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Environmental pollutant exposure can exacerbate COVID-19 neurologic symptoms

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A B S T R A C T

Neurologic symptoms have been reported in some COVID-19 patients. However, little is known on what factors influence the risk of developing these symptoms. While some studies suggest that exposure to pollution is associated with higher rates of SARS-CoV-2 infection, its role is unknown in the development of neurologic symptoms in COVID-19 patients. The response of the central nervous system (CNS) to a SARS-CoV-2 infection may be influenced by its inflammatory state. Interestingly, environmental pollutants such as particulate matter may have neuroinflammatory effects, providing a possible link between exposure to these pollutants and the outcome of SARS-CoV-2 infection in the CNS. This article explores the hypothesis that the neurologic symptoms in COVID-19 may be exacerbated through a neuroinflammatory mechanism that is promoted by environmental pollutant exposure.

Introduction

The coronavirus disease 2019 (COVID-19) caused by the newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a serious global health problem [1]. Clinical characteristics of the disease may range from asymptomatic to non-severe and severe, with compromised respiratory status as a driver of disease severity [2]. Majority of infected individuals experience fever and cough, while fatigue, dyspnea, and sore throat, were also reported in many patients [3].

SARS-CoV-2 primarily infects the respiratory system causing pneumonia; however, the virus may also have other organ targets in the body. Neurologic symptoms related to both central (CNS) and peripheral nervous system (PNS) impairments were reported among COVID-19 patients, suggesting that SARS-COV-2 infection may target the nervous system [4]. However, the factors influencing the development of neurologic symptoms among COVID-19 patients are poorly understood.

Reports have indicated that the stringent lockdown measures imposed to control the spread of COVID-19 has resulted to a decrease in environmental pollution [5,6], but how pollution may affect COVID-19 pathogenesis remains unknown. Some studies suggest that components of air pollution, such as particulate matter, may be associated with higher rates of COVID-19 infection [7,8]. However, it's not currently known whether pollutants such as particulate matter might also affect the development of neurologic symptoms in COVID-19.

The hypothesis

The neuroinflammatory state of the CNS may play a role in its response against an infecting agent. In particular, a stronger inflammatory response may lead to worse symptoms. Given that particulate matter may cause detrimental effects on the brain through chronic inflammation, it could be hypothesized that exposure to these pollutants may potentially increase the vulnerability of developing more severe CNS-associated neurologic symptoms in COVID-19 by promoting a stronger neuroinflammatory state when SARS-CoV-2 infects the brain.

Evaluation of the hypothesis

SARS-CoV-2 infection in the CNS may cause neuroinflammation

Common CNS-related symptoms reported in COVID-19 patients were dizziness and headache, while a lesser fraction of patients has also been reported to have impaired consciousness, encephalopathy, acute cerebrovascular disease, ataxia, and seizures [4,9–11]. Reports have also presented cases of COVID-19 with meningitis or encephalitis [12–14]. On the other hand, PNS-related neurologic symptoms such as anosmia and ageusia [4,15], and cases of Guillain-Barré syndrome were also reported [16,17].

Neuroinvasion by coronaviruses is not uncommon. Previous evidences show that infection of the CNS, which results to neurologic symptoms, is possible in Severe Acute Respiratory Syndrome (SARS)

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caused by SARS-CoV and Middle East Respiratory Syndrome (MERS) caused by MERS-CoV [18,19]. With the CNS-related symptoms observed among some COVID-19 patients and the high degree of similarity with SARS-CoV, it is very likely that SARS-CoV-2 may reach the brain as well. Cerebrospinal fluid (CSF) samples from COVID-19 patients presenting with meningitis or encephalitis were found to be positive of SARS-CoV-2 RNA [12,20]. Although it was not determined whether the isolated RNA was still complete and intact, this may suggest the potential of SARS-CoV-2 to reach the CNS. Indeed, postmortem examination of a COVID-19 patient detected viral particles in endothelial and neural cells through transmission electron microscopy (TEM) of brain tissue, which was confirmed to be positive of SARS-CoV-2 RNA through RT-PCR analysis [21].

Two main mechanisms have been proposed to explain how SARS-CoV-2 may reach the CNS [19,22,23]. SARS-CoV-2 in the general circulation may eventually enter the cerebrovascular circulation by crossing through the capillary endothelium. This may be possible through ACE2 receptors expressed in endothelial cells, which SARS-CoV-2 uses to enter [24]. Another way is through a neural path which occurs intranasally through the olfactory bulb via a trans-synaptic route, a mechanism that may be supported by the observed anosmia among some patients. Once it reaches the CNS through either mechanism, it may infect cells in the brain. Neurons and glial cells in the brain were found to express ACE2 receptors, making them possible targets [19,22]. Thus, SARS-CoV-2 could potentially cause direct damage to infected cells in the CNS.

