Cerebral strokes with coronavirus infection

Yo'lchiev Elmurod O'ktamjon o'g'li

Fergana Medical Institute of Public Health
Ferghana Multidisciplinary Medical Clinic

ABSTRACT

The main mechanisms of penetration of a new coronavirus infection into the central nervous system, risk factors for the development and forms of cerebral vascular complications, are considered, and their own clinical observation is described. Key words: coronavirus disease, vascular risk factors, neurological complications, strokes.

Keywords: Covid -19, neurological complications, acute cerebrovascular accidents, ischemic stroke

Coronaviruses (coronaviridae) are a family of RNA viruses capable of infecting humans and some animals that were first isolated in 1975. Representatives of this family are MERS- CoV coronaviruses (Middle-East respiratory Syndrome), SARS- CoV (severe acute respiratory syndrome). The last one, SARS- CoV , appeared in 2002 as the causative agent of SARS. The World Health Organization in February 2020 assigned the official name of the infection caused by the new coronavirus SARS-CoV-2 - " Coronavirus disease 2019, or COVID-19.

The coronavirus disease COVID-19 is a pandemic disease that currently affects millions of people. According to Johns Hopkins University , more than 114,000,000 cases of infection have been recorded, and 2,530,716 people have died. According to the Ministry of Health as of February 1, 2023, in Uzbekistan More than 250,000 people have been infected with the coronavirus .

The clinical picture of COVID-19 usually develops 5-7 days after infection and includes cough, fever, shortness of breath, myalgia, diarrhea, nausea and vomiting [3, 22, 26]. In most cases, the infection is mild and/or asymptomatic . The danger of the disease lies in the rapid increase in hypoxemia against the background of bilateral lung damage (pneumonitis), which requires respiratory support, and in the development of multiple organ complications. at Wuhan University Hospital neurological manifestations of a new coronavirus infection were described in 78 (36.4%) patients and divided into 3 categories [29]:

- symptoms from the central nervous system (dizziness, headache, impaired consciousness, acute cerebrovascular pathology, ataxia and convulsive seizures) - in 24.8% of cases;
- symptoms from the peripheral nervous system (impaired taste, smell, vision, neuropathic pain syndrome) - in 8.9%;
- damage to skeletal muscles (myalgia associated with an increase in the level of creatine phosphokinase) - in 10.7%.

According to statistical data, 450 patients, 198 (44%) men and 252 (56%) women, with cerebrovascular diseases of the brain, confirmed by neuroimaging and COVID-19 infection. Of these, cerebral infarcts were detected in 402 (89.28%) patients,

intracerebral parenchymal and subarachnoid hemorrhages - in 48 (10.72%) patients. Mortality was 20.66% (93 patients).

In a pandemic, neurological lesions appear in approximately 36.4% of Covid -19 patients [2, 29]. According to R. Daci et al . [14], complications from the central nervous systems (CNS) may occur in up to 50% of patients with novel coronavirus infection and include encephalopathy, anosmia, ageusia , headache, dizziness, seizures, stroke, increased intracranial pressure, meningitis- SARS - CoV ^, and necrotizing encephalitis.

The incidence of cerebrovascular disease in 221 cases of COVID-19 analyzed by Y Li et al . [25] was 5.9%. This subgroup of patients as a whole was characterized by a more severe course of the infectious process and severe comorbidity with the presence of such risk factors as arterial hypertension, diabetes mellitus, coronary heart disease.

a systematic review and meta analysis of the Ying-Kiat literature Tan , Claire Goh et al . noted [44] that the incidence of acute ischemic stroke in patients with COVID-19 ranges from 0.9 to 2.7%. Francisco observation series Hernandez-Fernandez et al ., AM Neishaboori et al . [23, 34] showed a similar incidence of cerebrovascular complications in patients with COVID-19 with high morbidity and mortality. Acute cerebrovascular accident (ACC) was registered in 2.8%, with 5.7% of patients with severe and 0.8% with non-severe infection [29]. Another systematic review and meta-analysis [38], based on 30 studies and 899 strokes, found that the mean incidence of stroke as a complication of COVID-19 was 1.74% with a mortality rate of 1.76%. Recently, a 7-fold increase in the chance of stroke was reported with COVID-19 compared with influenza [31].

The SARS-CoV-2 virus exhibits neurotropism in relation to the central and peripheral nervous systems. Various infectious mechanisms can be used by the virus to penetrate the CNS, some of them bypass the blood-brain barrier (BBB), others change its integrity [36].

