MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SUMY STATE UNIVERSITY
MEDICAL INSTITUTE

Eastern Ukrainian Medical Journal

2, Rymskogo-Korsakova st., Sumy 40007, Ukraine
e-mail: EUMJ@med.sumdu.edu.ua
eumj.med.sumdu.edu.ua
ISSN: 2663-5909 (print)

DOI: https://doi.org/10.21272/eumj.2021;9(3):219-227

Abstract

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CEREBROVASCULAR COMPLICATIONS OF COVID-19 (SYSTEMIC REVIEW)

The systematic online search of articles utilizing the search terms ”Coronavirus, SARS-COV-2 and Neurological complications”, published between January 2019 and September 2021, was performed.

Neurological manifestations are prevalent during infection with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There is a clear association between cerebrovascular disease and coronavirus disease 2019 (COVID-19). But today, whether this association is causal or incidental is still unknown. This systemic review presents the possible pathophysiological mechanisms linking COVID-19 and cerebrovascular disease, describes the most often neurological complications and their prognosis, discusses several clinical and laboratory characteristics.

A systematic literature search was conducted, and relevant information was abstracted. Angiotensin-converting enzyme-2 receptor dysregulation, uncontrollable immune storm with inflammation, coagulopathy, complications due to critical illness and prolonged hospitalization can all contribute as potential etiological and pathogenic mechanisms leading to diverse cerebrovascular clinical manifestations.

Acute ischemic stroke, intracerebral haemorrhage, and cerebral venous sinus thrombosis have been described in case reports and cohorts of COVID-19 patients, with a prevalence ranging between 0.5 % and 5.0 %. SARS-CoV-2-positive stroke patients have higher mortality rates, worse functional outcomes at discharge and longer duration of hospitalization as compared with SARS-CoV-2-negative stroke patients. Understanding of the specific demographic, clinical, laboratory and radiological characteristics may be used as ‘red flags’ in recognizing COVID-19-related acute neurological complications.

Keywords: ischemic stroke, coagulopathy, immune storm, COVID-19, hospitalization, symptom.

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Резюме

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ЦЕРЕБРОВАСКУЛЯРНІ УСКЛАДНЕННЯ COVID-19 (СИСТЕМНИЙ ОГЛЯД)

Систематичний пошук в інтернеті статей з використанням пошукових термінів «Коронавірус, SARS-COV-2 та неврологічні ускладнення», що були опубліковані з січня 2019 по вересень 2021 років.

Неврологічні прояви є дуже поширеними під час зараження коронавірусом 2 типу, що спричиняє тяжкий гострий респіраторний синдром (SARS-CoV-2). Існує чіткий зв'язок між цереброваскулярними розладами та коронавірусною хворобою 2019 року (COVID-19). Однак сьогодні невідомо, є ця асоціація причинною чи випадковою. Цей системний огляд представляє можливі патофізіологічні механізми, що пов'язують COVID-19 із цереброваскулярними захворюваннями, описує найчастіші неврологічні ускладнення та їх прогноз, а також деякі клінічні та лабораторні параметри неврологічних хворих.

Був проведений систематичний пошук літературних джерел із наступним аналізом відповідних даних. Дисфункція рецепторів ангіотензин перетворюючого ферменту-2, неконтрольований імунний шторм із запаленням, коагулопатія, численні ускладнення внаслідок тяжкої хвороби з тривалою госпіталізацією можуть сприяти розвитку потенційних етіопатогенетичних механізмів, що призводять до клінічних проявів різноманітних цереброваскулярних розладів.

Інфаркт головного мозку, внутрішньомозковий крововилив і тромбоз венозних пазух головного мозку описані у повідомленнях про випадки хворих на COVID-19, поширеність яких коливається в межах 0,5–5,0 %. Пацієнти з інсультами, що розвивалися на фоні SARS-CoV-2, мали вищі показники смертності, гірші функціональні результати після лікування та більшу тривалість госпіталізації порівняно з неінфікованими хворими. Глибше розуміння специфічних демографічних, клінічних, лабораторних та рентгенологічних характеристик може бути використано як «червоні прапорці» для розпізнавання гострих неврологічних ускладнень, пов'язаних із COVID-19.

Ключові слова: ішемічний інсульт, коагулопатія, імунний шторм, COVID-19, госпіталізація, симптом.