Microglia plays a role to protect the CNS from infections. These immune cells respond by promoting clearance of the infecting agent through the production of cytokines, chemokines, and other signals, which induces a proinflammatory environment in the CNS [25]. This was demonstrated through an *in vitro* experiment that showed infection of glial cells with a neurovirulent strain of coronavirus induced the mRNA expression of the following proinflammatory cytokines: tumor necrosis factor α (TNFα), interleukin-12 (IL-12) p40, interleukin-6 (IL-6), interleukin-15 (IL-15), and interleukin-1β (IL-1β) [26]. Analysis of plasma from COVID-19 patients revealed increased levels of many proinflammatory cytokines, including TNFα, IL-6, and IL-1β [27]. Although this evidence was neither based on direct production by cells from the CNS nor sampled from CSF, it nevertheless implied that SARS-CoV-2 may induce a proinflammatory environment. Taken together with the evidence that SARS-CoV-2 may reach the CNS, this suggests that SARS-CoV-2 may promote neuroinflammation.

However, the degree of neuroinflammation in the brain may result to either beneficial or harmful effects. Healthy levels of neuroinflammation may promote immune surveillance, tissue remodeling, or enhanced cognitive functions, whereas higher degrees of inflammation may lead to a diseased state [28]. Thus, a stronger inflammatory response may lead to a more pathologic outcome. Interestingly, exogenous factors such as pollutants may induce neuroinflammation, providing a possible mechanism through which exposure to environmental pollutants may worsen the pathology of SARS-CoV-2 infection in the CNS.

Environmental pollutants promote neuroinflammation

Particulate matter (PM) are airborne particles composed of a mix of both solids and liquids of varying chemical composition and sizes that come from the erosion of road, resuspension of soil and dust, wear and tear of tires, formation of agricultural dust, construction works, mining operations, and combustion [29]. The constituents of PM may be nitrates, sulfates, carbons, ammonium, organic compounds such as polycyclic aromatic hydrocarbons (PAH), and metals such as copper, nickel, iron, cadmium, and zinc. In addition, biological components such as endotoxins and cell fragments may also be found. Particulate matter may be classified according to size: coarse PM_{10} (< 10 μm), fine $PM_{2.5}$ (< 2.5 μm), or ultrafine $PM_{0.1}$ (< 0.1 μm). Because these particles are small, they can easily penetrate deep into the respiratory tract and eventually escape into the bloodstream and cause disease [29].

More known as a risk factor for the development of cardiovascular and respiratory diseases, exposure to PM is also now being recognized as a risk factor for neurologic disorders [30]. Indeed, several studies have shown that exposure to PM increases risk of development of neurodegenerative diseases [31]. Through the physical characteristics of the particle itself or the compounds adsorbed to it, PM may cause direct effects when it reaches the CNS environment via two recognized routes [30,31]. One route is intranasally by passing through the olfactory bulb to reach the brain, while another way is through inhaled particles escaping from the respiratory tract to the bloodstream and eventually crossing the blood-brain barrier [32].

Particulate matter may have different physical and chemical characteristics but they share a common mechanism of inducing inflammation that may cause disease. These PM are known to induce a proinflammatory environment in the brain that links them as a risk factor for neurodegenerative diseases. *In vitro*, microglia exposed to concentrated ambient particulate matter had increased mRNA expression of the proinflammatory cytokines IL-6 and TNFα [33]. This suggests that the CNS may respond to PM exposure by activating microglia which creates an inflammatory environment. *In vivo*, brain of mice experimentally exposed to $PM_{2.5}$ and $PM_{0.1}$ of mixed chemical composition had enhanced expression of NFκβ and increased protein levels of TNFα and interleukin-1α (IL-1α) [34]. In another study, brains of rats exposed to diesel exhaust had increased expression of the microglial marker ionized calcium-binding adaptor molecule 1 (IBA-1), suggesting increased number of microglia, and increased levels of the following proteins involved in inflammation: TNFα, IL-1β, IL-6, macrophage inflammatory protein-1α (MIP-1α), and receptor for advanced glycation end products (RAGE) [35]. In children and young adults with long-term exposure to air pollution, brain autopsy revealed increased mRNA levels of IL-1β, cyclooxygenase-2 (COX_2), and CD14 [36,37], while another study that collected CSF detected elevated protein levels of macrophage migration inhibitory factor (MIF), IL-6, and IL-2 [38]. These are some evidences showing exposure to PM may create a proinflammatory environment in the CNS.

