

COVID-19-Associated Stroke

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The COVID-19 pandemic has had significant influences on the incidence of acute cerebrovascular accidents and the structure of mortality. SARS-CoV-2 increases the risks of developing both ischemic and hemorrhagic stroke. The key pathogenetic element underlying the development of cerebral stroke in COVID-19 consists of impairments to the operation of angiotensin 2 receptors, which are accompanied by accumulation of excess quantities of angiotensin 2, endothelial dysfunction, hypercoagulation, overproduction of proinflammatory cytokines, and an oxidative storm. In patients with stroke and COVID-19, lesion severity is associated with dual mechanisms of ischemia – systemic and cerebral. The possibilities of medication-based correction of both systemic impairments associated with coronavirus infection and local impairments due to ischemic or hemorrhagic brain damage, are limited. Substances with antioxidant activity may potentially be effective in patients with stroke and COVID-19. Data from a number of clinical trials indicate that Mexidol significantly improves functional outcomes in ischemic stroke. Use of Mexidol in patients with stroke and COVID-19 is advised.

Keywords: ischemic stroke, coronavirus infection, angiotensin receptors, cytokine storm, oxidative stress, Mexidol.

WHO data indicate that stroke is the second most important cause of death and the third most important cause of disability throughout the world [1]. About 15 million people have strokes every day and about six million of these die, another five million experiencing persistent severe neurological deficit. In Russia, some 450–500,000 strokes are recorded annually [2]. In 2013, 10.3 million new strokes were registered around the world, of which 67% were ischemic. The incidence of stroke, both ischemic and hemorrhagic (IS, HS), is greater in men – 132 and 99 per 100,000 [3].

The COVID-19 pandemic has had significant influences on both the incidence of stroke and the structure of mortality. Provision of high-tech care for stroke patients in many regions is under threat due to changes in patient routing and the reprofiling of hospitals as covid hospitals. Thus, for example, a number of hospitals in Moscow which previously operated as regional vascular centers or primary

vascular departments were reprofiled to assist patients with SARS-CoV-2, which in turn led to an increase in the load on the remaining hospitals. The main difficulties in the operation of the healthcare system for stroke patients during the pandemic came from late presentation due to patients fearing infection or being left alone without caring relatives; emergency care, medical staffing, and diagnostics were refocused on COVID-19 patients, decreasing the effectiveness of healthcare provision to patients with other diseases; CT systems were prioritized for diagnosis of pneumonia; the number of additional investigations increased, which affected reperfusion therapy decision-taking time; it was not possible to provide staged rehabilitation, as rehabilitation centers were repurposed as COVID hospitals [4].

Data from non-Russian sources indicate that SARS-CoV-2 increases the risk of IS. The risk of developing IS was compared in 1916 patients admitted to hospital with COVID-19 with the risk of IS in 1486 patients admitted with seasonal influenza. The authors found that the relative risk of stroke in the group of patients with COVID-19 was 8.1 (95% CI 2.5–26.6), as compared with 4.6 (95% CI 1.4–15.7) in the reference group [5]. This study is of great interest, as the authors took into account the influence of infection

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spread predominantly by the air droplet route. A study in China in 1875 patients hospitalized with COVID-19 showed that 2.7% were diagnosed with IS, these being older patients (70 [64–80] and 62 [50–70] years, $p < 0.001$), who had higher incidences of arterial hypertension and other cardiovascular diseases [6]. A study reported by Qureshi and William [7] in 8163 patients hospitalized with COVID-19 showed that 103 (1.3%) were diagnosed with acute IS. The authors compared a whole series of measures in patients with stroke and SARS-CoV-2, patients with COVID-19 only, and a reference group with IS but not COVID-19. Lethal outcomes in patients with COVID-19 and IS were recorded significantly more frequently than in patients without IS (19.4% and 6.2%, $p < 0.0001$). In February 2021, a meta-analysis including 61 publications (108,571 patients with COVID-19) was published. The incidence of stroke cases was 1.4% (II 87.4%, GI 11.6%). Patients with stroke were older and, as a rule, had cardiovascular risk factors (CVRF) [8].

