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ВЕСТНИК
МЕДИЦИНСКОГО КОЛЛЕДЖА
ИМ. МЕГРАБЯНА

BULLETIN
OF THE MEDICAL COLLEGE
AFTER MEHRABYAN

VOL. 18 ТОМ

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Dear colleagues,

We represent “Natali Pharm”, the biggest chain of pharmacies in Armenia. Over two decades, the company has been importing and selling medicine and has secured its place in the pharmaceutical market of Armenia as a leader.

We are thrilled to extend our gratitude towards your devotion and invaluable contribution in the work. Your scientific journal is an indispensable and solid ground for specialists, practitioners, researchers and scientists to meet for the joint cause: healthcare and life quality improvement of our people.

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We sincerely wish you further professional achievements as well as progress and expansion of your scientific journal.

Best regards,

Karen A. Topuzyan

Director of “Natali Pharm” chain of pharmacies

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РЕСПУБЛИКА АРМЕНИЯ

ВЕСТНИК

МЕДИЦИНСКОГО КОЛЛЕДЖА

ИМЕНИ МЕГРАБЯНА

REPUBLIC OF ARMENIA

BULLETIN

OF THE MEDICAL COLLEGE

AFTER MEHRABYAN

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РЕАКЦИЯ МИКРОГЛИИ ГОЛОВНОГО МОЗГА НА КОРОНАВИРУСНУЮ ИНФЕКЦИЮ

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Аннотация. В данной статье подробно составлен список признанных неврологических проявлений у пациентов с SARS или COVID–19, которые были связаны с исследованиями молекулярной сигнализации микроглии, чтобы предвидеть клеточные мишени при долгосрочных последствиях инфекции SARS-CoV-2.

Ключевые слова: *микроглия, мозг, нейрон, коронавирус, пандемия, фагоцитоз, макрофаги, цитокины.*

BRAIN MICROGLIA REACTION TO CORONAVIRUS INFECTION

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Abstract. The aim of this article was to build a list of recognized neurological manifestations in SARS or COVID–19 patients that were related to microglia molecular signaling investigations in order to anticipate cellular targets in long-term SARS-CoV-2 infection repercussions.

Keywords: *microglia, brain, neuron, coronavirus, pandemic, phagocytosis, macrophages, cytokines.*

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Ամփոփագիր: Սույն հոդվածում նպատակն էր համակարգել SARS կամ COVID–19 ախտորոշում ունեցող անձանց մոտ դիտված նյարդաբանական դրսևորումները՝ կապակցելով դրանք միկրոգլիայի մոլեկուլային ազդանշանային ուղիների հետ: Սա հնարավորություն է տալիս գնահատելու SARS-CoV-2 վարակի երկարաժամկետ հետևանքների հնարավոր բջջային թիրախները և ուղղել հետագա հետազոտությունները դրանց պարզաբանման ուղղությամբ:

Հիմնաբառեր՝ *միկրոգլիա, ուղեղ, նեյրոն, կորոնավիրուս, համավարակ, ֆագոցիտոզ, մակրոֆագեր, ցիտոկիններ:*

INTRODUCTION

The severe acute respiratory syndrome 2 coronavirus (SARS-CoV-2) pandemic, which began in the 2020, have killed millions of people worldwide and infected even much more people by

the end of 2022. Although the number of cases of this infection has significantly decreased by 2025, there are studies indicating the spread of mutated strains, and there is a high probability of a recurrence of the epidemic. Even while SARS-CoV-2 mostly damages the respiratory system, there are reports that the heart, kidney, pancreas, and brain can also sustain harm. According to growing data, patients with coronavirus disease 2019 (COVID–19) may experience a variety of neurological symptoms as a result of SARS-CoV-2 infection. Microglia is formed by immune cells that predominate most in the brain and first cells reacting to infection. However, it is still unclear how neurological symptoms, neuroinflammation, and the host immunological response of microglia to SARS-CoV-2 are related.

Materials and methods. The key words were used to search for data in international databases. A total of 67 sources on suitable themes were selected.

