Review Article

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Journal of Neurology and Neuroscience
ISSN 2171-6625

2020
Vol.11 No.6:338

DOI: 10.36648/2171-6625.11.1.338

Neurological Manifestations of SARS-CoV-2: A Proposed Pathogenesis

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Citation: Fernando OJ, Beter M, Tao F, Tambo W, Cozar C (2020) Neurological Manifestations of SARS-CoV-2: A Proposed Pathogenesis. J Neurol Neurosci Vol.11 No.6:338

Abstract

Background: Severe acute respiratory syndrome (SARS-CoV-2) is a worldwide pandemic, was first reported in Wuhan, China. SARS-CoV-2 mainly affects the respiratory tract, but the nervous system is not immune to the effects of the virus.

Objective: To consolidate the knowledge of the effects of SARS-CoV-2 on the nervous system, subcategorized the manifestations were established as a central and peripheral possible pathogenic pathway of the virus on the nervous system.

Methods: A search strategy was made using PubMed, Google Scholar, and Medline using a combination of search terms: Coronavirus, Encephalitis, SARS-CoV-2, Delirium, and Gilliam Barre, Anosmia, Stroke, Miller Fisher. We reviewed only studies published in English between 2019 and 2020. Central nervous manifestations were subcategorized in central nervous system manifestations (CNM) and peripheral nervous system manifestations (PNM). The topics studied in each section were: delirium, headaches, encephalitis, acute necrotizing encephalitis, stroke for (CNM) and anosmia, dysgeusia, Guillain Barré, and Miller Fisher Syndrome for (PNM). A proposed pathogenic mechanism and the main clinical features in each section were described.

Discussion: Central Nervous manifestations are due to 3 mechanisms: invasion of the virus through ACE receptor, cytokine storm, and immune dysregulations while peripheral Nervous System manifestations are due to virus invasion in the epithelium mucosa and olfactory bulb, but also a central component could play a role. Additionally, molecular mimicry plays an essential role in the development of Guillain Barré and Miller Fisher.

Conclusion: More research needs to be done regarding the pathogenesis of neurological components of SARS-Co-2. Overall, there is no common pathway for the pathogenesis for all the components of the neurological manifestations of SARS-CoV-2. Each component has its own pathogenesis, but some neurological manifestations share common features.

Keywords: Coronavirus; Encephalitis; SARS-CoV-2; Delirium; Gilliam Barre Syndrome; Anosmia; Stroke; Neurological manifestations

Received: July 17, 2020; **Accepted:** September 09, 2020; **Published:** September 16, 2020

Introduction

This was the first time the new coronavirus Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) was described. There were two betacoronavirus epidemics in the 2000s: severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome (MERS) alarming the world due to the high fatality rates 10% and 37% respectively [1]. New cases of a virus with a similar structure emerged in 2019, rapidly spreading worldwide to become a pandemic and a public health emergency [2,3]. Although most cases have reported respiratory-related symptomatology, other systems seem to get affected by the virus, including the nervous system [4].

The symptoms of SARS-CoV-2, a virus that primarily affects the elderly with chronic medical conditions, usually appear after an

incubation period of 5 days [5]. The most common symptoms are fever, cough, shortness of breath, headache, and fatigue [6]. In the most severe cases, patients may develop pneumonia, acute respiratory failure, or multiorgan failure [5]. SARS-CoV-2 mainly affects the respiratory tract, but the nervous system is not immune to the virus's effects, as suggested by multiple reports of patients suffering from anosmia, dysgeusia. Interestingly, both the central nervous system and the peripheral nervous system can be affected by the virus as neural complications have been reported during the outbreak. Common central nervous system manifestations associated with the coronavirus disease 2019 (COVID-19) are seizures, change in mental status, and encephalitis, while Guillain Barré syndrome has been associated as peripheral nervous system manifestations [5].

Although the pathogenesis of COVID-19 seems to affect the pulmonary system preferentially, the effect of the virus on the nervous system is not well understood. However, it has been suggested that COVID-19 induces immune dysregulation, which may adversely affect the nervous system. It is, therefore, imperative to understand the potential underlying neurological manifestations of COVID-19.

