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Covid-19 Induced Neuroinflammation

Rajen Dey[1]*

[1]**Department of Medical Laboratory Technology, School of Allied Health Sciences, Swami Vivekananda University, Telinipara, Barasat-Barrackpore Rd, Bara Kanthalia, West Bengal - 700121, India.*

***Corresponding author:** Dr. Rajen Dey
*Department of Medical Laboratory Technology, School of Allied Health Sciences,Swami Vivekananda University, Telinipara, Barasat-Barrackpore Rd, Bara Kanthalia, West Bengal - 700121, India.
E-mail: rdrajen422@gmail.com*

Abstract

The respiratory illness COVID-19 started a global pandemic in 2019 and continued until 2020. Globally, the epidemic claimed the lives of around 480,000 persons and affected 9.5 million people. SARS-CoV-2 is the primary cause of this outbreak. SARS-CoV-2 is an RNA virus that is encapsulated and can infect multiple organs. It can enter the host through spike proteins. This epidemic had a serious impact on the brain as well. The recovered patients experienced neurological problems following COVID-19, neuropsychiatric symptoms, cognitive impairment, and difficulty concentrating. Nonetheless, the primary cause of all these clinical disorders or changes in psycho-behavioral patterns is consistently neuroinflammation. The neurological characteristics of COVID-19 patients and the neuroinflammatory effects of SARS-CoV-2 infection will be the main topics of this review. Studies have indicated that the brain inflammation caused by COVID-19 may be partly attributed to the overproduction of free radicals such as ROS and NO as well as the downregulation of antioxidant enzymes. Furthermore, cytokine storm, which is brought on by inflammatory cytokines like IL-1β, IFN-γ, and IL-6, may be the cause of major depressive disorder (MDD). Thus, it is clear from this analysis how critical it is to manage the harmful neuroinflammatory effects of SARS-CoV-2 infection, which ultimately result in the death of neurons and neurological impairment. Considering all the information, it is possible to conclude that controlling these inflammatory effects effectively may be a useful tactic for preserving normal brain function.

Keywords: Brain, COVID-19, Cytokine, Neuroinflammation, SARS-CoV-2

1. INTRODUCTION

Although COVID-19 is largely a respiratory illness, it has long-term negative consequences on important organs, including the brain, kidney, spleen, stomach, colon, and lungs [1]. Multiple organ failure and death were the eventual outcomes of those serious COVID-19 problems [2]. Over 500,000 individuals died and an

estimated 9.5 million people became sick worldwide [3]. The positive-stranded RNA virus known as SARS-CoV-2, or Corona virus, is enclosed. By using the entrance receptor angiotensin-converting enzyme 2 (ACE2), it may infiltrate the host through spike protein. The invasion of the host requires the co-expression of serine protease and cell surface ACE2 [4]. Pulmonary insufficiency, dry cough, nasal congestion, fever, dyspnea, exhaustion, and intestinal dysfunction are among the clinical signs of COVID-19 [5]. A growing body of research indicates that neurological and cognitive impairment could result after SARS-CoV-2 infection [6]. In COVID-19 recovered patients, neurological dysfunctions, inattention, or memory impairment are noted. According to research, SARS-CoV-2-induced neuroinflammation and its long-term repercussions on patients are the cause of all these brain-related problems. Our review will concentrate on the neuroinflammatory events of SARS-CoV-2 infection, which may pose a hazard to the brain health following COVID-19, in addition to the respiratory symptoms of the virus.

2. CHANGES IN THE NEUROLOGICAL AND NEUROPSYCHIATRIC SYSTEMS IN COVID-19

Patients experienced neurological symptoms during the COVID-19 pandemic, such as anosmia, ischemic stroke, cerebral thrombosis, meningitis, and vertigo [7]. While there is a dearth of documentation about neuropsychiatric symptoms and movement difficulties, certain reports have indicated that complications such as dyspraxia, a shuffling gait, anxiety, and bewilderment continue even after several days after recuperation [8]. These findings imply that neurons and glia may experience some functional changes in response to COVID-19. According to Mehta et al. [9], the primary cause of the neuroinflammatory effects of SARS-CoV-2 is a pro-inflammatory cascade that happens inside the brain and results in a cytokine storm. A virus's ability to activate glial cells can result in a variety of neurodegenerative illnesses and cognitive deficits. According to published research, SARS-CoV-2 causes the brain to release TNF-α, IL-1β, IFN-γ, and IL-6.

