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Neurological Effect And Pain Related Covid-19

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Abstract

In late 2019, the coronavirus (COVID-19) or SARS-CoV-2 virus was discovered worldwide and is currently spreading. Covid-19 virus Enters the nervous system through the olfactory nervous system, through immune and white blood cells. As is already known, COVID-19 virus infections cause respiratory symptoms in affected individuals. The most typical signs of COVID-19 in mild cases are exhaustion, wooziness, headaches, and loss of smell and taste. Encephalitis, cerebrovascular illness, or blockage are examples of severe symptoms. And additional difficulties. The evidence synthesis resulted in a categorical analysis of the central and peripheral neurological involvement brought on by COVID-19 and a full explanation of the documented pathophysiological pathways by which SARS-CoV-2 infection may cause neurological impairment. Through worldwide cooperation to complete neurological registries, we will learn more about how COVID-19 impacts the central and peripheral nervous systems and create methods for therapeutic decision-making.

Keywords: Covid-19, neurological symptoms, neuroinflammation, pain

Introduction

The respiratory system frequently encounters Coronaviridae infections.The severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) are two significant coronavirus outbreaks that have occurred in recent years [1]. Since December 2019, the number of people suffering with COVID-19,sometimes referred to as the coronavirus 2 causing severe acute respiratory syndrome , has increased (SARS-CoV-2). The virus's gene sequence shares 79.5% with SARS-CoV and 50% with respectively , MERS-CoV [1, 2]. The health care system has experienced any difficulties throughout consequently urrent outbreak [3, 4]. That according published epidemiology data, this virus and the pneumonia caused by SARS-CoV or MERS-CoV share a similar etiology and symptomatology [5, 6]. In addition, albeit less infrequently, COVID-19 has also been related, along with these respiratory symptoms, to the establishment of neurological symptomatology due to its impact on sensory, cerebrovascular, cognitive, as well as motor function [7, 8]. Regarding the infection in the brain can affect not just general wellbeing but also produce a risk of comorbidities and death, consequently ethod used to evaluate the impact this is novel viral on the function of the brain presents a new, major obstacle for neuroscience research project [9-11]. This review aims to explore the impact of COVID-19 that affect the nervous system and to discuss the mechanism involved to neurological effect and pain related Covid-19.

Neurophysiology of Covid-19

The beta-coronavirus SARS-CoV-2 belongs to the Orthocoronavirinae subfamily of the Coronaviridae family and has a 29,903 nucleotide single-stranded RNA genome [6, 12]. It is easy to distinguish the 14 binding residues that make up CoV-2's SARS-structure [13]. The spike (S) glycoprotein receptor on the surface of SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptors present on

multiple host organs, enabling the virion to be endocytosed [13, 14]. Data indicate that the neurovirulence of SARS-CoV-2 may be associated with the amount of ACE receptor expression in the nervous system [13]. However, this receptor is present in the endothelium's smooth muscle cells. Therefore, more investigation is needed into its role in the etiopathogenesis of neurological issues [5]. During the internalization phase of SARS-CoV-2, furin, cathepsins B and L (Cat B and L), and transmembrane protease serine 2 (TMPRSS2) trim the S glycoprotein to facilitate its binding to ACE2 and SARS-CoV-2 cell entry [15, 16].

It has been suggested that the virus can reach the neural system through the nasal olfactory epithelium and PNS terminals of the olfactory nerve, which are likely sites of enhanced SARS-CoV-2 binding [17]. Indicating that these cells may be involved in SARS-CoV-2 virus entrance and smell impairment, Bilinska et al. demonstrated that sustentacular cells of the olfactory epithelium express ACE2 and TMPRSS2 [18, 19]. Notably, older animals produce the entry proteins more frequently, which may help to explain why older people are more vulnerable to SARS-CoV-2 infection [20]. Additionally, a different transsynaptic pathway from the trigeminal nerve branch to the brain via the nasal respiratory epithelium has recently been proposed, albeit this has to be validated [21]. A different hypothesized method indicated a retrograde spread via transsynaptic transfer employing an endocytosis or exocytosis mechanism, as well as a quick axonal transport mechanism of vesicle transport carrying the virus along microtubules back to neuronal cell bodies [1, 21]. The CNS contains viral RNA, as according autopsies conducted on COVID-19 patients [3].