Accordingly, the goal of this review looks to consolidate the knowledge of the effects of SARS-CoV-2 on the nervous system. We also aim to subcategorize clinical manifestations as central or peripheral to establish possible transmission pathways and the pathogenic mechanisms of SARS-CoV-2 on the nervous system.

Literature Review

A search strategy was made by using PubMed, Google Scholar, using a combination of search terms: Coronavirus, Encephalitis, SARS-CoV-2, Delirium, Gilliam Barre, Anosmia, Stroke, Miller Fisher. The preprint was considered for a brief discussion, but we mainly use peer-reviewed scientific evidence. For our study, we reviewed only studies published in English between 2019 and 2020. The principal authors of this paper exanimated all retrieved information. We briefly discuss general pathogenesis on the nervous system and present a summary of the laboratory findings of hospitalized patients with neurological manifestation. We proceed to present the neurological manifestations in two groups: central nervous system manifestation (CNM) and peripheral nervous system manifestations (PNM). The topics studied in each section were: delirium, headaches, encephalitis, acute necrotizing encephalitis, stroke for (CNM) and anosmia, dysgeusia, Guillain Barré, and Miller Fisher Syndrome for (PNM). We use the following inclusion-exclusion criteria.

Inclusion criteria

- Paper published in English
- Studies in humans
- All full papers

Exclusion criteria

- Animal studies
- Non-English language studies
- Exclusion Meta-analyses

A significant doubt arises if the neurological manifestations of SARS-CoV-2 constitute a primary manifestation due to invasion of the virus or is a secondary problem related to the immune dysregulation, or the cytokine storm of the infection which may enter the blood brain barrier (BBB). The constellation of features is reminiscent of a family of syndromes broadly gathered under the umbrella of cytokine storm syndrome, in which hyper inflammation and multi-organ disease arise through excessive cytokine release from uncontrolled immune activation [7]. The rapidly increased cytokines and chemokines attract many inflammatory cells, such as neutrophils and monocytes, resulting in excessive infiltration of the inflammatory cells into tissues, leading to systemic injury.

It appears from studies that dysregulated and/or exaggerated cytokine and chemokine responses by SARS-CoV-infected, or MERS-CoV-infected cells could play an essential role in the pathogenesis of SARS or MERS [8]. The entry of the virus is mainly through the angiotensin 2 receptor (ACE) neurotropism. The receptor is mainly expressed in the vascular endothelia, kidney cells, airway epithelia, and small intestine cells. Nevertheless, the virus's entry through ACE receptors cannot be sufficient to cause infection in the nervous system, which is supported by the fact that SARS-CoV and MERS-CoV were reported to cause neurological complications, and the levels of ACE receptors in the nervous system are low. Findings show that angiotensin II signaling to astrocytes via AT1 plays an important role in regulating leukocyte infiltration to the CNS in response to a neurodegenerative stimulus, possibly coming from intense inflammatory response due to a systemic infection [9]. To better understand the initial step of infection at an atomic level, we determined the crystal structure of the receptor-binding domain (RBD) of the spike protein of SARS-CoV-2 bound to the cell receptor ACE2. Furthermore, SARS-CoV-2 RNA was found in the cerebrospinal fluid of infected patients which supports the theory of neurotropism [2].

The exact mechanism by which SARS-CoV or MERS-COV enter the nervous system was not clear. However, the more accepted model suggests that the infection first reaches the peripheral nervous system and then accesses the central nervous system [8]. Because of the similar structure of SARS CoV-2 to other viruses, like the other coronaviruses previously known as a common cause of cold in humans, SARS-CoV-2 particles are spherical. They have proteins called spikes protruding from their surface. These spikes latch onto human cells, then undergo a structural change that allows the viral membrane to fuse with the cell membrane. The viral genes can then enter the host cell to be copied, producing more viruses. Recent work shows that the mechanism of human cell entry, division, and spread is similar to the virus that caused the 2002 SARS outbreak [10], so it would make sense to think that the virus follows a similar pathway. Other mechanisms like hypoxia, cell membrane damage, ACE (Angiotensin-converting enzyme) II regulation, haematogenic dissemination, synaptic transference,

and others could play an important role in determining better or worse neurologic outcome in patients infected by COVID-19 [11].