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How to cite/ Як цитувати статтю: Lychko VS, Burtyka MM. Cerebrovascular complications of COVID-19. *EUMJ*. 2021;9(3): 219-227
DOI: https://doi.org/10.21272/eumj.2021;9(3):219-227

Introduction/Вступ

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection triggered a global pandemic, resulting in more than 220 million confirmed cases and 4.5 million deaths in the middle of 2021 [1]. The clinical manifestations of the coronavirus disease 2019 (COVID-19) are highly variable, with 40–45 % of COVID-19 positive cases being asymptomatic [2]. According to current reports, SARS-CoV-2 is associated with neurological complications affecting the central (CNS) and peripheral nervous systems. Neurological manifestations can be nonspecific, such as headache, myalgia, psychosis, or more specific diseases and syndromes that

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require immediate medical attention [3, 4]. Pathological complications of COVID-19 are caused in most cases by a cytokine storm due to a strong release of pro-inflammatory cytokines [5].

Materials and methods of research. The systematic online search of articles utilizing the search terms ”Coronavirus, SARS-COV-2 and Neurological complications”, published between January 2019 and September 2021, was performed.

Results. The mechanisms of neurological manifestations associated with SARS-CoV-2 are still not fully understood. There are several mechanisms to explain these neurological disorders [6]. Angiotensin-converting enzyme-2 (ACE2) receptors, which are expressed in brain tissue, are the entry point for SARS-CoV-2 [7]. Often, postmortem analysis of patients with neurological manifestations of meningitis or encephalitis reveals the virus in the frontal lobe [8]. On the other hand, some studies have shown that the SARS-CoV-2 virus was not detected in the CNS [9-11]. It was believed that the detection of the virus is associated with the destruction of the blood-brain barrier (BBB) or the presence of viral particles in situ [9, 11]. Many patients with severe COVID-19 disease experience a surge in pro-inflammatory cytokines, a condition known as a cytokine storm [12]. This causes damage to the BBB, which is documented in acute necrotizing encephalopathy [13]. A cytokine storm can also cause headaches, which on average appear on days 7–10 of COVID-19 [14]. The role of hyperactivation of the immune system is also confirmed by the response of patients with Guillain-Barré syndrome to therapy with immunoglobulin and the presence of GD1b-IgG in patients with Miller-Fisher syndrome [15-17].

SARS-CoV-2 viral-like particles may be detected in the brain capillary endothelium [8]. This finding supports viral neurotropism and potentially implicates one directly affecting cerebral vessels with subsequent endothelial dysfunction [18]. SARS-CoV-2 has also been involved in triggering CNS vasculitis due to an inflammatory response mediated by the cytokine storm [19]. Inflammation of cerebral vasculature may lead to arterial remodelling with either stenosed or dilated, fragile vessels with subsequent ischemic or hemorrhagic strokes. Reversible cerebral vasoconstriction syndrome and posterior reversible encephalopathy syndrome may mimic primary angiitis of the CNS in COVID-19 patients, which provoke ischemic stroke (IS), intracranial and convex subarachnoid haemorrhages [20].

Another way includes the discoordination of kinesins and dynein proteins in the transport of the virus into the CNS using infected motor or sensory nerves [21]. The SARS-CoV-2 can also enter the CNS through olfactory sensory neurons. It’s a more familiar route for respiratory coronaviruses [22]. For the first time, the potential mechanism of CNS infection is known from a 2004 study, which reported the presence of HCoV-OC43 in the nasopharynx and cerebrospinal fluid (CSF) in a child with acute disseminated encephalomyelitis [23]. Additional studies in mice confirmed the development of acute encephalitis in mice infected with HCoV-OC43 and HCoVOC43-induced apoptosis in neuronal cells of mice and rats [24]. This demonstrates the neurotropic characteristics of HCoV and the ability to infect the CNS.

One of the explanations for this immune response was molecular mimicry when a foreign antigen could induce immune cells against an autoantigen, which is due to the similarity of the sequences of foreign and self-peptides [25]. This phenomenon is always involved in many neurological diseases, such as multiple sclerosis and Guillain-Barré syndrome [26]. The role of autoantibodies in neurological complications was first suggested in connection with the occurrence of Guillain-Barré syndrome in patients with COVID-19 [25]. A typical immunogenic sequence was found between SARS-CoV-2 and HSP90B, a heat shock protein [27]. A high titer of autoantibodies against broad epitopes of the nervous system was revealed in critically ill patients with unexplained neurological complications [28]. These autoantibodies were against some neuronal proteins like endothelial cells, N-methyl-D-aspartate receptors, astrocytes and neuropils of the basal ganglia, hippocampus, and olfactory bulbs [28].

