

Clinical and Neurological Factors in the Formation of Individual Predisposition to Covid-Associated Ischemic Stroke

Kazakov Bekzod Shodiyorovich¹, Khodjiyeva Dilbar Tadjiyevna²

¹Assistant of the Department of Neurology, Bukhara State Medical Institute, Bukhara, Uzbekistan

²Head of the Department of Neurology, Bukhara State Medical Institute, Bukhara, Uzbekistan

Abstract Long duration of mechanical ventilation makes patients with COVID-19 who require invasive respiratory support more vulnerable to complications associated with the development of critical illness, including the risk of hypotension and inadequate cerebral perfusion; risk of relative hypertension leading to posterior reversible encephalopathy syndrome; the possibility of septic embolism in the event of a bacterial infection; the possibility of cardiomyopathy and a concomitant decrease in the left ventricular ejection fraction.

Keywords COVID-19 pandemic, SARS-CoV-2, Rehabilitation, Recommendations, Atrial fibrillation, Cognitive impairments

1. Introduction

Acute disorders of cerebral circulation are the most important medical and social problem. There are more than 1 million people with ischemic stroke in Uzbekistan, and more than 80% of them have disabilities. The mortality rate of ischemic stroke, in the acute stage, is 35% [1]. Cognitive impairments of varying severity are detected in 40 - 70% of patients with ischemic stroke. The prevalence of dementia in the first 3-6 months after stroke ranges from 5 to 32%, and after 12 months - from 8 to 26% [2].

Endocrinopathies are one of the significant risk factors for cerebrovascular diseases. The number of such patients is increasing in all economically developed countries of the world. Diabetes mellitus is the most common endocrine disease associated with cerebrovascular accident. According to the results of statistical studies of recent years, more than 10% of patients with type 2 diabetes mellitus die due to impaired cerebral circulation [3]. Cognitive impairments in patients with ischemic stroke and type 2 diabetes mellitus differ in a number of features, however, studies on this problem are few and contradictory.

At the end of 2019, an outbreak of a new coronavirus infection occurred in the People's Republic of China (PRC) with an epicenter in the city of Wuhan (Hubei province), the causative agent of which was given the temporary name 2019-nCoV. On February 11, 2020, the World Health Organization (WHO) assigned the official name of the

infection caused by the new coronavirus - COVID-19 ("Coronavirus disease 2019"). On February 11, 2020, the International Committee on Virus Taxonomy assigned the official name to the infectious agent - SARS-CoV-2. The COVID19 pandemic was declared by WHO on 9 March 2020.

Taking into account the development of the epidemic process in the world, the health professionals were assigned tasks related to the rapid diagnosis and provision of medical care to patients. Along with the methodological recommendations aimed at the prevention, diagnosis and treatment of new coronavirus infection in the general population scale, it became necessary to focus on certain categories of patients at special risk groups. WHO has identified the leading non-communicable diseases that increase the likelihood of infection with COVID-19: cardiovascular and chronic respiratory diseases, diabetes mellitus (DM) and oncology. These patients are not only at high risk of infection. The course of COVID19 in this category of patients is complicated by the decompensation of chronic diseases, the progression of complications, atypical manifestations of the infectious process, which are additional risk factors for premature death. It is also necessary to take into account drug interactions in comorbid patients and the effect of the discussed specific therapy on the course of chronic diseases.

Various possible and non-mutually exclusive mechanisms may play a role in the development of ischemic stroke in patients with COVID-19. Long duration of mechanical ventilation (ALV) makes patients with COVID-19 who require invasive respiratory support more vulnerable to

complications associated with the development of critical illness, including the risk of hypotension and inadequate cerebral perfusion; risk of relative hypertension leading to posterior reversible encephalopathy syndrome; the possibility of septic embolism in the event of a bacterial infection; the possibility of cardiomyopathy and a concomitant decrease in the left ventricular ejection fraction.

In addition, severe COVID-19 has been associated with a hyperinflammatory condition (“cytokine storm”) [16]. COVID-19 increases levels of pro-inflammatory molecules, including interleukin (IL) -1 and -6 [17]. The systemic inflammatory response can also lead to rupture or erosion of atherosclerotic plaque and destabilization of previously asymptomatic cardiovascular conditions such as myocardial infarction (MI), heart failure, and myocarditis [18,19].

Moreover, patients with COVID-19 may develop more severe coagulopathy, defined as “coagulopathy associated with COVID-19”, which is induced by an acute systemic inflammatory response, presumably mediated by an infectious agent or its products. SARS-CoV-2 can lead to severe inflammation, including an inflammatory “cytokine storm,” which in turn leads to “COVID-19-associated coagulopathy” or thrombosis [20].