Recent research found that COVID patients experienced neurological and cognitive disturbance up to 19 months after the viral infection. These symptoms included ageusia, anosmia, asthenia, headaches, and brain fog. New findings increase knowledge of microglia-mediated neurological diseases associated with COVID–19 so that treatment plans can be created for the affected patients. It should be noted that the precise response of microglia to COVID–19 is still being investigated, and our understanding of their function in the disease is evolving. The relationship between SARS-CoV-2 and microglia is complex and varies depending on a number of circumstances, including illness severity and stage, the individual's immunological response, and other underlying disorders.

The purpose of this work was to build a list of recognized neurological manifestations in SARS or COVID–19 patients that were related to microglia molecular signaling investigations in order to anticipate cellular targets in long-term SARS-CoV-2 infection repercussions.

DISCUSSION

The coronavirus disease 2019 (COVID–19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, was assumed to damage solely the respiratory system at the start of the pandemic. However, rising reports of olfactory and taste symptoms in infected patients raised the possibility of CNS impairment [1]. Further reports of neurological manifestations in COVID–19, such as encephalopathies, cerebrovascular disease, and psychiatric symptoms of depression or anxiety, emerged as the scenario progressed [26]. At the same time, the pandemic imposes a significant level of psychosocial stress on the general population [8], which is a major predictor of mental health issues [56]. SARS-CoV was also recently associated with psychiatric and neurological disorders [20]. The purpose of this article was to summarize known neurological pathologies in patients with SARS or COVID–19 and brain microglia role in it.

In order to preserve homeostasis by getting rid of cellular waste, the microglia's function in resting conditions is to continuously scan the brain's surroundings [45]. Microglia activation is a process that happens when there is damage to neural structures. Cytokines, chemokines, and inflammatory substances are released during this process [34]. However, an enhanced release of proinflammatory cytokines happens when the immune response is dysregulated, and this has been linked to a high mortality in COVID–19 patients [38]. Through multisystem inflammatory syndrome [51] and systemic inflammatory response syndrome, these individuals exhibit hyperactivated microglia.

COVID–19 was first identified in December 2019 in Wuhan, China, and has since spread globally, resulting in a pandemic [64]. Symptoms of COVID–19 can range from mild to severe and may include fever, cough, difficulty breathing, fatigue, body aches, sore throat, loss of taste or smell, and in some cases, gastrointestinal symptoms. However, it's important to note that some individuals may be asymptomatic, meaning they show no symptoms but can still transmit the virus to others. COVID–19 primarily spreads through respiratory droplets when an infected person coughs, sneezes, talks, or breathes. It can also spread by touching contaminated surfaces and then touching the face, although this is considered a less common mode of transmission.

The family of enveloped positive-single-stranded RNA viruses known as coronaviruses affects both humans and animals, causing mild to severe respiratory, gastrointestinal, and neurological illnesses [63]. SARS-CoV-2, a new coronavirus, was responsible for a pneumonia outbreak that was reported at the end of 2019 in Wuhan, China. This outbreak gave rise to the Pandemic of the 2019 coronavirus illness (COVID–19) [28]. SARS-CoV-2 pandemic have killed 6.55 million people worldwide and infected 619 million people by the end of 2022. Even while SARS-CoV-2 mostly damages the respiratory system, there are reports that the heart, kidney, pancreas, and brain can also sustain harm. to COVID–19 situation reports from WHO [64].

Although coronavirus disease 2019 is typically categorized as a respiratory sickness, neurological symptoms may also be accompanied by a variety of organ dysfunction syndromes in the brain [23].

COVID–19 can have various neurological manifestations, affecting the central nervous system (brain and spinal cord) and the peripheral nervous system. While respiratory symptoms are the most common, neurological symptoms have also been reported in a significant number of COVID–19 cases. There are two pathways for SARS-CoV-2 to reach CNS, which include damage of the blood brain barrier causing neuronal cell death due to viremia, and the entry of SARS-CoV-2 through the olfactory bulb and subsequent transport to neurons of the brain [67].