Studies of the nature of stroke and COVID-19 showed that of 423 patients, 323 (74.8%) developed IS and 68 (15.7%) HS, while 23 (5.3%) developed subarachnoid hemorrhage and 18 (4.2%) developed cerebral vein or sinus thrombosis. Among patients with IS, 33% had atherothrombotic, 27% cardioembolic, and 10% lacunar strokes; 22% developed cryptogenic stroke; 8% had other causes of stroke [9]. The results of this study indicated more frequent development of atherothrombotic IS with large artery occlusion in patients with COVID-19 than in the global population, where the frequency was 19–23% [10]. Other studies also demonstrated a high frequency of large artery occlusion in patients with COVID-19 [11, 12]. A high frequency of young adults was noted – 36% of patients were younger than 55 years, while 46% were below 65 years old [9], which was also significantly different from the mean value in the pre-pandemic population – 12.9–20.7% [13]. Among patients with HS ($n = 91$, and COVID-19, 28% did not have CVRF or comorbid diseases [9] which is significantly different from the proportion in the population. In addition, 70% of patients with subarachnoid hemorrhages showed anomalous development of the brain vessels – aneurysms or arteriovenous malformations (AVM), which is also significantly different from the standard rate, i.e., aneurysm and AVM in subarachnoid hemorrhage are absent or present in only 5–34% of cases [14].

Mechanisms of Development of Acute Cerebral Stroke in COVID-19. The presence of CVRF such as ischemic heart disease, diabetes mellitus, arterial hypertension, smoking, age, and previous stroke is linked with a severe course of COVID-19 [15]. The “gate” for penetration of virus into cells is the angiotensin type 2 receptor (ACER2) [16]. Binding with ACER2, SARS-CoV-2 inactivates it, which in turn leads to impaired regulation of arterial pressure (BP) [16]. On the one hand, this can lead to a peak increase in BP and the development of HS; on the other, there are data showing that patients with HS and

COVID-19 show lower values for systolic BP than patients without COVID-19 [17], which requires further investigation. Impairment to the operation of ACER2 receptors promotes triggering of the postischemic inflammatory cascade due to accumulation of angiotensin 2, which has nothing to bind to, which in turn exacerbates hypoperfusion in the cerebral ischemia zone and promotes expansion of the volume of cerebral infarct [18]. Experimental studies have shown that activation of the renin-angiotensin axis (ACE/Ang II/AT1R) with excessive formation of angiotensin 2 leads to cerebral vasoconstriction, activation of inflammation, and oxidative stress in the brain [19]. Angiotensin 2 has also been shown to elicit marked constriction of isolated middle cerebral arteries [20]. Binding of SARS-CoV-2 with ACER2 in cerebral vessels can lead to excessive release of proinflammatory cytokines and chemokines, such as interleukin 6 (IL-6) and tumor necrosis factor (TNF), which in turn leads to lymphocyte, neutrophil, and macrophage activation and extravasation and subsequent brain tissue damage [21]. Endothelial dysfunction arising as a result of exclusion of ACER2 and subsequent penetration of SARS-CoV-2 virus into endotheliocytes plays an important role in the development of both cerebral IS and HS [22].

Activation of the coagulation cascade is associated with a severe course of COVID-19. The causes of coagulopathy include virus-induced impairment of homeostasis (activation of systemic inflammation, increases in fibrinogen levels, platelet activation, endothelial dysfunction) and external causes associated with the patient’s clinical condition (dehydration and immobilization of the patient) [23]. Hypercoagulatory status potentially increases the risk of developing IS and cerebral venous thromboses [24]. Activation of the coagulatory component of hemostasis in COVID-19 is accompanied by increases in D-dimer and ferritin levels, the appearance of lupus anticoagulant in the blood, anticardiolipin and antiphospholipid antibodies, and antibody to β 2-glycoprotein-1 [25]. The key pathophysiological element in the development of coagulopathy in COVID-19 is the emerging interaction between activated tissue coagulation factors, immune cells, platelets, endothelial cells, and extracellular filaments formed by neutrophils (neutrophil extracellular traps, NET), which activate the contact pathways of the coagulation system [23]. The larger quantities of proinflammatory cytokines released in COVID-19 (cytokine storm) also promote progression of hematological impairments. IL-6 promotes the expression of tissue factors in mononuclear cells and immune defense cells intended for countering viruses and bacteria. In turn, mononuclear cells are already activated by SARS-CoV-2. Tissue factors activate endothelial cells, which also promotes increases in the expression of tissue factors, though now by endotheliocytes. Infected and damaged endothelial cells are regarded as key pathophysiological elements in prothrombotic status in COVID-19. Two mechanisms for the involvement of the endothelium can be distinguished: on the one hand, a direct

cytotoxic action of the virus and, on the other, the inflammatory reaction promoting the development of so-called endotheliitis. Endothelial damage leads to overexpression of tissue coagulation system activation factors, excessive thrombin formation, blockade of fibrinolysis, and activation of the complement system, which plays a key role in the development of the systemic inflammatory reaction [26].