Results and Discussion

Analyzing a total of 214 hospitalized patients, Mao et al. found that patients with SARS-CoV-2 with central nervous system manifestations had lower lymphocyte and platelet counts and higher blood urea nitrogen (BUN) in comparison to patients without central nervous system manifestations. In contrast, regarding laboratory findings, no significant difference was found among patients with and without peripheral nervous system manifestations [2].

Central nervous system manifestations

Delirium: Initial studies have indicated that the prevalence of delirium in the ICU was 7.5%. However, the term delirium was not described, and the term impaired consciousness was used instead [2]. Another study found an even more significant incidence with 64% of patients in the ICU having confusion [12].

Beach et al. described a case series study of 4 patients over 65 years of age presenting with delirium and comorbid psychiatric conditions without the core symptoms of SARS-CoV-2. 3 of the 4 cases presented with myoclonus, suggesting global brain dysfunction. Alogia was another major symptom, suggesting a problem in the mesolimbic or mesocortical pathways. The study suggested that older people, mainly those suffering from dementia or depression, could be more susceptible to developing delirium and mentioned how important it is to screen ICU patients with delirium for SARS-CoV-2 [12]. It will be important to determine whether delirium is a primary problem of the nervous system caused by the invasion of the virus or a secondary problem like prolonged mechanical ventilation, overuse of sedatives, immobility, and social isolation are all risk factors for delirium [2].

Headaches: Initial reports by Huang et al. showed that the prevalence of headaches was 8% in a pool of 41 hospitalized patients [1]. A further study by Chen et al. found an incidence of 8% in 99 hospitalized patients [11]. Another study by Wu et al. indicated that 34% of hospitalized patients with SARS-CoV-2 reported headaches. Pathogenesis has not been discussed in any of these reports [9]. We hypothesize that headaches are related to secondary factors rather than a primary effect of the virus. Further research needs to be this collection of reports shows the wide spectrum of COVID-19 infections and the daily increase in the number of cases worldwide.

Encephalitis: We found only one case of meningoencephalitis reported by Moriguchi et al. the patient presented with generalized fatigue and fever and was treated under a suspected diagnosis of influenza. Over the next few days, the patient's condition worsened. On day nine, he was transferred to the emergency department due to loss of consciousness (Glasgow 6) and generalized seizures. On physical examination, the patient had meningeal signs. In due course, the patient also developed respiratory failure requiring mechanical ventilation.

Lumbar puncture findings: A substantially elevated pressure of 320 mm H_2O, lymphocytic pleocytosis, and no red blood cells were found.

Imaging: Initial CT scan showed no brain edema. Weighted images: Hyperintensity along the wall of the inferior horn of the right lateral ventricle. Flair MRI: Hyperintense signal changes in the right mesial temporal lobe and slight hippocampal atrophy. The author concluded that the findings indicated right lateral ventriculitis and encephalitis on the right mesial lobe and hippocampus [13].

Fortunately, encephalitis associated with SARS-CoV-2 in this case was self-limited. Although the definitive diagnosis of viral encephalitis largely depends on virus isolation, this is difficult for COVID-19 because SARS-CoV-2 dissemination is transient, and its CSF titer may be extremely low. Consistently, anti-SARS-CoV-2 IgM and IgG were not detectable in the patient's CSF sample. The pathophysiological characteristic of SARS-CoV-2 associated encephalitis is still not fully understood. In agreement with Wu and colleagues [14], the speculation was that SARS-CoV-2-induced immunologic response might cause inflammatory injury and edema, leading to alterations in consciousness as a consequence. With the clearance of the virus and mannitol therapy, the CSF pressure gradually reduces, and the patient's consciousness gradually improves [15].

COVID-19–associated Acute Hemorrhagic Necrotizing Encephalopathy: In the United States, a case of acute necrotizing encephalopathy (ANE) with symmetric multifocal lesions with thalamic involvement was reported. ANE mainly presents in the pediatric population with less prevalence in adults. The case presented in a female airline worker with fever, cough, and altered mental status as the main symptoms, which was confirmed with COVID-19 after laboratory testing. CT and MRI images showed lesions with symmetric hypoattenuating sections and hyperintense signs due to internal haemorrhage secondary to COVID-19; other image studies did not show positive results. The pathogenesis was unknown and not discussed in the article described [16].