Several possible mechanisms for the introduction of this new virus are described and analyzed, including direct neuronal injury, acute ischemic injury from respiratory distress and/or hypercoagulability , autoimmune changes from an induced " cytokine storm" with BBB damage, and vasculitis [36].

Currently, four ways of penetration of coronavirus infection into the structures of the nervous system are suggested [4].

- The first way is airborne , through the olfactory nerves [3].

- The second way of penetration of the virus into the CNS is cellular invasion. In this case, coronavirus- infected monocytes and macrophages penetrate the BBB and mediate neuroinvasion [12]. Research in vitro showed that the affected monocytes and macrophages can be a reservoir for the virus and contribute to its spread to other tissues [16, 17].

- BBB endothelial cells are the third possible route of neuroinvasion ; they are able to express two types of receptors - ACE2 and CD209L [25], interacting with which SARS-CoV-2 can enter the CNS.

- The fourth possible way for coronavirus to enter the nervous system is transsynaptic transmission through peripheral nerves [28].

Angiotensin-converting enzyme 2 (ACE2), a vascular protective factor for various organs, the nervous system, and skeletal muscles, is an input receptor and target for SARS-CoV-2 [2, 4h]. The binding sites of the spike protein of this virus to ACE2 are on the surfaces of epithelial cells lining the mucous membranes of the nose, upper respiratory tract and oral cavity, type II bronchoalveolar cells in the lung parenchyma, intestinal enterocytes, which makes the epithelial mucous membranes the most likely points of entry for the virus . Neuronal and glial, endothelial cells of the central nervous system also have localization of the ACE2 enzyme (Fig. 1) [7].

Cerebral complications can manifest themselves with systemic endothelial dysfunction, interaction of the new coronavirus spike protein in the capillary endothelium. Studies have shown [41] that SARS-CoV-2, an infection that affects endothelial cells and contributes to the development of endothelitis , vasoconstriction , edema, and a procoagulant

state, is a significant risk factor for the occurrence of cerebrovascular stroke. It is believed that through ACE 2 receptors coronavirus can induce direct damage to neurons in the cardiorespiratory centers of the brainstem [33].

C. Esenwa , N. T. Cheng, E. Lipsitz And et al . _ [20] proposed a new stroke mechanism: CoviD -associated atherothrombosis of the carotid artery. Areas of mild carotid atherosclerosis may be particularly prone to thrombus formation in patients with COVID-19 due to the unique combination of endotheliitis and COVID-19-associated coagulopathy . Recently, von Willebrand factor has been identified [19] as a marker of endothelial injury in COVID-19. Thrombocytopenia, increased levels of D- dimer and C-reactive protein, fibrin, fibrinogen or fibrinogenic decay products are often described in ischemic cerebrovascular accidents accompanying COVID-19, which indicates an intense inflammatory reaction and pathology of the coagulation cascade in the pathogenesis of cerebral arterial and venous thrombosis [3, 10, 24]. The studies also revealed a notable number of cases of positive testing for anti-phospholipid antibodies.

One of the possible pathways for the development of cerebral vascular complications of coronavirus infection may include destabilization of atherosclerotic plaques and promote atherothrombosis , another pathway contributes to cardioembolic stroke due to myocardial dysfunction and arrhythmia [9].

Respiratory viruses, including coronaviruses , damage the CNS also through an immune-mediated mechanism and/or by direct damage to nerve cells after a viral invasion [16]. Coronavirus COVID-19 causes a systemic inflammatory cascade of cytokines - the so-called " cytokine storm" (Fig. 2) [24]. It has been suggested that systemic H syndrome hypothetically alternative routes of entry of SARS-CoV-2: 1) the affected enterocytes of the intestine through the capillary network of the portal veins of the liver create the possibility of a hematogenous mechanism for the virus to enter the CNS; 2) hematogenous way - the mechanism of the "Trojan horse" after infection of the submucosal connective tissue; 3) retrograde path through the mesenteric nerve plexuses and sensory neurons of the spinal ganglia (according to Francisco J. Barrantes)

Recently, many publications [5, 28] indicate that coronaviruses first penetrate peripheral nerve endings and, propagating retrogradely through synapses, reach the CNS. PCR tests can be pseudo-negative, while chest tomography of patients can show up to 96% of pathological changes [42] .