The first pathway relies on angiotensin-converting enzyme 2 (ACE 2) as the SARS-CoV-2 functional receptor. The virus's spike protein interacts with ACE 2 receptors found in brain neurons

and glial cells, making the brain vulnerable to neuroinvasion. The transmembrane protease serine 2 (TMPRSS2) causes proteolytic cleavage and priming of the spike protein after attaching to the ACE 2 receptor, allowing the virus to enter host cells [17]. SARS-CoV-2 can enter the bloodstream after infecting the airways and passing past the epithelial barrier by infecting endothelial cells of the blood brain barrier or the blood-CSF barrier in the choroid plexus. SARS-CoV-2 can also infect leukocytes, which spread to other tissues in the human body and subsequently overcome the barrier to obtain access to the CNS, a process known as the Trojan horse mechanism [17]. TNF, a pro-inflammatory cytokine released by leukocytes, destroys oligodendrocytes and neurons. They secrete chemokines like CCL5, CXCL10, and CXCL11, which induce the chemoattraction of activated T lymphocytes. Chemokines such as CCL2, CCL5, and CXCL12 are released by astrocytes and serve to recruit additional infected leukocytes. Overall, we believe that many additional variables are at work in the inflammatory process, and that SARS-CoV-2 eventually creates a vicious circle of neuroinflammation [17].

The second neuropathological pathway describes SARS-CoV-2 spreading transneuronally to different areas of the brain via the olfactory bulb and the upper nasal transcribial channel. Regardless of the virus's mode of transmission, once the virus enters the CNS, neurotropism and the ensuing immune response produce CNS pathology, resulting in illness. Because of the high expression of ACE 2 in the gastrointestinal system, a fecal-oral pathway has been proposed as a potential SARS-CoV-2 transmission pathway [3]. Furthermore, another possible neuropathological mechanism reported in COVID–19 patients is indirect immune-mediated CNS injury via cytokine storm [2].

TASTE AND SMELL (HYPOSMIA/ANOSMIA) IMPAIRMENT

Gustatory and olfactory problems are the most prevalent COVID–19 secondary neurologic symptoms linked with PNS involvement, which appear to arise in the early stages of the disease and therefore qualify as useful diagnostic markers [13].

Anosmia (loss of smell) and ageusia (loss of taste) are among the early and most common neurological symptoms reported in COVID–19. These symptoms can occur without any nasal congestion or blockage [25, 49]. Giacomelli et al reported olfactory and taste disorders in patients with severe acute respi-ratory coronavirus 2 infection [26].

According to preliminary data, olfactory sensory neurons do not express ACE 2, which prevents SARS-CoV-2 from infecting these cells. Cells in the olfactory epithelium, on the other hand, express ACE 2 and are thus susceptible to SARS-CoV-2 infection. Anosmia appears to be caused by damage to the olfactory epithelium rather than neuronal impairment [7].

In a study conducted by Lee et al, acute anosmia or ageusia was found in 15.3% of COVID–19 patients in the early stage and 15.7% of patients with asymptomatic-to-mild disease severity. Females and younger people were substantially more likely to have them. The majority of patients with anosmia or ageusia healed after three weeks. For both symptoms, the median time to recovery was 7 days. Anosmia and ageusia appear to be key symptoms and clues for COVID–19 diagnosis, particularly in the early stages of the disease [30, 36]. Further testing of olfactory function in COVID–19 patients, who have a high prevalence of olfactory abnormalities, has been done on both hospitalized and non-hospitalized patients [35]. Interestingly, olfactory impairment has been proposed as a biomarker for COVID–19, and smell testing may aid in the early discovery of COVID–19 patients who require early treatment or quarantine as part of COVID–19 prevention measures [43]. Given the importance of these two senses, various psychological, social, and emotional consequences can be expected. These consequences include a decrease in self-esteem and the development of mental health difficulties. Long-term changes in taste experience can also lead to the formation of poor eating habits, raising the risk of diabetes and hypertension. A few treatments for these chemosensory dysfunctions have been examined, including olfactory training, corticosteroids, theophylline, and acupuncture [30]. COVID–19 individuals who have lost their sense of smell or taste may benefit from neuroprotective, anti-inflammatory, or depolarizing medications. According to the available evidence, phosphodiesterase inhibitors, insulin, and corticosteroids may be useful in the treatment of COVID–19 smell and taste loss [32].