Stroke: Recent reports have shown increasing cases of acute cerebrovascular disease such as acute ischemic stroke, cerebral venous sinus thrombosis, and cerebral hemorrhagein patients hospitalized with COVID-19 [17]. Association of viruses with thrombotic events is not new. HIV-1 and HCV have also been described as to cause thrombotic events. Many cases of stroke related to SARS-CoV-2 have been described. Umapathi et al. reported five cases of large-vessel stroke in patients less than 50 years of age. Over the course of a week, one patient developed progressive hemiparesis, numbness, and dysarthria, and the CT scan showed partial occlusion of the right carotid artery and middle cerebral artery. On further workup to find the cause of the thrombus, the source was not identified, and it was treated appropriately. Likewise, another author reported a further four patients with the same clinical picture who tested positive for COVID-19 [15]. Although the mechanism of stroke related to COVID-19 is not fully understood, there is a rising concern about this serious neurologic complication. The SARS-CoV-2 virus binds

to ACE II receptors present on the CNS endothelium, producing depletion of ACE II receptors through the endocytosis mechanism inside the neuron. Once this happens, ACE I and angiotensin II produce an unbalanced proinflammatory and vasoconstriction effects which damages the endothelium on the brain [15]. Hypercoagulative also seems to play a role in stoke, Zhang et al. reported 3 patients positive for COVID-19 who developed antiphospholipid antibodies which were associated with both arterial and venous thrombosis events. From all those patients, two had multiple cerebral infarcts, and one had multiple limb ischemia [9,18]. Hypercoagulability is already a well-established hallmark of this infection, but how this translates into large-vessel occlusion (LVO) strokes in the young population (20's and 30's) who demonstrated massive strokes due to COVID-19 infection with no prior risk factors is unknown. A series report of five cases of large-vessel stroke in patients younger than 50 years of age who presented to a health system in New York City, where severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections was diagnosed, demonstrated partial infarction of the right middle cerebral artery in the CTA [19]. The pathogenesis of the stroke in these cases could be associated with vasculitis caused by intravascular cytokine release and intense lumen vessel inflammation, leading to partial occlusion and stroke signs and symptoms without the evidence of previous risk factors of atherosclerosis and cardiovascular diseases [2]. There is still limited data on this topic, and more evidence is needed for establishing the pathogenesis of stroke in risk-factor free patients infected by the novel coronavirus. This collection of reports shows the wide spectrum of COVID-19 infections and the daily increase in the number of cases worldwide.

Peripheral nervous system manifestations

Anosmia and Dysgeusia: Olfactory dysfunction due to viral infections is very common. Rhinovirus, Epstein-Barr, parainfluenza, and other coronaviruses produce an inflammatory reaction of the nasal mucosa, which produces rhinorrhea and olfactory dysfunction. Interestingly, olfactory dysfunction due to SARS-CoV-2 does not seem to be related to rhinorrhea [20]. Initial studies in hospitalized patients showed incidences of hypogeusia (5.6%) and hyposmia (5.1%) [2]. A further study with a more specific questionnaire (National Health and Nutrition Examination Survey) in a multicenter study in Europe found that 85.6% and 88.0% of 418 hospitalized patients had olfactory and gustatory dysfunctions. This study also found that olfactory and taste dysfunction was not significantly associated with rhinorrhea or nasal obstruction ($p<0.001$) [20]. Another study by Boscolo-Rizzo et al. reported that the prevalence of olfactory and taste dysfunction was 1.5% and 63.0% in patients that tested negative and positive respectively for SARS-CoV-2, and the predictive and negative predictive value of these patients among symptomatic patients was 97.1% and 76.7% respectively [21]. There seems to be a local inflammation response which damages the epithelium and the ACE receptors. It has been discovered that dopamine decarboxylase (DDC) co-regulates ACE2 receptors and hampering of the receptors could interfere with the dopamine and serotonin pathways that are required for the normal function of the olfactory and gustatory systems [22]. Another possibility is a direct invasion of the virus to the olfactory bulb. Then the virus reaches the uncinate fascicule, moves to the anterior cingulate, and finally goes to the basal forebrain. This would suggest that anosmia has a central component [23]. Regarding Ageusia, ACE2 receptors are expressed in oral mucosa, especially in the tongue. As mentioned previously, ACE2 receptors are modulated and play an important role in the perception of taste. Recent investigations have shown that the SARS-CoV-2 virus attaches to the sialic acid receptor. Sialic acid is a fundamental component of the salivary mucin. When sialic acid is reduced, gustatory molecules are degraded prematurely, and the gustatory threshold is increased. As a result, it has been hypothesized that SARS-CoV-2 occupies that space of sialic acid and interferes with the function of the gustatory system [24]. Anosmia and Ageusia could play an important role in screening patients with COVID-19. Gane et al. reported 10 cases presenting with olfactory dysfunction, with half of them having anosmia as the only feature [21]. With these data, it could be suggested that patients presenting with anosmia with or without respiratory symptoms should be promptly screened for SARS-CoV-2 due to the positive and negative predictive values reported by Boscolo-Rizzo et al. This strategy could be a useful tool for preventing the rapid spread of the virus in times where diagnostic tests are not always rapidly found.