2. Materials and Methods

Disseminated intravascular coagulation syndrome (DIC) is more common in patients with COVID-19 compared with patients with other causes of critical illness. N. Tang et al. reported 8.7% of cases of disseminated intravascular coagulation, while mortality was 94% [1]. It was also found that mortality was associated with higher levels of fibrin degradation products, prolonged prothrombin time and partial activated thromboplastin time [2]. According to data from Wuhan, D-dimer levels were elevated in 36% of patients with COVID-19 [3], which was associated with a higher mortality risk [14], presumably associated with an increase in thrombotic complications. Although many patients with COVID-19 have suffered strokes due to cardioembolism and atherosclerotic lesions of large vessels [9], it has been suggested that inflammatory and hypercoagulable mechanisms, including the presence of antiphospholipid antibodies, may contribute to the occurrence of thrombotic complications [4]. Preliminary reports from China describe patients with COVID-19 who developed multiple bilateral ischemic cerebral infarctions, antiphospholipid antibodies, and hematologic findings consistent with acquired thrombophilia [24].

Z. Varga et al. demonstrated that SARS-CoV-2 causes an infection that affects endothelial cells and promotes the development of endotheliitis [5]. The development of systemic vascular endotheliitis contributes to vasoconstriction, edema and procoagulant state [6], which is of great importance for the development of cerebrovascular stroke. According to A.J. Flammar et al. [7] endothelial microvascular dysfunction leads to vasoconstriction with subsequent organ ischemia, inflammation with associated

tissue edema and prothrombotic state [9]. Endothelial dysfunction is also an important factor in the development of atherosclerosis [7].

During the first outbreak of atypical pneumonia in the early 2000s, in postmortem studies, vasculitis was detected in several arterial regions [28], and it is not known whether this pathology occurs in severe acute respiratory syndrome caused by coronavirus infection. COVID-19 may also indirectly affect cardiovascular disease through heightened emotional responses in patients, such as stress [29].

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At the moment, there is a situation in the world in which reliable professional information about the provision of medical care, especially rehabilitation, to patients with COVID-19 (Corona virus Disease - a coronavirus disease that arose in 2019) is not enough, since this disease is new. The traditional method of obtaining the necessary information by drawing on data from previously performed scientific studies has proved ineffective, since the experience of treating patients with a new coronavirus infection is measured in only a few months. Given the unusual situation of the pandemic itself and the peculiarities of the pathogenesis of the disease caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome-related CoronaVirus 2, severe acute respiratory syndrome associated with coronavirus 2), the routine use of generally accepted developments may be unsafe or ineffective. Reports from organizations and clinics that are currently providing assistance for patients with COVID-19 and already have initial experience in providing rehabilitation assistance to these patients come to the fore in the development of recommendations. A timely revision of the recommendations is required, and a huge responsibility in this work falls on the professional associations of rehabilitation therapists [1].

It has now been shown that neurological symptoms are more common in patients with severe infection who develop IS, GI, and encephalopathy [8]. Thus, among 214 patients hospitalized in Wuhan (China), 78 patients had neurological symptoms [8]. Cerebrovascular disease was observed in 6 (2.8%) patients and was more common in more severe disease (5 out of 6 patients). J. Helms et al. investigated 58 patients with COVID19, of whom 13 underwent MRI of the brain, Ischemic stroke developed in 3 out of 13 patients (23%) [1]. Li Y et al. reported that of 221 patients with COVID-19, 11 (5%) had acute ischemic stroke, 1 (0.5%) had venous sinus thrombosis, and 1 (0.5%) had intracerebral hemorrhage [9] ...

Among hospitalized patients with COVID-19, Ischemic stroke was the most common and more common among elderly and middle-aged people with vascular risk factors,

with 38% of them dying [8,9]. It was also noted that COVID-19 developed more often in people with vascular risk factors, and among them there was a higher mortality rate [10]. In a recent meta-analysis of 76,993 COVID-19 patients [11], the overall prevalence of hypertension, cardiovascular disease, history of smoking and diabetes mellitus (DM) was estimated at 16.37% (95% CI: 10.15-23.65 %), 12.11% (95% CI 4.40-22.75%), 7.63% (95% CI 3.83-12.43%) and 7.87% of cases (95% CI 6, 57-9.28%), respectively. Another systematic review also showed that hypertension and diabetes mellitus were the predominant comorbidities [12].

