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EFFECT OF THE COVID-19 PANDEMIC ON NEUROINFLAMMATORY DISEASES

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ABSTRACT

In December of 2019, SARS-CoV-2 surfaced and the global COVID-19 pandemic began. The pandemic has had far-reaching effects, socially, economically, and especially for healthcare, presenting challenges to patients with neuroinflammatory disorders. Apart from the well-known respiratory, pulmonary, and cardiovascular symptoms that COVID-19 is responsible for, studies continue to show its role in generating neuroinflammation and the different neurological effects that can arise. This review summarizes the relationship between the COVID-19 pandemic and neuroinflammatory diseases, with an emphasis on the effects on patients with neuroinflammatory disorders.

KEYWORDS: *neuroinflammation, pandemic, SARS-CoV-2, COVID-19, immunity*

INTRODUCTION

In December of 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China in the city of Wuhan. The coronavirus disease (COVID-19) spread and quickly became a global pandemic (1). On January 30th, 2020, The World Health Organization proclaimed the COVID-19 outbreak as an International Public Health Emergency (2), and an official report stated that as of November 22, 2021, there have been approximately 250,000,000 confirmed cases and over 5,000,000 confirmed deaths (3).

SARS-CoV-2 can be asymptomatic or cause a range of symptoms, spanning from mild to severe, such as shortness of breath, dry cough, fatigue, fever, pneumonia, respiratory failure, and systemic inflammation (4). Older individuals and those with a weakened immune system and other comorbidities are more at risk for serious complications.

The pandemic has reshaped society and social habits, has had negative effects on the economy, and has presented great challenges in healthcare (5). COVID-19 can also be linked to neuroinflammation, and in this article, the effects of the pandemic are summarized with respect to neuroinflammatory diseases.

Neuroinflammatory diseases

The nervous system is comprised of two parts: the central nervous system (CNS) and the connective nerves of the peripheral nervous system. Neuroinflammation occurs in the CNS, affecting the brain, spinal cord, and optic nerves. When the CNS is damaged by an overly active immune response, neuroinflammatory diseases occur.

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The role of the immune system is to protect the body against injury and infection, which it performs by engaging in inflammatory challenges in response to harmful stimuli. But it may be over-reactive and attack healthy cells in response. Innate immune cells called microglia, which are central to immune surveillance, produce cytokines and chemokines and mediate the innate immune capacity of the CNS (6). In the situation of neuroinflammatory disorders, there is immune cell infiltration or glial cell activation, which can damage the CNS (7).

In many cases of neuroinflammatory diseases, inflammation may originate from another inflammatory response in the body. This chronic systemic inflammation may eventually pass through the blood-brain barrier (BBB) and enter the CNS, causing neuroinflammation by activating microglia and astrocytes. Neuroinflammatory disorders are variable, having different etiology and different pathogenic mechanisms, but they all result from this inflammation of the nervous system (8).

Multiple sclerosis (MS) is one of the better-known neuroinflammatory disorders. It is a demyelinating disease, meaning that the myelin sheath, which shelters nerve cells and axons, becomes damaged, and this results in neurological problems. Other CNS disorders that can be influenced by inflammation include neurodegenerative and even psychiatric disorders.

Some other neuroinflammatory disorders include:

- Alzheimer's disease
- Parkinson's disease
- amyotrophic Lateral Sclerosis
- acute disseminated encephalomyelitis (ADEM)
- Rasmussen's syndrome
- acute necrotizing encephalopathy
- opsoclonus-myoclonus ataxia syndrome (OMAS)
- autoimmune Encephalitis
- optic Neuritis
- transverse Myelitis
- neuromyelitis Optica (NMO)
- anti-myelin oligodendrocyte glycoprotein antibody disease (MOG)

Unfortunately, a cure for neuroinflammatory disorders is yet to be discovered. However, some treatment is available to reduce symptoms and disease severity.

Neuroinflammation and neurological diseases

Recent research continues to shed light on the role of neuroinflammation in neurodegenerative diseases that were not previously associated with inflammation, such as Alzheimer's disease or stroke. Due to this association, neuroinflammation needs to be focused on because it may be implicated in many pathologies and can enhance further research and treatment (9).

Upon immune system activation, inflammatory mediators are produced and can infiltrate the brain and create the CNS inflammatory response (10). Growing evidence continues to link the connections between immune cells and neurons, and the way in which neuroinflammation upsets the equilibrium of this homeostatic system (11).

Cytokine networks have been shown to vary between neuroinflammatory disorders and neurodegenerative diseases. Pro-inflammatory cytokine production may help distinguish neuroinflammatory disorders from neurodegenerative diseases; in the case of neuroinflammatory disorders, such as MS and encephalitis, leukocytes are usually responsible, whereas in neurodegenerative disease, CNS-resident cells are mainly responsible (12).

The effect of SARS-CoV-2 on neuroinflammation

Pulmonary and cardiovascular complications are well-recognized in COVID-19 patients, and now research is beginning to explore the neurological complications and effects, as patients continue to present neurological symptoms. It has been reported that neurological symptoms were present in 36.4% of patients with SARS-CoV-2 (13).