Microplastics is also another environmental pollutant of growing health concern. These plastic particles, which are defined to be those that measure less than 5 mm in size, could pose a big health risk because of the ability of very small particles to easily enter the human body [39]. Recent reports have found that these microplastics may also be airborne, making the potential for human exposure greater [40]. Because these plastic particles are very small and may be airborne, it could possibly reach the CNS through routes similar with other particulate matter. While research on the possible toxic effects of microplastics to humans is still limited, evidences suggest that it may also induce inflammation. For instance, treatment of mice with polyethylene microplastics increased serum levels of IL-1α [41]. On the other hand, an *in vitro* study has shown that microglia may internalize carboxylated polystyrene microplastics [42], suggesting that microplastics could possibly induce neuroinflammation as well.

Given that particulate matter may have inflammatory effects on the brain and that neuroinflammation may play a role in the outcome of CNS infections, a possible link between environmental pollutants and SARS-CoV-2 infection in the CNS can then be established. This leads to the hypothesis that exposure to environmental pollutants may increase the susceptibility of COVID-19 patients to develop more severe neurologic symptoms by promoting a stronger neuroinflammatory response when SARS-CoV-2 infects the CNS.

Exposure to environmental pollutants may aggravate neurologic symptoms in COVID-19 through neuroinflammation

Neuroinflammatory responses are mediated by proinflammatory

cytokines, such as TNFα, IL-6, and IL-1β, produced by the cells in the CNS. As described in the previous sections, exposure to particulate matter could promote neuroinflammation through the release of such proinflammatory cytokines, and on the other hand, SARS-CoV-2 infection may also promote inflammation by induction of the same proinflammatory signals. Thus, given that both exposure to environmental pollutants and SARS-CoV-2 infection may induce neuroinflammation through the release of similar proinflammatory signals, the two may have an additive effect on the inflammatory state of the CNS. This could then result to an increased risk of developing a stronger neuroinflammatory response when SARS-CoV-2 infects a CNS that has already been primed by exposure to particulate matter.

Whether neuroinflammation will bring positive or negative effects to the CNS, it will depend on the degree of inflammation which may be influenced by intensity and duration. In general, low to moderate levels of inflammation occurring briefly may have beneficial effects, while moderate to severe levels of inflammation occurring chronically may have harmful effects [28]. In response to stress, injury, or infection, proinflammatory cytokines released by glial cells may activate more immune cells promoting immunosurveillance. Immune preconditioning may also occur in which low-level stimulation of immune cells may protect from a hyperinflammatory response [43]. However, when there is a significantly high level of proinflammatory cytokines, immunopathology may happen. Uncontrolled inflammation is known to cause damage in the CNS through neuronal death, tissue damage, infiltration of peripheral immune cells, breakdown of the blood brain barrier, or vascular occlusion [28,44]. Thus, a stronger inflammatory response may lead to more severe symptoms.

The neurologic symptoms in some COVID-19 patients, such as dizziness and headache, may be caused by the neuroinflammatory response of the CNS to SARS-CoV-2 infection. However, if SARS-CoV-2 infects a CNS that has already been primed by exposure to particulate matter, then it may lead to a stronger inflammatory response. Thus, it could be speculated that if neuroinflammation due to particulate matter exposure is intensified by SARS-CoV-2 infection in the CNS, then it could possibly create a hyperinflammatory state that may damage the neurons or occlude the cerebrovascular circulation (Fig. 1). This may then lead to the more severe neuropathology in COVID-19 such as impaired consciousness, encephalitis, meningitis, or cerebrovascular disease. Conversely, it may also be possible that neuroinflammation due to exposure to particulate matter promotes immunosurveillance that enhances the clearance of the virus or preconditions the microglia that results to a less inflammatory environment upon SARS-CoV-2 infection. This may then result to protection from developing CNS-related symptoms. However, the overall negative effects of particulate matter on the brain may suggest that it is more plausible for it to have harmful effects rather than play a protective role in the development of neurologic symptoms in COVID-19.