Guillain Barré Syndrome: Guillain Barré is a rare autoimmune disorder characterized by bilateral lower extremity weakness and loss of reflexes of the inferior limbs. Acute inflammatory demyelinating polyradiculoneuropathy is the most common phenotype in which antibodies attack the myelin membranes. The syndrome has been described with other coronaviruses such as severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS), mainly in case reports. We found 10 case reports in the literature. All the cases presented with signs of Guillain Barré, mostly ascending paralysis, which varied between 3 days to 3 weeks after the COVID respiratory symptoms (average 7 to 10 days). Most cases showed increased levels of protein in CSF or nerve conductive studies that suggest Guillain Barré syndrome, and none showed positive PCR for the coronavirus on CSF; this fact suggests the pathophysiology of ganglioside molecular mimicry of the coronavirus antigens, with the immune system mistakenly attacking myelin or axons, the nerve conduits for signals to and from the brain [14,18,20,21,25-37].

Mao et al. found no difference in patients with and without peripheral nervous system manifestations [2]. Nevertheless, we found six patients that presented lymphocytopenia and one patient that presented with thrombocytopenia similar to the patients with central nervous system manifestation in CoVID-19 hospitalized patients that Mao et al. described [36]. All patients except one survived [37]. All patients were treated with immunoglobulin to reverse the GBS symptoms, and five patients required mechanical ventilation due to COVID-related respiratory failure. Some patients were treated with hydroxychloroquine based on the severity of respiratory symptoms, some were put on antibiotics for concurrent bacterial pneumonia, and some

were given antiretroviral therapy. The outcome of 3 patients was deterioration due to respiratory failure; three patients had severe neurologic symptoms related to GBS but recovered with IVIG. Respiratory severity was not comparable with neurologic severity [14,18,20,21,25-37].

Miller Fisher like syndrome: Miller Fisher is a rare variation of Guillain Barré that presents with a triad of areflexia, ophthalmoplegia, and ataxia. One case of Miller Fisher like syndrome associated to a SARS-CoV-2 infection was reported in a 74-year-old female with no neurological deficit background. The patient presented with a bilateral pneumonia secondary to coronavirus infection. 15 days after discharge, she presented with progressive gait impairment and lower limb areflexia. Strength and sensitivity were preserved, and no signs of ophthalmoplegia were found. Additionally, there was no demonstration of peripheral demyelination or axonal damage through 2 electromyographies (EMG), and no GD1-b antibodies were found. However, the patient displayed clinical improvement after 20 g/day of IV immunoglobulin for 5 days. On day 12, she was followed up, and CSF SARS-CoV-2 PCR was negative. More information is required to establish an association between this rare variation of Guillain Barré and SARS-CoV-2 infected patients [38,39] while pathogenesis of this syndrome could have similar pathways as Guillain Barré.

Conclusion

More research needs to be done regarding the pathogenesis of neurological components of SARS-Co-2. Overall there is not a common pathway for the pathogenesis for all the components of the neurological manifestations of SARS-CoV-2. Each component has its own pathogenesis, but some neurological manifestations share common features. The virus's entry also seems to be different between the central nervous system and the peripheral nervous system.

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