; Natoli et al. 2020; Ueha et al. 2020; Wu et al. 2020). However, considering the high expression of ACE2 in nonneuronal cells of the olfactory epithelium and the olfactory bulb, it can be hypothesized that the infection of
these nonneuronal cells initiates an inflammatory response that affects the function of the olfactory neurons. From a different point of view, the direct damage of nonneuronal cells by the virus influences the function of the neuronal cells by impairing water and ions balance or compromising the initial levels of the odor perception mechanism. It finally leads to anosmia or hyposmia (Brann et al. 2020). Nevertheless, it has been reported that mice lacking proteins essential for the virus entry are still vulnerable to olfactory bulb infection (Brann et al. 2020; Youngentob et al. 2001).

Anosmia and olfaction complications have been associated with some viral infections. While in viral infections, anosmia occurs with congestion or inflammation and manifestations like rhinosinusitis and coryzal symptoms, the inflammation in the olfactory epithelium is not reported in COVID-19 cases with anosmia (Lechien et al. 2020). Considering studies about the olfactory transmission of neurotrophic viruses (Mori et al. 2005; van Riel et al. 2015) and several case reports and observational studies representing neurological manifestations in patients with COVID-19, a probable neurotropism tendency for COVID-19 can be proposed. This hypothesis is strengthened by evidence on the neurotropism of other coronaviruses (Arabi et al. 2015 2017; Burks et al. 1980; Desforges et al. 2013; Hung et al. 2003; Kim et al. 2017; Morfopoulou et al. 2016; Tanaka et al. 1976; Yeh et al. 2004). Regardless of the lack of high ACE2 expression in the blood vessels (Harmer et al. 2002; Li et al. 2020a), the CNS involvement through damage to the blood vessels and endothelial cells has been proposed as potential pathogenesis of COVID-19–associated anosmia (Sharifi-Razavi et al. 2020).

Table 1 compares coronaviruses known to involve the nervous system in terms of findings derived from animal models, human investigations, and virus detection in the CSF.

## CNS involvement in the presence and absence of SARS-CoV-2 in the CSF

Considering the presumed involvement of the CNS by SARS-CoV-2, there would be a possibility that the respiratory failure in patients with COVID-19 might be due to the infection of the brain stem and the resident cardiorespiratory centers (Li et al. 2020c). Therefore, the neurological manifestations caused by direct or indirect COVID-19 CNS infection need urgent attention. Several reports and surveys on neurologic aspects of COVID-19 infection are available. Mao et al. (2020) collected the data of 214 patients with confirmed COVID-19 from three designated special care centers for COVID-19 in Wuhan, China. They calculated the prevalence of neurological manifestations and reported that patients with severe COVID-19 infection represent more neurological manifestations such as cerebrovascular diseases, impaired consciousness, and skeletal muscular injury. According to this study, the prevalence of anosmia and ageusia was 5.1 and 5.6%, respectively. There are more case reports that propose the CNS involvement in COVID-19 infection (Farhadian et al. 2020; Filatov et al. 2020; Moriguchi et al. 2020; Poyiadji et al. 2020; Sharifi-Razavi et al. 2020; Ye et al. 2020; Zanin et al. 2020; Zhou et al. 2020) due to various nervous system manifestations such as intracerebral hemorrhage, encephalopathies, demyelination, meningitis, and encephalitis.

A report of five patients with Guillain-Barre syndrome related to COVID-19 (Toscano et al. 2020) further supports the possibility of CNS involvement by SARS-CoV-2 (Gregory et al. 2005). However, the reverse transcription-polymerase chain reaction (RT-PCR) on all five patients’ CSF sample was negative. Also, there was no positive result for RT-PCR on CSF samples from seven patients with confirmed COVID-19 and neurological manifestations, as reported by Helms et al. (Helms et al. 2020). In addition to the mentioned reports, two cases of COVID-19 meningitis and encephalitis had a negative CSF SARS-CoV-2 test. However, the authors declared that the negative result could be due to transient or low viral load in the CNS or lack of testing availability (Ye et al. 2020). Finally, an autopsy study described hyperemia, edema, and neurodegeneration in the brain tissues from patients with COVID-19 (Mao et al. 2020). Most of the CSF samples, however, tested negative for COVID-19 RNA.

On the contrary, Moriguchi et al. (Moriguchi et al. 2020) reported a case of COVID-19–associated encephalitis, who had a positive CSF SARS-CoV-2 result. Consistent with this, there are numerous reports of the detection of viral RNA in brain tissues and CSF samples from patients infected with other human coronaviruses who had neurological manifestations (Arabi et al. 2015; Desforges et al. 2013; Gu et al. 2005; Hung et al. 2003).

There is a possibility that SARS-CoV-2 might conceal in the nervous system. Li et al. (Li et al. 2020c) have suggested this possibility to SARS-CoV-2 due to the evidence on other members of the Coronaviridae family. Of note, a survey in 2005 revealed the presence of the SARS-CoV-2 in the brain.
Table 1: Coronaviruses known to involve the nervous system in terms of findings derived from animal models, human investigations, and virus detection in the cerebrospinal fluid (CSF).

