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Could SARS-CoV-2 Infection Be a Novel Risk Factor for Multiple Sclerosis?

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Abstract
The outbreak of the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has challenged the healthcare community worldwide. The SARS-CoV-2 primarily affects the respiratory system; however, strong evidence suggests that SARS-CoV-2 can be neuroinvasive, resulting in several neurological complications. It was previously assumed that some coronaviruses are involved in multiple sclerosis (MS) pathology via various mechanisms. The mechanisms involved in coronavirus-induced central demyelination are complex and largely redundant. Molecular mimicry was proposed to be one of the possible mechanisms. Disruption of the blood-brain barrier, dysregulation in several inflammatory cytokines, and upregulation of matrix metalloproteinases were also thought to induce central demyelinating pathology. This raises a question about the possible role of SARS-CoV-2 as a novel risk factor for MS.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a new coronavirus that was not known to humankind before, causing a life-threatening disease known as coronavirus disease-2019 (COVID-19) [1]. The etiology of multiple sclerosis (MS) remains a mystery, despite ongoing research to uncover the cause of the disease for more than a hundred years. Both environmental and genetic factors play a role in the pathophysiology of MS [2]. It has previously been assumed that some coronaviruses are involved in MS pathology through various mechanisms, including molecular mimicry between coronaviruses and myelin, disruption of the blood-brain barrier (BBB), regulation of matrix metalloproteinases (MMP), and increased production of inflammatory cytokines [3, 4].

Accordingly, does this emerging virus have a role in initiating the immunopathogenic events in MS? To prove this hypothesis or not, we must first identify the common features between SARS-CoV-2 and other coronaviruses; second, explore the pathogenic mechanisms of MS caused by some ancient coronavirus described earlier; and third, can these mechanisms be applied to the emerging SARS-CoV-2?

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SARS-CoV-2 versus Other Coronaviruses: Differences and Similarities

Coronaviruses are enveloped, crown-like viruses with a long single-stranded RNA genome. Seven coronaviruses are known to infect humans, namely, human coronavirus (HCoV)-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1), Middle East respiratory syndrome (MERS-CoV), and SARS-CoV-2 [1]. Among this family, the virus most structurally similar to SARS-CoV-2 is SARS-CoV-1. About 79.6% of the sequence identity was shared between SARS-CoV-1 and SARS-CoV-2 [5]. Some human coronaviruses are known to have a neuroinvasive potential: HCoV-229E, OC43, MERS-CoV, SARS-CoV-1, and SARS-CoV-2 with variable degrees of neurotropism between them [6].

Coronavirus entry into host cells begins by binding the spike protein (S) to cellular receptors. SARS-CoV-2 resembles SARS-CoV-1 in the cellular receptors that bind to the S protein, specifically, angiotensin-converting enzyme 2 (ACE2), which differs from other coronaviruses [6]. In humans, ACE2 was abundantly expressed in many neurons, astrocytes, and oligodendrocytes in the middle temporal gyrus, posterior cingulate cortex, pons, medulla oblongata, striatum, and hypothalamus [7]. This may explain the neurotropism of SARS-CoV-1 and SARS-CoV-2 [8]. However, it was found that the S protein of SARS-CoV-2 has a higher affinity for ACE2 than that of SARS-CoV-1 using high-resolution cryo-electron microscopy [9]. This may indicate the higher neurotropism of SARS-CoV-2 compared with SARS-CoV-1.

Proposed Mechanisms of How SARS-CoV-2 May Initiate Immunopathogenic Pathway of MS

SARS-CoV-2-mediated neuroinvasion may occur through several routes, either through axonal transport via the olfactory nerve and olfactory bulb, blood-borne transport, infection via vascular endothelium, or disruption of BBB. Evidence is mounting that SARS-CoV-2 may affect the gray and white matter of the brain, causing edema, demyelination, and neuronal degeneration [10].

The association between MS and other coronaviruses was previously studied. First, titers of HCoV-229E and OC43-specific antibodies were higher in the cerebrospinal fluid (CSF) in MS patients compared to controls [11]. Second, coronavirus RNA was detected in the brain samples of MS patients [12]. The following mechanisms are proposed of how SARS-CoV-2 may initiate the immunopathogenic pathway of MS.