The current assessment of the CSF virus invasion is minimal, and positive results are rare [29]. A systematic review [30] showed that only 6.0 % of patients who underwent CSF analysis tested positive for SARS-CoV-2. The number of lymphocytes in the cerebrospinal fluid increased in 43 % of deaths, 25.7 % of severe cases and 29.4 % of non-severe instances [30]. Most of these patients had neurological symptoms associated with damage to the CNS. The most common finding in CSF in patients with COVID-19 is increased protein content [31]. Fatal patients in 100.0 % of cases had higher levels of proteins in the CSF, on average 6.12 g/l, compared with moderate (65%), on

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average 5.67 g/l. It was also found that the level of protein in the CSF is increased in 74.5 % of patients with mild COVID-19.

There is evidence of immune compartmentalization in the CNS of patients with COVID-19. This is evidenced by specific immunological changes in the CSF when elevated levels of interleukin (IL)-12 and IL-1b were detected, but not in the plasma of patients with COVID-19 with neurological complications. Also, the profiles of antibodies to SARS-CoV-2 differed in the CSF and plasma of patients with COVID-19 [32].

The presence of autoantibodies has also been associated with a higher incidence of neurological and thrombotic complications [33]. In the search for homologous sequence between human proteins and SARS-CoV-2, four substances have been identified: heat shock protein A5 (HSPA5), titin, ryanodine receptor 2 (RYR2), and heat shock protein 90 alpha, member 1 of class B (HSP90AB1) [34].

Another factor influencing the neurological complications of COVID-19 is related to the severity of the disease. Coagulation disorders accompanying COVID-19 can cause ischemic stroke [35]. Also, hypoxia and electrolyte changes of brain tissue mediated by COVID-19 can cause severe complications up to changes in mental status [36]. Some histopathological examinations reveal diffuse petechial cerebral haemorrhage accompanying lymphocytic encephalitis or meningitis. Loss of neuronal cells and degeneration of axons have been reported in many parts of the brain [37, 38]. This occurred more often in the dorsal motor nuclei of the vagus nerve, the trigeminal nerve, nucleus tractus solitarii, dorsal raphe nuclei, and fasciculus longitudinalis medialis [39].

A characteristic subcortical white pathology with axonal loss, macrophage infiltration, and perivascular acute disseminated encephalomyelitis were also found. Still, deep grey nuclei of the brain stem are not involved in the pathological process. These features are not typical for viral or post-viral encephalitis and cannot be explained by global hypoxic damage to the brain tissue [40].

Nonspecific neurological symptoms in patients with COVID-19 include headache, changes in mental status, dizziness, decreased level of consciousness, ageusia, anosmia, myalgia, and general weakness [3, 4]. Patients with severe clinical manifestations of COVID-19 are more likely to experience neurological symptoms than those with mild disease. CNS lesions were more common (24.8 %) than the peripheral nervous system (8.9 %). Musculoskeletal symptoms were observed in 10.7 % of patients [3]. Headache frequency was about 8.0 %, myalgia and general weakness 44.0 % [4], altered mental state 9.0 % [41]. Olfactory (35.7–85.6 %) and gustatory (33.3–88.8 %) disorders are common neurological manifestations of COVID19 [42]. Among these patients, 11.8 % indicated that the olfactory dysfunction preceded other symptoms and was significantly associated with fever and taste symptoms, but not with rhinorrhea or nasal dysfunction [43].

Headache is the fourth most common neurological symptom (70.0 %) [42–44]. It can sometimes be an isolated symptom of COVID-19 [45]. Today, we view headache as an independent predictor of lower mortality risk in hospitalized patients with COVID-19 [46].

The presence of coagulation disorders indicates a potential link between the pathogenesis of COVID-19 and stroke. Some patients with COVID-19 develop acute focal neurologic symptoms without any previous potential comorbidities [47]. Almost all patients have occlusion of large vessels against the background of hypercoagulability [48]. The presence of hypertension and hypercoagulability in stroke patients indicated a poor prognosis [49]. Cerebrovascular complications have been documented in 5.0 % of COVID-19 patients, with 60.0 % of these events attributed to an acute IS [50]. Patients with COVID-19 are more likely to develop the severe illness than patients without COVID-19 [51]. Several studies have reported a significant increase in the neutrophil-to-lymphocyte ratio, C-reactive protein and serum ferritin, which could predict mortality in these patients [52, 53].

The hypercoagulability and the increase in thrombi formation could be explained by impaired fibrinolysis, low levels of natural anticoagulants and high levels of coagulation factors [54]. The appearance of thrombi is further potentiated by SARS-CoV-2-mediated damage of the endothelium, which results in nitric oxide synthase (NOS) depletion and subsequent deficiency of the nitric oxide (NO). That increases the risk of stroke because NO is a potent vasodilator, an inhibitor of platelets and leukocytes adhesion to the endothelium [55].