HEADACHE

Headaches, including tension-type headaches and migraines, have been reported in some COVID–19 patients. The exact cause is not yet fully understood but may be related to the inflamematory response or vascular changes [52]. Headache was frequently observed at the time of admission, 14.7%is the estimated pooled prevalence of this symptom [21]. Half of COVID–19 patients present with headache, which is more common in younger patients, those with past primary headache or migraine, and those who have also presented with anosmia, ageusia, and myalgia. The headache usually starts early in the symptomatic period, is bilateral, moderate to severe, and follows a pattern similar to tension-type headache. The migraine and tension-type headache patterns were shown to be frequent patterns in all investigations. Direct viral harm, the inflammatory process, hypoxia, coagulopathy, and endothelial involvement are all plausible pathophysiological pathways [54]. In the acute phase of COVID–19, the most widely utilized medicines for headache are conventional analgesics and nonsteroidal anti-inflammatory drugs. The headache may last longer than the acute phase, in which case there has been progress throughout time. However, not all people experience relief from their headaches. It appears that a bigger proportion of patients' hea-

daches improve within the first three months following the acute phase of the disease than beyond this period. COVID–19 could cause a new daily chronic headache [54].

DIZZINESS AND VERTIGO

Some individuals with COVID–19 have experienced dizziness and vertigo, which is a false sensation of spinning or movement [52]. Pooled prevalence of dizziness at 8.77% in a systemic review regarding neurological characteristics of COVID–19 patients [48]. A retrospective, observational case series even describes dizziness to be the leading neurologic finding even before head ache. COVID–19 clinical signs include vertigo and dizziness, which is not surprising given that SARS-CoV-2 neurotropism can cause a wide range of neuropathic consequences. The broad distribution of central and peripheral audiovestibular circuits suggests that multiple pathogenic processes are possible. The cytokine storm, virus invasion of the CNS via ACE 2 receptors, and other systemic variables may be responsible for the high proportion of COVID–19 patients who have reported vertigo and dizzy symptoms [33].

COGNITIVE IMPAIRMENT (CONFUSION/ DELIRIUM)

COVID–19 has been linked to cognitive dysfunction, such as brain fog, trouble concentrating, memory issues, and confusion. This is known as «COVID brain» or «brain fog» [50]. Acute confusion/delirium may be the only presenting symptom of COVID–19 in the absence of overt respiratory symptoms [48]. According to a Chinese study, the prevalence of confusion is roughly 9%, which corresponds to the pooled prevalence of disturbances in consciousness/altered mental status of around 9.6% [21; 42].

NEUROLOGICAL COMPLICATIONS

Biological and clinical data imply that SARS-CoV-2 is responsible for a wide range of neurological symptoms, which can be divided into three major categories based on the putative underlying processes listed below. The first mechanism covers the neurological effects of pulmonary disease as well as accompanying systemic disease such as systemic inflammatory response syndrome, sepsis, and multiorgan failure. This category includes encephalopathy and stroke. The second mechanism involves neurological signs caused by the virus's direct invasion of the CNS (e.g., encephalitis). The final pathway is post-infectious, immune-mediated problems such as GBS and its variations.

STROKE

While rare, COVID–19 can increase the risk of blood clots forming in the body, including in the blood vessels of the brain, leading to a stroke. Strokes related to COVID–19 tend to occur in younger individuals without typical risk factors for stroke [50]. The incidence of acute ischemic

stroke in COVID–19 patients is estimated to be 2.3%, with a pooled prevalence of acute cerebrovascular disease of 2.6% [21]; the prevalence of acute cerebrovascular disease in hospitalized COVID–19 patients with more severe infection approaches 6% [41]. The majority of these patients had an arterial stroke. The increased thrombus formation under hypoxic settings could explain the prevalence of coagulation problems in COVID–19 patients, represent the final mechanism.