SARS-CoV-2 enables the alternative route (ACE2-Ang-(1-7)-Mas) of the renin-angiotensin system (RAS) to be underactivated in the neurological system. Such underactivation in turn causes the traditional RAS pathway to become overactivated (ACE-Ang II-AT1R) [13, 14]. These could lead to thrombotic events, vasodilation, neuroinflammation, oxidative stress, and more [10]. Animal models demonstrated that SARS-CoV-2 can cause an alteration in the vascular architecture the inside of the cortex and found, with the exception of the cerebellum, the cerebral cortex was negatively affected widely, with infected cells visible in columnar patches and sensory regions and a high density of infected cells in most brain regions [19, 22]. The virus is thought to impact the respiratory centers of the brainstem [23].

Contributions on Neurological Symptoms During the Acute Phase

Current iformation on COVID-19's neurological symptoms have been revealed in an amount of articles [24]. The neurological symptoms in a retrospective series of 1682 Wuhan patients [25]. Of them, neurological symptoms were present in 30.3% of the patients (12.8% with headache). 79 studies were assessed, and 63 were chosen to be included in the meta-analysis. According to these researchers, 35% of patients had olfactory changes, 10.7% had headaches, and 8.1% had strokes examined data from 69 patients with possible SARS-CoV-2 infection out of 358 patients with neurological symptoms conducted a cross-sectional research to assess the impact of the virus in a facility that mostly treated neurological patients. 33 of the 280 articles they reviewed for this research were selected [18]. Apparently, neurological changes those with such myalgia (19.2%), headache (10.9%), stroke (4.4%) [18]. Additionally, they examine the prevalence and characteristics of neurological symptoms throughout the epidemic. give a thorough analysis of the effects of neurological symptoms and the underlying causes [1]. By taking a fairly broad approach, examining potential pathogenic pathways, and addressing existing disputes, the article by particularly investigates the prevalence and pathophysiology of anosmia; it also contributes an intriguing piece on the condition. examined if seizures occurred in 4 of their own patients who had SARS-Cov-2 infection, reviewed the relevant literature, and described the frequency of electroencephalographic seizures. examined a case report and a meta-analysis of 29 research to look at people with COVID-19 who have Guillain-Barré syndrome [26]. Examine the SARS-CoV-2 infection-induced vocal cord paralysis.Research by looks at individuals with COVID-19 with a history of alcohol addiction and their neuropsychiatric symptoms [27]. give a thorough clinical analysis of transverse myelitis linked to COVID-19 and the disease's vaccination, a very educational contribution [17].

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Contributions to the Study of the Invasion of the Central Nervous System

There were studies examined the connection between the biochemical and molecular components of the viral infection and their potential effects on the central nervous system [28, 29]. Scholar have suggested the murine hepatitis virus as a model for exploring the involvement of coronaviruses in the CNS in an article discussing the neurological symptoms of COVID-19 and offering an overview of the clinical presentation and infection processes [23]. They also emphasise this model in their examination of experimental SARS-CoV-2 models [25]. Examine the underlying causes of neurological symptoms associated with COVID-19 after reviewing 484 papers using a pre-established technique addressing many domains, including host variables, immunological processes, and virology [25]. Examine specific processes associated with SARS-CoV-2. This exhaustive study presents both practical and clinical information. Conducted a comprehensive examination of neurological symptoms, viral entry locations, and possible immunological and viral processes and outlined a vast array of potential neurological disorders affecting the central and peripheral nervous systems [23]. This intriguing paper examines the relationship between neurological symptoms and SARS-CoV-2 [23]. Examining cerebrospinal fluid transcriptomes by researchers who studied neuropathological features of the illness found that the virus is complicated to detect or undetectable in the cerebrospinal fluid of individuals infected with SARS-CoV-2, even those with encephalitis [17, 23].