Furthermore, the cohort study involving elderly COVID-19 patients verified that the cognitive decline could be an indication of psychological stress, which is brought on by increased levels of pro-inflammatory cytokines, reactive oxygen species (RNS), brain-derived neurotrophic factor (BDNF), and other inflammatory markers like C-reactive protein (CRP). Hence, it is thought that being older makes one more susceptible to stress brought on by infections [10]. According to Klein et al. [11], pro-inflammatory cytokines also alter the blood-brain barrier, which is the first step in the development of neurological disorders.

3. RECEPTORS AND COMPOUNDS IMPLICATED IN NEUROINFLAMMATION CAUSED BY COVID-19

Previous research indicates that the severity of SARS-CoV-2 clearance depends on Toll-like receptors (TLRs) and retinoic acid-inducible gene (RIG)-I like receptors (RLRs) [12]. In particular, TLR3 plays a crucial role in the recognition of RNA patterns and attracts the adaptor protein TRIF, which starts the NF-κB signaling pathways that facilitate inflammation [13].

TLR4 has a great affinity to connect with spike protein, as demonstrated by a recent in-silico study [14]. It's interesting to note that TLR4 prevented SARS-CoV-1 infection in a mouse model as well [15]. Humans express the SARS-CoV-2 entry receptors, transmembrane protease serine subtype 2 (TMPRSS2) and angiotensin converting enzyme 2 (ACE2), as has been well-documented [16]. Using a mouse model, molecular studies revealed that SARS-CoV-2 activates the NLRP3 inflammasome [17]. Thus, based on the data now available, it is possible to hypothesize that COVID-19-related neuroinflammation ultimately results in neurological impairment, changes in psychobehavioral patterns, and cognitive impairment. But further research is needed to determine the underlying biological mechanism, which is now being investigated.

4. CYTOKINE STORM TRIGGERED BY COVID-19

Patients with COVID-19 experience multiorgan damage as a result of the cytokine storm that follows SARS-CoV-2. However, glial activation induced by cytokines may cause common neurological dysfunctions such as headache, anosmia, and ageusia, and ultimately result in fatal conditions such as meningitis, acute necrotizing hemorrhagic encephalopathy, ischemic stroke, and seizures in hospitalized patients [8, 18]. During COVID-19's early disease stage, higher levels of IL-6 and IL-10 were found [19]. The mRNA study of spike protein injected mice demonstrated considerable elevation of TNF, IL-1β, IFNα/IFNβ coupled with IFN receptors in

the hippocampal region, according to investigations conducted not only in human beings but also in animals [20].

5. OXIDATIVE STRESS BROUGHT ON BY FREE RADICALS IN THE BRAIN

Brain inflammation brought on by COVID-19 is directly linked to a persistently low level of oxidative stress brought on by an excess of free radical generation [21]. Oxidative stress is primarily caused by increased generation of free radicals and antioxidant depletion [22]. The cytokine storm-exacerbated signaling or mitochondrial malfunction brought on by virus infiltration into the cell could be the cause of the rise in reactive oxygen species (ROS) [9]. Researchers hypothesize that increased production of nitric oxide synthase (NOS) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase may be involved in the beginning of oxidative stress during SARS-CoV-2 infection [23]. Consequently, the neuropathology caused by COVID-19 may also be significantly influenced by reactive ROS/RNS. Psychiatric disorders may arise as a result of ROS and RNS's ability to alter neurotransmitter signaling [24].

6. CONCLUSION

We are able to comprehend the neuropathologic features of COVID-19 thanks to this review. In summary, neuroinflammation is a major factor in the development of a number of neurological, cognitive, and psycho-behavioral disorders. Free radical levels are raised by metabolic changes in the brain, and oxidative stress is brought on by the body's natural antioxidant reserves being depleted. Furthermore, the hallmark of COVID-19-induced neuroinflammation, cytokine storm, may be caused by pro-inflammatory cytokines. Thus, it stands to reason that effective control of those inflammatory markers or cytokines may be a useful strategy for preventing neurological changes in COVID-19 patients that continue long after their infection has cleared. It should be noted that further investigation is required to comprehend the cellular and molecular causes of SARS-CoV-2 infection in order to improve treatment of brain inflammation.

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Conflict of interest

All authors declare that there are no conflicts of interest.

Data availability statement

No data was used for the research described in the article.

Author's contribution

Rajen Dey (RD) participated in the conception of the study. RD participated in literature searches and extraction. RD wrote the manuscript for submission to this journal.

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