ENCEPHALITIS AND MENINGITIS

In some severe cases, COVID–19 can cause inflammation of the brain (encephalitis) or the membranes surrounding the brain and spinal cord (meningitis). These conditions can result in neurological symptoms such as confusion, seizures, and altered consciousness [50, 52]. Several case reports of COVID–19 patients show signs of meningitis and encephalitis. COVID–19 patients may first experience headaches, fever, and seizures. SARS-CoV-2 was detected in the CSF of certain COVID–19 patients, indicating that this neurological symptom is caused by the virus [44]. Zamani studied 182 cases with encephalitis, acute disseminated encephalomyelitis, and necrotizing encephalopathies. All patients had altered mental status, either through diminished consciousness or psychological/cognitive impairment. Among the related symptoms were seizures, cranial nerve signals, motor and reflex problems. COVID–19-associated encephalitis has a particular profile that necessitates a detailed diagnosis and, as a result, a complete understanding of the condition. The clinical profile of COVID–19 brain inflammation shows the majority of aberrant imaging and electroencephalography results, with mild/moderate pleocytosis or proteinorrhachia as common as normal cerebrospinal fluid (CSF). Their results suggest that oligoclonal bands and autoantibody evaluations are effective in further evaluating neuro-covid patients. Despite the fact that direct viral invasion cannot be easily assessed, immune-mediated or autoimmune reactions are more likely to play a role in SARS-CoV-2 neuroinflammation [45, 66].

GUILLAIN-BARRÉ SYNDROME (GBS)

GBS is a rare but serious neurological disorder characterized by muscle weakness, numbness, and tingling. It has been reported in some COVID–19 patients, possibly triggered by an abnormal immune response [39]. COVID–19 individuals with GBS can present with a variety of neurological symptoms as an inflammatory polyradiculoneuropathy linked with a variety of infections (e.g., Campylobacter jejuni, Epstein-Barr virus, CMV). The majority of COVID–19 patients with GBS had a demyelinating electrophysiological subtype (acute inflammatory demyelinating polyneuropathy) [61].

It's important to note that while these neurological manifestations have been observed in COVID–19 cases, they are relatively uncommon compared to respiratory symptoms and are more frequently seen in severe or hospitalized cases. COVID–19 CNS symptoms may be caused in part

by SARS-CoV-2 infection in the brain. The literature has hypothesized two basic routes for CNS invasion, based on either neuronal or hematogenous transport [64].

THE IMPACT OF COVID–19 ON MICROGLIA

Human coronavirus OC43 (HCoV OC43) has been proven in studies to be capable of entering the CNS via retrograde axonal transport from infected peripheral nerves, such as the olfactory or vagus nerves [18], and viral migration across neurons [19]. SARS-CoV has been observed to reach the CNS by both blood circulation (blood-brain barrier, BBB) and the olfactory bulb [5]. SARS-CoV-2 could also use the blood-cerebrospinal fluid (CSF) barrier to enter the CNS, which is a more permeable barrier than the BBB and is constituted by a single layer of choroid plexus epithelial cells [47].

In contrast to all other CNS cells, microglia emerge from erythro-myeloid progenitors in the fetal yolk sac and are present in the brain during embryonic development, self-renewing throughout life [27]. In most, if not all, physical, viral, psychiatric, or neurodegenerative exposures to the CNS, these cells are essential participants in the inflammatory response of the brain, i.e., neuroinflammation. Microglia are the resident immune cells of the central nervous system (CNS), including the brain and spinal cord. They play a crucial role in maintaining CNS homeostasis and protecting the brain from infections, injuries, and diseases.