SARS-CoV-2 mediates neuroinflammation and induces fibrosis in CNS

The BBB is composed of tight junctions between the epithelial cells of the choroid plexus, cerebral, and arachnoidal epithelium [10]. According to one hypothesis, the virus gains access to the CNS by binding to the ACE2 receptor on BBB endothelial cells and causing neuroinflammation [22]. The virus may also circumvent the BBB's protection by infecting macrophages and monocytes that infiltrate the CNS [30]. A further mechanism by which the virus can compromise the BBB is systemic inflammation caused by a viral infection in the lungs [23]. As a component of the BBB, astrocytes would receive signals from pro-inflammatory cytokines [8]. This could result in SARS-CoV-2 entering the CNS and causing neuroinflammation [8]. Microglia, the native immune cells of the CNS, become active in response to brain injury or infection [14]. In addition to neuronal plasticity, clearing of debris, synaptic pruning, regulating brain parenchyma, and receiving input from the peripheral immune system, they perform many functions [20]. As described previously, patients infected with SARS-CoV-2 may significantly increase systemic pro-inflammatory cytokines [31]. SARS-CoV-2 infection may induce the pro-inflammatory microglia phenotype, which may manifest in a patient as a neurodegenerative disorder because microglial cells in the CNS have such a diverse array of functions [24]. Additionally, reactive, pro-inflammatory microglia can increase the expression of neuroinflammation-causing genes [15].

Infection with SARS-CoV-2 can facilitate neuronal damage and neurological alterations [19, 20]. With infection, encephalitis and the formation of lethal microthrombi can occur. Brain fibrosis and thrombosis can result from the multisystem inflammatory syndrome in severely affected patients [32]. The interaction between viruses and ACE2 receptors on neurons may result in axonal damage, thereby causing neurological damage [33]. Alarmingly, the varying levels of ACE2 in the brain may hasten the progression of several neurodegenerative diseases [14, 34].

Neurobiology of pain caused by viruses

Unlike bacteria, viruses possess small genomes that encode a small number of proteins. The SARS-CoV-2 genome contains 14 open reading frames encoding 27 proteins, including the known ACE2-binding spike protein [25]. Furin can also cleave the spike protein, priming it to bind to NRP1 and NRP2 [35]. ACE2, furin, and neuropilins probably increase the likelihood that SARS-CoV-2 can invade a cell [35]. Although this provides a degree of diversity in how viruses can act on neuronal receptors, many viral proteins lack well-defined targets within host cells [18]. In addition, different viruses use different receptor mechanisms to enter host cells (ACE2 for SARS-CoV-2; CCR5 for HIV; and nicotinic acetylcholine receptors, p75 NGF receptors, and neuronal cell adhesion molecule for rabies), and they

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frequently infect different host cell types [35]. Because these mechanisms are not conserved across viruses, it is unlikely that widespread aches and pains, one of the earliest symptoms of many viral infections, are caused by viral proteins interacting directly with nociceptors [36]. The production of nucleic acids found in the extracellular space is an early sign of viral infection [14]. As a positive-sense RNA virus, SARS-CoV-2 generates extracellular single-stranded structured RNA [14]. These extracellular nucleic acids (either RNA or DNA) indicate infection or cellular damage and elicit a robust immune response as a result [35]. Extracellular RNA, a clear indicator of RNA virus infection, acts on toll-like receptor 3 to stimulate the production of type I interferons in host cells. First, the host's antiviral response produces and releases interferons of type I [14].