Regarding the IS subtype, COVID-19 is associated with a higher incidence of cryptogenic

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stroke when it can be 35.0 % among patients with IS. Decreasing the prevalence of lacunar infarction (⩽10.0 %) among them indicate the potential lack of association between COVID-19 and intrinsic small-vessel disease [56].

Many patients with SARS-CoV-2 infection may need intubation, mechanical ventilation, and prolonged hospitalization in intensive care units. Hypoxemia and systemic hypotension due to primarily immune-mediated critical illness may further induce hypoxic encephalopathy or IS, mostly in watershed territories or presenting as cortical necrosis. Prolonged hypoxemia has been associated with cerebral microbleeds and leukoencephalopathy [57].

Venous thromboembolic events, such as pulmonary embolism and deep venous thrombosis, are detected in COVID-19 patients despite anticoagulation treatment. Cases with more atypical presentations, such as cortical or deep cerebral venous thrombosis (CVT), have been described [58]. Headache and impaired consciousness may complicate or even be the presenting symptoms of both COVID-19 and CVT. For that reason, clinicians should be vigilant to diagnose CVT, complicating COVID-19 on time [59].

The COVID-19-induced severe inflammation and inflammatory infiltrate consisting of T cells, macrophages and neutrophils contribute to the rupture of atheromatous plaques in patients with pre-existing atheromatous disease due to the production of proteolytic enzymes and endothelial cell disruption [60].

In addition to ischemic stroke, intracranial haemorrhage was observed in 0.5 % of COVID-19 patients [61]. It's also possible that reduced levels of ACE2 on endothelial cells of the brain microvasculature lead to blood coagulation and increased blood pressure, which may result in the rupture of blood vessels [62].

Discussion. By the end of 2021, the causative relationship between SARS-CoV-2 and stroke is less debatable. The review presents the potential underlying mechanisms of the association between COVID-19 and cerebrovascular disease: ACE2 receptor dysregulation, immune storm, coagulation disorders, and critical illness.

The COVID-19-positive cohort had more severe strokes and a higher prevalence of cryptogenic stroke mechanism and lobar stroke location. They had mild coagulopathy, but the majority had elevated inflammatory markers. Most significantly, outcomes were much worse in the COVID-19-positive cohort compared with the COVID-19-negative cohort, and 33.3 % suffered in-hospital death. The overall IS incidence during the COVID-19 pandemic decreased, perhaps because people avoided seeking health care for more minor symptoms or symptoms that went unrecognized in hospitalized patients whose deficits may have been masked by other sequelae of critical illness or sedation.

Cryptogenic ischemia due to large-vessel occlusion appears to be the most common manifestation of acute cerebral ischemia, while lacunar stroke is rarely reported to complicate SARS-CoV-2 infection. Lobar or subcortical intracranial haemorrhages are the most prevalent hemorrhagic CNS manifestation of COVID-19. Importantly, cerebral venous thrombosis may seldom (0.5 %) represent the initial manifestation of COVID-19 in patients with underlying hypercoagulability.

During the COVID-19 limitation period, patients admitted with large vessel occlusion may require mechanical thrombectomy. Patients with significant delays for fear of contracting COVID-19 were initially admitted to the emergency department outside the time window for available acute reperfusion therapy.

Current treatment and management of patients presenting with active ischemic or hemorrhagic strokes don't differ from current recommendations, based on patients' pre-existing conditions. But current recommendations for monitoring hospitalized at-risk patients should include complete blood count, fibrinogen levels, D-dimer, prothrombin time, activated partial thromboplastin time, and inflammatory markers such as C-reactive protein and IL-6.

A generalized inflammatory state may cause nonspecific clotting factor dysfunction and may be seen in other disease entities such as influenza. Viral translation through ACE-2 receptors expressed in vessel walls may cause endotheliitis. Along with this mechanism, metalloproteinase activation and procoagulant gene expression may contribute to thrombus formation and explain the phenomenon of intramural thrombi and large vessel occlusions, which seem to be more common in infected patients with varying disease severity.

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Conclusions/Висновки

We are posed with a massive challenge of the current COVID-19 pandemic. Several cerebrovascular complications have been described in COVID-19 patients. However, more research is required today to understand the pathogenic mechanism behind each of them to treat such patients better. Some of the available treatment options might potentially lead to a decreasing in neurological sequelae. Therefore, treating COVID-19 patients with neurological complications should consider the existing or yet unknown mechanisms that may be developed.

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(received 01.09.2021, published online 29.09.2021)

(одержано 01.09.2021, опубліковано 29.09.2021)

Conflict of interest/Конфлікт інтересів

The authors declare no conflict of interest.

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