Microglia are also essential for brain development, plasticity, and homeostasis, contributing to the turnover (bothelimination and survival) of neuronal precursors and neurons, oligodendrocyte progenitor cell maturation, neuronalsignaling, synaptic maturation, activity, and plasticity, myelination, as well as BBB integrity, and blood flow regulation [62].

Considering, that microglia respond to direct SARS-CoV-2 CNS infection and changes in the CNS imposed by systemic COVID–19 response due to their complex role in the brain's immunological and physiological processes. When it comes to COVID–19, microglia can exhibit several responses to the viral infection [6].

In response to viral infection, including SARS-CoV-2, microglia can become activated and release pro-inflammatory cytokines and chemokines. This inflammatory response aims to eliminate the virus and recruit other immune cells to the site of infection. However, excessive or prolonged activation of microglia can contribute to neuroinflammation, which may cause damage to surrounding neurons and disrupt normal brain function [6].

Microglia are proficient phagocytes that can engulf and remove cellular debris, dead cells, and pathogens. In the context of COVID–19, activated microglia may contribute to the clearance of infected cells and viral particles from the CNS. This phagocytic activity helps limit viral spread and reduce the overall viral load in the brain [22].

In some cases, the activated microglia can release cytotoxic substances, such as reactive oxygen species (ROS) and pro-inflammatory molecules, that can damage neurons and other cells in the CNS. This neurotoxicity can contribute to neuronal dysfunction and neuronal cell death [59].

Microglia can influence the integrity and function of the BBB, which acts as a protective barrier between the blood circulation and the brain. During inflammation, microglia may release factors that affect the permeability of the BBB, potentially allowing immune cells and molecules to enter the CNS more easily [9, 10].

A human microglial cell line is directly infected by SARS-CoV-2, which causes cytopathic consequences. In a postmortem research, immune filtration was connected to axonal injury, and more than half of the COVID–19 patients had high microglial immunological activation with microglial nodules [58]. Another investigation revealed that in dead COVID–19 patients, viral nucleocapsid protein was localized in the brain cortex's microglia. The microglial NLRP3 inflammasome was involved in human SARS-CoV-2 cerebral pathogenicity [11].

To investigate whether SARS-CoV-2 can infect human microglia, Jeong with colleagues used immortalized human embryonic brain-derived primary microglia (HMC3). According to their research, SARS-CoV-2 can directly infect human microglia, causing M1-like proinflammatory reactions and cytopathic consequences. Particularly, SARS-CoV-2 infection caused inflammatory activation and cell death in human microglial clone 3 (HMC3). Additionally, endoplasmic reticulum stress, immunological responses, and apoptotic processes were generated in the early and late phases of viral infection, respectively, according to RNA sequencing study [32]. HMC3 infected with SARS-CoV-2 exhibited the M1 phenotype and failed to produce the anti-inflammatory cytokine IL-10 while secreting proinflammatory cytokines such interleukin (IL)-1b, IL-6, and tumor necrosis factor (TNF)-a. SARS-CoV-2 infection enhanced intrinsic and extrinsic death receptor-mediated apoptosis in HMC3 following this proinflammatory activation. These findings imply that microglia may act as possible mediators of SARS-CoV-2-induced neurological issues and may, thus, be the focus of therapeutic approaches to treat neurological illnesses in COVID–19 patients [29, 32].

It was also reported that Angiotensin converting enzyme 2 (ACE-2) expression can be down-regulated as a result of immunological dysregulation brought on by the SARSCoV-2 infection, which affects the activation and balance of the inflammatory system [37]. The concentration of Ang-II rises due to the decreased expression of ACE-2, favoring the ACE/Ang-II/AT1R pathway. As a result, the NF-kB transcription factor is activated, which in turn triggers the creation and release of proinflammatory cytokines [23, 24]. Both samples from patients with acute SARS-CoV-2 and those from individuals with symptoms linked to extended COVID showed altered cytokine concentrations [16]. The IL-1ß, IL-6 and TNF-a cytokine triad was also associated with post-

acute sequelae of COVID–19 in a digital research done by Schulthei [57]. Besides the Ang-II/aminopeptidase-A/Ang-II/Ang-III/aminopeptidase-A/Ang-IV/AT4R pathway is also favored by the rise in Ang-II concentration [*38*]. The overproduction of hormones like vasopressin in the hypothalamus and aldosterone in the adrenal gland is caused by an increase in Ang-III concentration [65]. Increased peripheral vascular resistance and blood pressure are the results of these modifications. Additionally, Ang-III disrupts the Na+/K+ equilibrium, leading to vascular harm, stroke, and heart attacks [46].