<table>
<thead>
<tr>
<th>Coronavirus (CoV)</th>
<th>Animal model</th>
<th>Human neurological manifestations</th>
<th>Virus detection in the human nervous system</th>
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<tr>
<td>SARS-CoV-1</td>
<td>The virus intranasally inoculated caused no significant infiltration of inflammatory cells in tissues, neuronal damage, and neuronal death (Netland et al. 2008).</td>
<td>Reports of GBS (Tsai et al. 2004) Reports of ischemic stroke (Tsai et al. 2005)</td>
<td>Viral RNA in all the brain tissue samples obtained at autopsy (Gu et al. 2005; Xu et al. 2005) and CSF of a patient with seizure (Lau et al. 2004).</td>
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<tr>
<td>MERS-CoV</td>
<td>The virus intranasally inoculated caused lymphocytic perivascular cuffing and neuronal degeneration (Li et al. 2016).</td>
<td>An observational study of 70 patients revealed confusion (26%), headache (13%), and seizure (9%) as the most frequent neurological symptoms (Saad et al. 2014). Case series of acute disseminating encephalomyelitis, widespread ischemic infarct, and encephalitis (Arabi et al. 2015). Case series of neuromuscular involvement, GBS, and a report of Bickerstaff encephalitis (Kim et al. 2017).</td>
<td>No virus detection.</td>
</tr>
<tr>
<td>Mouse hepatitis virus</td>
<td>The virus could inoculate the nervous system via both hematogenous and intranasal routes (Salimi and Klein 2019; Schwob et al. 2001) and caused fatal encephalomyelitis demyelinating disorders (Schwob et al. 2001).</td>
<td>Observational studies from France and China reported that neurological manifestations ranging from confusion to encephalopathy and corticospinal tract signs (Helms et al. 2020) are common in patients with SARS-CoV-2 infection and correlate to a spectrum of severity (Mao et al. 2020). An observational study about the onset of acute cerebrovascular disease revealed that 10 (of 219) patients experienced an acute ischemic stroke and one patient developed intracerebral hemorrhage (Li et al. 2020b) Report of five cases aged younger than 50 years with large-vessel stroke (Oxley et al. 2020). Case reports of meningoencephalitis (Moriguchi et al. 2020), acute necrotizing hemorrhagic encephalopathy (Poyiadji et al. 2020), GBS (Sedaghat and Karimi 2020; Toscano et al. 2020), Miller Fisher syndrome, polyneuritis cranialis related to this infection (Gutiérrez-Ortiz et al. 2020), one patient with encephalopathy (Farhadian et al. 2020), one patient with encephalitis (Ye et al. 2020), and even from one patient who developed demyelinating lesions (Zanin et al. 2020).</td>
<td>Studies found no virus in the CSF samples (Helms et al. 2020) obtained from patients with SARS-CoV-2 infection including five patients with GBS (Toscano et al. 2020), two patients with Miller Fisher syndrome and polyneuritis cranialis related to this infection (Gutiérrez-Ortiz et al. 2020), one patient with encephalopathy (Farhadian et al. 2020), one patient with encephalitis (Ye et al. 2020), and even from one patient who developed demyelinating lesions (Zanin et al. 2020). There has been a case report of meningoencephalitis with the CSF sample tested positive for viral RNA (Moriguchi et al. 2020).</td>
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<tr>
<td>SARS-CoV-2</td>
<td>The virus could replicate in the brain and the olfactory bulb of animals; however, the study failed to detect the virus in the brain and olfactory bulb of these hamsters (Imai et al. 2020).</td>
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tissues from all patients with confirmed SRAS infection and recorded autopsies. It is further strengthened by a report from a German patient with COVID-19 who transmitted infection to his colleagues when he was in the period of convalescence (Chen et al. 2020a; Rothe et al. 2020).

**Table 1**: (continued)

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<td>cranialis (Gutiérrez-Ortiz et al. 2020), intracerebral hemorrhage (Sharifi-Razavi et al. 2020), encephalopathy (Farhadian et al. 2020), and encephalitis (Ye et al. 2020). There has been a report of a case who developed demyelinating lesions in the brain and spine. The patient initially required admission due to pneumonia and seizure (Zanin et al. 2020).</td>
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CSF, cerebrospinal fluid; GBS, Guillain-Barre syndrome; MS, multiple sclerosis; N/A, not applicable; HCoV-OC43, human coronavirus OC43; SARS-CoV-1, severe acute respiratory syndrome coronavirus-1; MERS-CoV, middle east respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