In New York, a retrospective cohort study of patients with ischemic stroke who were admitted to hospital between March 15 and April 19, 2020 was conducted [7]. During the study period, of 3556 hospitalized patients with COVID-19, 32 patients (0.9%) had visually confirmed ischemic stroke. Out of 32 patients, stroke was the cause of hospitalization in 43.8%, symptoms of COVID-19 were the cause of hospitalization in 56.2%, while the stroke developed during hospitalization. The average age of 32 patients with COVID-19 and stroke was 62.5 (52.0-69.25) years, 71.9% (23/32) were men. The cryptogenic subtype Ischemic stroke was diagnosed in 65.6% of patients (21/32), and 34.4% (11/32) met the criteria for embolic stroke of unknown source. The average time from the first symptoms of COVID-19 to the detection of a stroke averaged 10 (5-16.5) days. The most prominent clinical manifestations were cough (84.4%), fever (71.9%) and hypoxia (78.1%). At the last follow-up, 81.3% of patients (26/32) met the criteria of a severe illness, while 75.0% of them (24/32) died or were seriously ill. The mean pre-stroke D-dimer level was 3913 ng / ml (2549-10,000), and the mean C-reactive protein level was 101.1 ng / ml (38.8-214.3). Treatment prior to the onset of stroke symptoms / diagnosis included hydroxychloroquine (40.6%, n = 13), lopinavir / ritonavir (3.1%, n = 1), and tocilizumab (6.3%, n = 2). Based on the study, the authors concluded that compared with modern controls, patients with COVID-19 and stroke were younger (mean 63 years versus 70 years, $p = 0.001$), had a higher NIHSS score upon admission (mean NIHSS 19 versus 8 points, $p = 0.007$), higher peak D-dimer level (mean value: > 10,000 versus 525 ng / ml, $p = 0.011$), were more often treated with anticoagulants (78.1% versus 23.9%, $p < 0.001$), more often had the cryptogenic subtype of stroke (65.6% versus 30.4%, $p = 0.003$), there was a higher mortality rate in the hospital (63.6% versus 9.3%, $p < 0.001$) [7].

Epidemiological data on the incidence of stroke during the COVID-19 pandemic have not yet been published, but individual studies indicate an increase in the incidence of thrombotic stroke in young patients [13].

3. Result and Discussion

In the setting of COVID-19 infection, patients with vascular risk factors may have an increased risk of stroke

[11,14]. So, in Italy, out of 355 patients who died from COVID-19, 352 had concomitant diseases, including diabetes mellitus - in 35.5%, coronary heart disease - in 30%, atrial fibrillation - in 24.5% and stroke - in 9.6% [15].

In recent years, a number of clinical studies have been carried out to study the effectiveness and safety of the drug. In one of the first studies (multicenter comparative open clinical study), the therapeutic efficacy and tolerability of Cellex in the treatment of patients with ACVA was assessed on the basis of 6 Russian clinical centers with the inclusion of 178 patients aged 35 to 80 years (146 with ischemic stroke and 32 with GI). Upon completion of 4-week therapy in the group of patients receiving Cellex, significantly better outcomes with regression of motor, visual, speech, and sensory disorders and a good safety and tolerability profile of the drug in real clinical practice were observed [41]. In 2013, upon completion of the TSEL-IV-2013 double-blind randomized controlled trial, conducted in 8 large Russian clinics with the inclusion of 480 patients, the efficacy and safety of the drug in the treatment of patients with IS were also shown. In the main group (240 patients, including 136 men, 104 women; average age - 62.6 years), in addition to standard stroke therapy, Cellex was prescribed at a dosage of 0.1 mg (1 ml) 1 r / day (in morning or afternoon hours), starting from the first day of the patient's inclusion in the study, and in the control group (240 patients, including 139 men, 101 women; mean age 63.8 years), in addition to the ongoing therapy, patients were injected subcutaneously 1 , 0 ml of 0.9% sodium chloride solution 1 r / day for 10 days. The results showed that the use of Cellex in the acute period of ischemic stroke led to a significant decrease in the number of patients with progression of neurological symptoms by the end of the acute period of the disease: in the main group, the proportion of patients with clinical improvement was 84.6%, in the placebo group - 67.0% ($p < 0.05$). Also, in this study, it was revealed that the most significant differences in indicators between groups are characteristic for a more severe course of the disease [42]. A number of studies have noted a positive effect of the drug on the restoration of impaired speech functions in patients after stroke and a decrease in cognitive impairment [40,43-46].

4. Conclusions

Thus, the COVID-19 pandemic has put a huge strain on health systems. Patients with severe COVID-19 symptoms can also have acute cerebrovascular accidents. IS in these patients may result from complications associated with COVID-19, or decompensation of previously asymptomatic cerebrovascular disorders, or due to the presence of common risk factors for stroke in COVID-19. The COVID-19 pandemic has had a huge impact on the management of neurological patients, whether they are infected or not, and has negatively impacted most stroke services around the world.

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