BBB Disruption and Cytokines Storm

In systemic infections such as those caused by SARS-CoV-2, BBB can be subject to disruptive or non-disruptive pathology. The disruptive pathology involves loss of tight junctions' integrity, apoptosis of endothelial cells, and astrocyte damage. The non-disruptive pathology develops through cellular and molecular mechanisms that increase the permeability of BBB [13]. Increased permeability of the BBB allows pathological agents such as viral particles to enter the CNS, which may trigger disruption of end feet and astroglial death, creating a vicious cycle of further damage to the BBB [14]. T lymphocytes migrate into the CNS through the disrupted BBB and initiate cellular events leading to inflammation and demyelination in the white matter [15].

Strong evidence suggested dysregulation of several inflammatory cytokines in patients with COVID-19 infection. These cytokines include IL-1β, IL-2, IL-6, IL-10, IFN-γ, granulocyte colony-stimulating factor, granulocyte-monocyte colony-stimulating factor, and tumor necrosis factor-α (TNF-α) [16]. Such dysregulated cytokines may escalate vascular and BBB permeability and consequently exacerbate neuroinflammation in MS [17].

T-helper cell 17 (Th17)-mediated cytokine storm, which has a pivotal role in the pathogenesis of MS, was also evident in patients with COVID-19 infection [18]. Th17 cells contribute to the disruption of the BBB, and in cooperation with Th1, regulate the functions of astrocytes by downregulating neurotrophic factors and the upregulating inflammatory cytokines [19, 20]. Th17 cells also inhibit oligodendrocyte maturation and survival [21].

In acute MS lesions, MMP-9 predominates, whereas MMP-2 predominates in chronic MS [22]. Interestingly, in vitro infection of human astrocytic and microglial cell lines with HCoV-OC43 resulted in upregulation of MMP-2 and -9, suggesting a crucial role for coronavirus infection in upregulating MMP expression within the CNS. The mechanisms by which MMPs were upregulated were unknown. However, they were most likely thought to be upregulated by some inflammatory cytokines such as tumor necrosis factor-α and IL-6 [23]. Similarly, damage to the CNS by SARS-CoV-2 may be mediated by MMPs, primarily through the upregulation of MMP-9 [24, 25].

Strong evidence suggests that sustained activation of the nuclear factor kappa-light-chain enhancer of activat-

ed B cells (NF-κB) pathways is observed in MS. NF-κB is a transcription factor that promotes gene expression of many cytokines in inflammatory states and viral infection. NF-κB is reported to be elevated in a dose-dependent matter in response to coronaviruses [26].

Molecular Mimicry

Molecular mimicry had been proposed to explain how a viral infection could initiate the immunopathogenic pathway leading to an autoimmune disease in genetically susceptible individuals. Sequences shared between coronavirus and myelin proteins, such as myelin basic protein (MBP) and proteolipid protein (PLP), have been identified [4]. Boucher et al. [27] identified coronavirus-myelin cross-reactive T-cell clone (TCC) in MS patients, involving two major myelin antigens (MBP and PLP) and two HCoV serotypes (HCoV-229E and OC43). Sharing genomic sequences between these serotypes and SARS-CoV-2 [28] may suggest that the SARS-CoV-2 may play the same action.

It should be noted that the lack of data indicating that the SARS-CoV-1 may trigger MS, the virus that has the most similarity with the SARS-CoV-2, should not disappoint our hypothesis that SARS-CoV-2 may trigger MS. First, to the best of our knowledge, no studies have embraced the idea of whether or not the SARS-CoV-1 might cause MS. Secondly, The SARS-CoV-1 outbreak was on a smaller scale compared to SARS-CoV-2. In addition, the outbreak of SARS-CoV-1 was mainly in countries whose populations do not have a high genetic predisposition for MS [29].

To our knowledge, 2 cases of clinically isolated syndrome were reported after SARS-CoV-2 infection. The viral genome of SARS-CoV-2 was detected in the CSF of the second case [30, 31]. We hope that this article will encourage a large, multicenter study of whether SARS-CoV-2 infection may provoke a first demyelinating attack in genetically susceptible patients.

Conclusion

Taken together, all these proposed mechanisms strengthen the hypothesis that the SARS-CoV-2 may be a novel risk factor for MS, leaving the question to be answered by future studies.

Conflict of Interest Statement

The authors have nothing to disclose.

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Author Contributions

R.M. and M.H. participated in writing and collection of scientific material, helped in drafting the manuscript, and read and approved the final manuscript.

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