Along with coagulopathy, endothelial damage to cerebral vessels by SARS-CoV-2 virus in cytokine storm conditions, especially an excess of IL-6, can lead to the development of cerebral vasculitis [27]. Both IS and HS can develop on this background, while vasculitis of the cerebral vessels produces uncontrollable changes in their lumens – constriction and dilation – vessels become fragile, creating conditions in which they can rupture and/or develop thrombosis. The development of rare states such as reversible cerebral vasoconstriction syndrome and posterior reversible encephalopathy syndrome can occur in COVID-19 patients, though angiitis is believed to be one of the causes [28].

Heart damage due to COVID-19 is associated with ACER2 dysfunction, cytokine injury, hypoxia, and treatment complications [29]. Decompensated heart failure, myocarditis, acute myocardial infarction, and severe arrhythmias can develop in COVID-19 patients [29]. These forms of heart damage may cause cardioembolic stroke.

Severe COVID-19 is an independent predictor of stroke. In particular, prolonged hospitalization and being in the resuscitation and intensive care departments, prolonged mechanical ventilation of the lungs, and postresuscitation disease can lead to hypoxemia and posthypoxic encephalopathy, as well as cerebral stroke [30]. Prolonged hypoxemia associated with respiratory failure in COVID-19 patients can lead to the development of cerebral microhemorrhages and leukoencephalopathy [31].

An important pathophysiological mechanism for damage to various organs and systems, including the central nervous system, in COVID-19 is the development of oxidative stress with release of large quantities of reactive oxygen and nitrogen species [32]. In patients with stroke and COVID-19, oxidative stress arising on the background of viral infection is layered onto the oxidative stress of cerebral damage, these potentiating each other and aggravating the course of illness. Its development is directly linked with cytokine storm. It has been suggested that by analogy with other viral infections (such as influenza), COVID-19 triggers the expression of various cytokines via activation of particular receptors by the virus, including Toll-like receptors 3, 7, and 8, and NOD-like receptors on the surfaces of epithelial cells, macrophages, and dendritic cells [33]. An important participant in cytokine storm is the inflammasome – a complex consisting of a set of proteins forming a component of innate immunity. Reactive oxygen species are direct activators of inflammasome NOD-like receptors [34]. Activation of NOD-like receptors leads to increases in the activity of nuclear factor κ B (NF- κ B), one of the key mediators trigger-

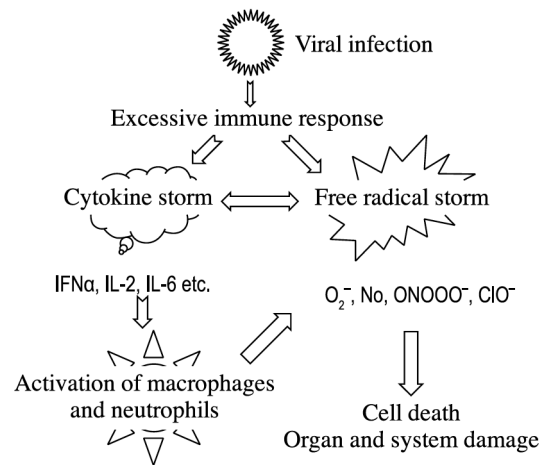


Fig. 1. Cytokine storm and free radical storm in COVID-19.