Neurologic symptoms can vary greatly and can include headache, anosmia, encephalopathy, encephalitis, stroke, hemorrhagic lesions, and neuronal impairment. A common symptom is impaired olfaction, the loss of smell, as the olfactory bulbs in the nasal cavity are affected (14). Neurological symptoms may also arise in response to microvascular injuries and thromboembolic events, which is supported by findings in autopsy tissue of cerebrospinal fluid and neuroimaging (15). Edema in the brain may result from SARS-CoV-2 neuroinflammation (16), and the acute autoimmune disorder, Guillain-Barré syndrome (GBS), has been linked to SARS-CoV-2 infection, especially amongst older patients (17).

Studies have shown that SARS-CoV-2 generates neuroinflammation. During infection with SARS-CoV-2 and lung invasion, there is an activated immunoinflammatory response with pro-inflammatory compounds being released and creating a "cytokine storm". These can cross the BBB, enter the CNS, and create neuroinflammation (18). With the activation of the immune system, cytokine, chemokine, and free radical levels are raised at the BBB, thus permitting the infiltration of inflammatory cells into CNS immune cells (19). The hyperinflammatory state induced by SARS-CoV-2 can also generate interleukins-2, 6, 7, and 10, TNF, and granulocyte colony-stimulating factor (20). COVID-19 can cause neuroinflammatory cascades and provoke the "cytokine storm", which can result in patient death (21).

Neuroinflammatory disorders and COVID-19 vaccination

SARS-CoV-2 vaccine hesitancy has surfaced amongst patients with neuroinflammatory diseases. This hesitancy arises from the exclusion of these patients in vaccine trials. Furthermore, such as in some cases of neurological diseases, hesitancy can also arise from the fear that immunotherapy may negatively affect the vaccine response. However, a study by Epstein et. al has shown that vaccine side effects do not differ between patients with neuroinflammatory disorders and the general public, and apart from a higher incidence of reported headaches, that their disorders did not degenerate after vaccination (22).

This supports the safety of SARS-CoV-2 vaccines for patients with neuroinflammatory diseases, although further research is still needed. The benefits of the protection provided by the vaccine are likely to outweigh the risks for persons with neuroinflammatory disorders.

Immunotherapies during COVID-19

Patients with neuroinflammatory disorders are often on immunosuppressive therapies, and this may, unfortunately, be a risk for infections, including SARS-CoV-2, and their resulting complications. Immunosuppressive treatment often includes the use of drugs such as methotrexate, mitoxantrone, azathioprine, cortisone, and cyclophosphamide, which may be linked with higher SARS-CoV-2 infection rates. At the same time, the benefits of this therapy in treating the neuroinflammatory disorder may take precedence (23).

The weight of the pandemic

The COVID-19 pandemic has presented significant challenges to the healthcare sector, putting hospitals and staff under immense stress, and anxiety and depression were shown to be higher among patients suffering from pre-existing conditions during the pandemic (24).

Many challenges were also presented for patients suffering from neuroinflammatory disorders. These patients need routine care with clinical visits and ongoing monitoring, and certain conditions such as MS have higher incidences of hospitalization. This care was severely affected by the pandemic and subsequent lockdowns, and the required hospitalizations during the COVID-19 pandemic also put patients at a higher risk of direct exposure to SARS-CoV-2 in the hospital setting.

Reduced access to physicians and medical services, loneliness, and the anxiety and uncertainty resulting from the COVID-19 pandemic are some factors of psychological stress that can lead to problems for patients with neuroinflammatory disorders, causing anxiety and depression, and exacerbating the disease condition (25). In their article, *Manifestations, and impact of the COVID-19 pandemic in neuroinflammatory diseases*, Levin et al. presents the results of a year-long study that explored the effects of the COVID-19 pandemic on patients with neuroinflammatory disorders. It was shown that the social distancing practices implemented during the pandemic can limit the access to healthcare resources and home care for patients with neuroinflammatory diseases and that patients perceived a lowered level of social support (26). Another example is a study revealing that during the COVID-19 pandemic, people with MS suffered from post-traumatic stress disorder, anxiety and stress, depression, and insomnia (27).

CONCLUSIONS

Since December 2019, SARS-CoV-2 continues to spread and remains a global pandemic and a public health emergency. It has been shown to cause neuroinflammation and cause neurological symptoms ranging from mild to severe. An overly active immune response can cause the "cytokine storm", changing the balance between neurons and immune cells in the CNS and causing damage and death.

Patients with neuroinflammatory diseases are at a higher risk of suffering more severe complications. Psychologically, the pandemic has been challenging for these individuals, as healthcare access has been limited and social restrictions have created anxiety and isolation. There was fear of the uncertainties concerning vaccinations and potential complications of their condition from SARS-CoV-2.

There is a need for more research focusing on the potential implications of COVID-19 for patients with neuroinflammatory diseases. Studies must continue in order to build a more concise pathological basis for the neuroinflammatory effect of SARS-CoV-2.

Conflict of interest

The authors declare that they have no conflict of interest.

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