**From anosmia to the immunopathogenesis of COVID-19 and vice versa**

Despite the previous opinion of the CNS as an immune-privileged area, the CNS is an immunocompetent area, reflecting that it is in dynamic interaction with the immune system (Louveau et al. 2015). The antiviral immune responses induced by specific anatomical regions, such as meninges, choroid plexus, CNS parenchyma, and the olfactory epithelium, are in charge of protecting the CNS. The type I interferon (INF) signaling pathway critically contributes to antiviral immune response (Saghazadeh and Rezaei 2020a), including those related to the CNS. INF-1 release occurs upon recognition of viral nucleic acid by pattern recognition receptors (PRRs), especially Toll-like receptors (TLRs), present on the innate immune cells, such as macrophage, microglia, dendritic cells, and astrocytes. IFN response inhibits the virus propagation by upregulating antiviral proteins, recruiting peripheral immune cells, and decreasing the BBB permeability (Manglani and McGavern 2018). Cupovic et al. (Cupovic et al. 2016) have investigated the role of meninges-induced immunity in coronavirus infection. They have reported that fibroblastic reticular cells and vascular endothelial cells produce CCR7 ligands, CCL19, and CCL21 leading to the reactivation of the CD8+ T cells, cytotoxic T cells that substantially contribute to the clearance of virus-infected cells.

OECs function to support OSNs. These glial cells have the phagocytic ability and can induce the secretion of INF-1 upon the recognition of bacterial pathogen-associated molecular patterns (PAMPs) by TLR2 and TLR4 (Nazareth et al. 2015; Panni et al. 2013). However, their response to viral infections is not clear. The OECs are potential candidates to be involved in viral immune responses, though the olfactory epithelium (OE) benefits another mechanism in fighting viruses. The OSNs are renewable neurons that can induce apoptosis in themselves in case of viral infections to inhibit the propagation of the virus to the CNS and thereby to attenuate the degree of damage (Mori et al. 2002). Such a defense mechanism can cause temporary or permanent anosmia or hyposmia.

To support this hypothesis, Sepahi et al. (2019) studied on crypt neurons (specialized OSNs present in fish). They proposed that the interaction between G protein of the virus (infectious hematopoietic necrosis virus) and the tropomyosin-related kinase A receptor of the mammalian nervous system makes crypt neurons to initiate an immune response that acts in two different ways. It triggers an ultrarapid proinflammatory response in the olfactory organ and, on the other hand, would suppress inflammation in the olfactory bulb. Hence, as crypt neurons substantially resemble OSNs, the olfactory immune response in humans and other vertebrates can be related to OSNs.

Another defense mechanism of the OE against viral infections lies in the nasal-associated lymphoid tissue (NALT) located to the nasal cavity and is involved in
immune responses (Pabst 2015). There are various antigen-presenting cells (APCs) in the NALT that initiate the immune response by representing the exogenous antigens to the T cells. Upon pathogen recognition, the CD8+ T resident memory cells localized in the surrounding tissues, such as OE, initiate a defense mechanism in response to the reexposure with a heterologous strain of the initial virus and hence restrict the infection from expansion to the lower respiratory airways (Pizzolla et al. 2017).

Conclusion

COVID-19 has continued human-to-human transmission regardless of the triad of knowledge (both professional and nonprofessional) (Moazzami et al. 2020), biological factors (both men and women), and the physiological condition (Mirbeyk and Rezaei 2020; Saghazadeh and Rezaei 2020a). In such critical time, it is not satisfactory to remember the previous pandemics (Jabbari et al. 2020), though none of the lessons learned could be satisfactory, revealing with the COVID-19 pandemic the limitation of national strategies and the need for reliable research and international collaboration (Kafeh et al. 2020; Mohamed et al. 2020a; Mottazmanesh et al. 2020; Moradian et al. 2020; Rzymski et al. 2020). After the six-month effort, there is a lack of specific treatment and vaccine, though numerous efforts have taken place to find potential therapeutic and preventive options (Moazzami et al. 2020; Rabiee et al. 2020; Yazdanpanah et al. 2020) from repurposing drugs (Mohamed et al. 2020b) and the design and manufacturing of antibodies (Jahanshahlu and Rezaei 2020b) to the development of cell-based therapies (Basiri et al. 2020). It is, therefore, mandatory to promote understanding of the pathogenesis of the disease. Anosmia might be a critical factor in the management of patients with COVID-19. As discussed earlier, patients who have anosmia experience a mild to moderate disease, and this might be due to the ultrarapid initial immune response of the olfactory epithelium that prevents the spread of the virus to the lungs. Also, it might be possible to use the olfactory tissue to detect COVID-19 and diagnose patients at the primary stages of the disease (Butowt and Bilinska 2020). Earlier diagnosis helps to recognize asymptomatic patients and patients with mild to moderate symptoms and consider them for self-isolation before they progress to severe or critical condition. In this manner, we might be able to slow down the spread of the virus and help to cease the pandemic. Another critical issue in this field is the recovery period and the prognosis of patients with anosmia. The complete or partial recovery from postviral anosmia is reported about two weeks to several months, depending on the mechanism of the anosmia (conductive olfactory dysfunction or sensorineural dysfunction) (Gane et al. 2020; Hummel et al. 2017). Nevertheless, there is a case of SARS-CoV-2-associated anosmia that was persistent for two years (Hwang 2006). There are a lot of unanswered questions in COVID-19–related anosmia, and its potential complications require further investigations.

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References


case of meningitis/encephalitis associated with SARS-CoV-2. 