Both Ang-III and Ang-IV have the ability to bind to AT1R, activating both this receptor and the NF-kB transcription factor as a result [15]. Increased levels of Ang- IV disrupt the vasodilatetion process, cause an increase in sodium excretion, and release plasminogen activator inhibitor-1, which favors the development of thrombotic events in the brain and the lungs [42]. Transcriptome databases show that ACE2 is expressed in astrocytes, oligodendrocytes, excitatory and inhibitory neurons, as well as endothelial cells [12, 14]. Manik et al studied the role of toll-like receptors in modulation of cytokine storm signaling in COVID–19. It is quite possible that one of the initial mechanisms causing immune response damage to the CNS is ACE-2 downregulation brought on by SARS-CoV-2 infection [40].

When the virus infects the cell and the innate immune system recognizes viral RNA genome as ssRNA or one of dsRNA's intermediaries via the Toll-Like Receptors including TLR3, TLR7, and TLR8, this is another mechanism related with the activation of pro-inflammatory cytokines [4].

IRF3, IRF7, NF-kB, ISRE3, and API are among the transcription factors that are activated by these receptors. The expression of TNF-α, IFN-α, IFN-β, and IFN-γ, which are important pro-inflammatory cytokines in the antiviral response, is influenced by these transcription factors. Genes involved in apoptotic processes, immune response modulation, cellular attraction and adhesion, and genes involved in antiviral and pathogenic detection are all activated by IFN-α and IFN-β. The equilibrium between IFN-α and IFN-β concentrations plays a crucial role in controlling the inflammatory response [29].

The microglia also maintains the equilibrium between the innate immune response and the adaptive immune response in addition to their direct involvement in the removal of a viral infection [55]. Reactive oxygen species (ROS) are created when proinflammatory cytokines are released in excess during acute COVID–19, which affects brain tissue by stressing cells and causing cell damage on a systemic level [60]. These cellular activities in some COVID–19 individuals cause symptoms such ischemia, brain tissue inflammation, blood flow obstruction, headaches, loss of consciousness, cerebral edema, and neuronal death [53].

CONCLUSION

Thus, microglia respond to multiple CNS insults during the COVID–19 pandemic, including viral infection, hypoxic damage, increased circulating cytokines, and psychosocial stress. SARS coronavirus 2 (SARS-CoV-2) can infiltrate the brain via peripherally infected neurons, infected microvascular brain endothelial cells, and infiltrating leukocytes. In turn, infected cells emit damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), which microglia detect and respond to by becoming reactive. At the same time, COVID–19 disease adds to low oxygen levels, which may lead to hypoxic brain damage. Neurons are very susceptible to oxygen deprivation, becoming destroyed quickly and generating DAMPs and PAMPs. Microglia detect this and respond by altering their shape, molecular signature, and cytokine release.

It's important to note that the specific response of microglia to COVID–19 is still being studied, and our understanding of their role in the disease is evolving. The interaction between SARS-CoV-2 and microglia is complex and can vary depending on various factors, including the severity and stage of the disease, the individual's immune response, and other underlying conditions.

Further research is needed to fully elucidate the role of microglia in the context of COVID–19 and determine how their response contributes to the neurological manifestations observed in some patients.

The goal of this study was to compile a list of known neurological manifestations in SARS or COVID–19 patients, related to microglia molecular signaling investigations in order to anticipate cellular targets in long-term repercussions of SARS-CoV-2 infection.

CONFLICT OF INTERESTS

Authors declare no conflict of interests. All authors contributed equally to this work.

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