However, there is still no absolute evidence that stroke is directly related to COVID-19. Cerebrovascular neurological disorders found in patients with coronavirus infection COVID-19 have a wide range of clinical signs: headache, dizziness, altered level of consciousness, acute ischemic stroke, intracerebral hemorrhage, dissection of cerebral vessels, cerebral venous sinus thrombosis.

Against the background of a new SARS-CoV-2 coronavirus infection, the predominance of cases of ischemic stroke (86.4%) in the basin of the middle cerebral artery according to unspecified (41.4%), embolic and atherothrombotic (35.7%) pathogenetic subtypes was noted [1] (according to TOAST). With COVID-19, a higher rate of cryptogenic stroke was found than in individuals without coronavirus infection (69% vs. 17%, respectively) [18]. A retrospective study of 1683 patients with COVID-19 in Spain found [23] that 17 (73.9%) of all 23 patients with stroke had ischemic stroke, 5 (21.7%) had intracerebral hemorrhage, and 1 had posterior reversible leukoencephalopathy (or PRES).

The severity of ischemic stroke observed in COVID-19 is usually moderate (NIHSS score - 19 ± 8) and is characterized by significant occlusion of a large vessel (40.9-58.8%) and a high mortality rate - 35.3-38, 0% (Fig. 3) [23, 44].

Analysis of cases of cerebral infarction in patients with COVID-19 by other authors [8, 23] revealed the involvement of the posterior cerebral circulation pool (35.3%) and multiterritorial lesions of the brain parenchyma. The data obtained corresponded

to the thrombotic endothelial microangiopathy (Fig. 4).

The most characteristic feature of neuroimaging in cerebral strokes is symmetrical, multifocal lesions involving the thalamus. Other common lesions are found in the brainstem, white matter, and cerebellum. Extensive lesions in the corpus callosum of C. Rasmussen et al . [36] associated with the " cytokine storm". An atypical increase in the signal along the medullary veins has also been described, which occurs in vasculopathies such as posterior reversible encephalopathy syndrome, Susac syndrome , neurosarcoidosis , as well as in patients infected with HIV [13].

Patients with COVID-19 are predisposed to venous and arterial thromboembolism, which may increase the risk of ischemic stroke in young and middle-aged patients, even in early stages and in mild forms of COVID-19. A study of individuals with COVID-19 in the intensive care unit showed that the incidence of thrombotic complications was extremely high (31%) (Fig. 5) [23].

Recently, COVID-19, inducing a hypercoagulable state , has been postulated as a risk factor for cerebral venous sinuses (Figures 6, 7) [15]. Pulmonary embolism and deep vein thrombosis are already well described in patients with novel coronavirus infection, but so far few reports of cerebral venous sinus thrombosis have been published [11, 35]. Thus, cerebral venous thrombosis was detected in 14 middle-aged people (43 years) with frequent lesions of the transverse (75.0%) and sigmoid (50.0%) sinuses of the brain and in 33.3% with involvement of deep cerebral veins [35 , 39].

It is assumed that COVID-19 infection can also contribute to another complication - hemorrhagic stroke, the frequency of which, according to various authors, is quite variable (Fig. 8). DJ Altschula et al . [6] analyzed 35 (0.66%) different types of intracranial hemorrhage (ICH) (followed 5227 patients with COVID-19) and emphasized that these cerebral hemorrhages may be without primary pulmonary symptoms, but they are accompanied by high mortality (up to 45, 7%). In other studies, individuals with ICH revealed an elevated level of ferritin , a marker of the severity of coronavirus infection [23]. According to V.V. Andreeva et al . [1], parenchymal hemorrhage is observed with a higher frequency (54.5%) in hemorrhagic stroke. A retrospective cohort study of 416 middle-aged patients (69.3 ± 16.2 years) with confirmed COVID-19 who underwent neuroimaging revealed intracerebral hemorrhage in 7.9% (33/416) [30]. According to Sanskriti Mishra et al . [37], COVID-19-associated ICH was diagnosed in 65 (20%) of 324 stroke patients.

Conclusions. Thus, C0VID-19 is a new infection that is not yet well understood. It is accompanied by micro- and macrovascular complications from various organs and systems, including severe cerebral catastrophes. Acute ischemic and hemorrhagic strokes are life-threatening complications. They lead to a worse clinical prognosis in patients with coronavirus disease.

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