Due to the prominent role of type I interferons as the body's initial response to viral infection, we recently tested the hypothesis that interferon and the two type I interferons may promote pain by acting directly on nociceptors [35]. Nociceptors strongly express the receptor complex for type I interferons in mice, and injection of these interferons results in mechanical hypersensitivity in male and female mice [15]. In addition to these behavioural effects, in vitro application of type I interferon to mouse nociceptors increased their excitability, consistent with the observed behavioural effects [36]. Interferons of type I trigger a signalling cascade in host cells that protect them from viral replication [35]. This involves the induction of phosphorylation of elongation initiation factor 2 (eIF2) that inhibits translation, preventing the virus from producing the necessary viral coat proteins for replication [35]. In several pathological conditions associated with sensory neuropathy, the induction of eIF2 phosphorylation is known to promote pain [35]. The researcher discovered that type I interferons did not induce a nociceptors' response mediated by eIF2 [35]. Instead, we observed the induction of mitogen-activated protein kinase–interacting kinase (MNK1/2)-mediated eIF4E phosphorylation, a different pathway that promotes the synthesis of proteins from a subset of mRNAs associated with pain promotion [35, 37]. In mice lacking this MNK1/2-eIF4E signalling pathway, the pain-promoting behavioural effects of interferon type I was absent . These results support the conclusion that type I interferons promote virus-induced pain via an action on sensory neurons in which these antiviral proteins induce a distinct signalling response that increases the excitability of nociceptors [19, 38]. Importantly, we found no evidence that extracellular viral RNA directly affects the nociceptors of mice [15]. This suggests that additional cell types are required to detect the presence of viruses and produce type I interferons, which then act on nociceptors [39].

Based on this information, one might hypothesise that type I interferons produced by COVID-19 patients are the primary cause of headaches and general aches and pains associated with the disease. This may be the case in some patients, but not all [27, 40]. Despite evidence of a robust type I interferon response in mild disease, several recent studies in patients with severe COVID-19 has shown that the virus appears capable of evading type I interferon induction, which may be a key reason why a subset of patients is unable to mount an antiviral response [28, 41]. The lack of type I interferon induction may result from SARS-CoV-2 proteins such as nsp6, nsp13, ORF3b, and ORF6 inhibiting interferon signalling pathways [29, 42]. This evasion can result in uncontrolled viral replication and systemic hyperinflammatory response, also known as a cytokine storm, typical of severe COVID-19 disease [26, 43]. According to a recent finding, people with inborn errors in the type I interferon response or with autoantibodies to type I interferons are particularly susceptible to severe disease and mortality [7, 44]. Increasingly, it is evident that deficiencies in various types of type I interferon responses are crucial factors in severe COVID-19 [45, 46].

The effects of SARS-CoV-2 on the brain represent a new challenge for neuroscientific research, in which we can only make progress with as much data as possible, such as that contained in this special issue [47]. Until it is determined whether the virus or its RNA can remain within CNS structures or whether it can remain latent or cause disease over the long term, necropsy studies are imperative [5, 23]. It is also essential to identify any regions of the CNS that may be more susceptible to infection (although the hippocampus and basal ganglia have been suggested), whether some CNS cells are more susceptible to viral structures, and whether the virus or its RNA can be transported by cell substructures such as vesicles or

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exosomes [9, 48]. In addition, it is unknown whether existing lesions, such as demyelinating plaques in multiple sclerosis, may facilitate the virus's entry and serve as viral reservoirs [39]. The effect of different types of vaccines on the viral invasion of the central nervous system is another area requiring additional research [49, 50].

Conclusions

The evidence synthesis resulted in a categorical analysis of the central and peripheral neurological involvement by COVID-19 and provided a thorough explanation of the reported pathophysiological mechanisms by which SARS-CoV-2 infection may cause neurological impairment. International efforts to work together and complete neurological registries will improve our understanding of how COVID-19 affects the central and peripheral nervous systems and develop strategies for making therapeutic decisions.

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