Testing the hypothesis

Neurologic symptoms in COVID-19 are gaining more attention. As we know more about the prevalence of neurologic symptoms in COVID-19, it will be very interesting to see if there are any associations between levels of particulate matter and the occurrence of neurologic symptoms which could then give a starting point in proving the proposed hypothesis. *In vitro* studies may be performed to test the hypothesis. For instance, levels of proinflammatory cytokines, such as TNFα, IL-6, and IL-1β, can be measured in microglia exposed to particulate matter then infected with SARS-CoV-2 and compared with those infected with SARS-CoV-2 but not exposed to particulate matter. This will tell if particulate matter may increase the production of proinflammatory cytokines when SARS-CoV-2 infects microglia. *In vivo* experiments may also be done by measuring proinflammatory cytokines in CSF samples from mice or macaque monkeys exposed to particulate matter then infected with SARS-CoV-2 and compared with those infected with SARS-CoV-2 but not exposed to particulate matter. Brain magnetic resonance imaging (MRI) can be performed to observe for any signs of encephalitis, meningitis, or vascular occlusions. Postmortem histopathologic analysis may also aid in examining the extent of damage in the brain. These are some experiments that may be performed to test whether particulate matter may aggravate neurologic symptoms

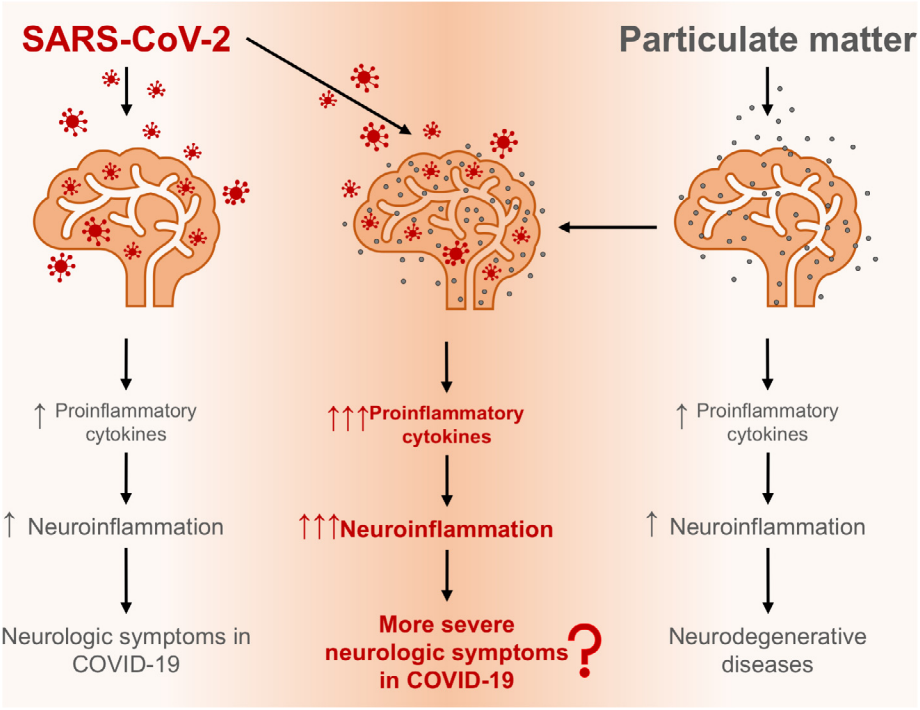

Fig. 1. Proposed hypothesis showing a stronger inflammatory response due to increased production of proinflammatory signals when SARS-CoV-2 infects a brain that has been primed by exposure to particulate matter. The increased inflammatory state may then result to more severe neurologic symptoms in COVID-19.

in COVID-19 by promoting neuroinflammation.

Consequences of the hypothesis

The numerous reports of COVID-19 cases with neurologic involvements indicate that it is a serious concern. Therefore, understanding the factors influencing the development of these neurologic symptoms will be of great value in controlling the pandemic. If the hypothesis was proven to be true, then it may help in identifying the risk of developing neurologic symptoms in COVID-19. It may also imply that regulations to reduce production of environmental wastes may help in the management of these neurologic symptoms. Nevertheless, whether particulate matter has any effects on neurologic symptoms in COVID-19, its known associations with the development of cardiovascular and respiratory problems, which are risk factors for the severity of SARS-CoV-2 infection, suggests that it may still play a role in this pandemic. Therefore, policies that regulate activities and products that create high amounts of harmful environmental wastes may help in our fight against COVID-19 and in promoting better health for all.

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Conflict of interest

The authors declare no conflicts of interest.

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