ing expression of proinflammatory cytokines – IL-6, TNF- α , IL-1 β , and interferon- γ – in patients with COVID-19 [34]. Apart from direct and reverse connections with cytokine storms, free radicals can damage erythrocyte membranes, inducing hemolysis; they can also activate phagocytosis by macrophages and neutrophils, promoting the latter to form free radicals, which has repeatedly been described in sepsis; a severe course of COVID-19 is believed by some authors to be nothing other than viral sepsis [35]. Further transformation of hemoglobin leads to release of iron, which is toxic to tissues. The hypoxia typical of COVID-19 has the result that superoxide radicals (O_2^-) and hydrogen peroxide (H_2O_2) form in mitochondria. In the presence of hydrogen peroxide, the superoxide radical oxidizes iron III to iron II with formation of the extremely toxic hydroxyl radical (OH^-), inducing lipid and protein peroxidation triggering cell death by necrosis or apoptosis [36]. Data have been obtained indicating that iron III activates coagulation by forming OH^- , which converts normal plasma plasminogen into dense fibrin clots not subject to enzymatic cleavage [37]. The hypoxia seen in COVID-19 is accompanied by a systemic inflammatory reaction and leads to the formation of excessive quantities of reactive oxygen species, promoting increases in the expression of proinflammatory cytokines IL-1, IL-6, and TNF- α ; furthermore, inducible NO synthase (iNOS) is activated via the NF- κ B signal pathway [38]. A closed circuit then forms – proinflammatory cytokines and iNOS activate macrophages, neutrophils, and also endothelial cells via the NADP oxidase (NOx) system, these in turn starting to produce H_2O_2 [39]. O_2^- in turn starts to react with nitric oxide (NO) formed by iNOS to generate peroxynitrite ($ONOO^-$), which is a very active oxidant in its own right. NO and $ONOO^-$ are highly toxic to mitochondria, which exacerbates hypoxia and, thus, energy deficit [40]. The interaction between the development of a cytokine storm and a free radical storm involving OH^- is shown in Fig. 1 [41].

Principles of the Treatment of Patients with Stroke and COVID-19. The possibility of using antioxidants in

COVID-19 is widely discussed. By analogy with other viral infections, it has been suggested that substances with antioxidant activity may potentially be effective in this group of patients. Superoxide dismutase (SOD) is one of the most powerful antioxidants; this blocks superoxide activity in viral infections [42]. There is currently no SOD for clinical use, though there is a series of substances which stimulate SOD formation, and which may be effective in patients with COVID-19 [43]. Vitamins C and E are powerful free radical blockers and their efficacy has been demonstrated in a number of respiratory infections [44]. Use of high doses of vitamin C may also have some value in the treatment of COVID-19 [45]. Also considered in antioxidant therapy in patients with COVID-19 are zinc formations (a cofactor of SOD), glutathione, and N-acetylcysteine, though there are as yet no data on their efficacy [41]. The ability of the antioxidant MitoQ, which blocks free radical activity at the level of mitochondria, to decrease SARS-CoV-2 replication activity has been demonstrated [46].

Thus, the use of drugs with marked antioxidant effects with previously demonstrated efficacy, particularly in patients with acute cerebrovascular accidents (aCVA), may also be highly effective in patients with stroke on the background of SARS-CoV-2. One drug with strong antioxidant and antihypoxic activity with efficacy demonstrated in patients with stroke is Mexidol (ethylmethylhydroxypyridine succinate), which has a multimodal mechanism of action. The pyridine base (2-ethyl-6-methyl-3-hydroxypyridine) of Mexidol has direct antioxidant activity, suppresses NADPH₂-dependent (enzymatic) iron-induced and ascorbate-dependent (nonenzymatic) lipid peroxidation (LPO), increases SOD and Se-dependent glutathione peroxidase activities, decreases iNOS activity, promotes binding of the superoxide anion radical, and decreases glutamate excitotoxicity. Mexidol also has a marked membrane-protective effect, which is apparent as the ability to stabilize erythrocyte and platelet membrane structures, decreasing the probability of hemolysis [47]. The second part of the molecule – the succinate moiety – has antihypoxic action mediated by maintaining succinate oxidase activity in hypoxic conditions. This is the FAD-dependent part of the Krebs cycle, which in hypoxia suppresses the subsequent NAD-dependent oxidases, thus maintaining energy production within cells when mitochondria contain the oxidation substrate succinate. Succinate can influence its specific receptor GPR91, triggering a cascade of reactions supporting adaptation to hypoxia [48]. Mexidol has displayed efficacy in the complex therapy of influenza. Its use in the complex treatment of moderate and severe forms decreased the durations of illness and the period of reduction of the main clinical symptoms, increased the efficacy of treating endogenous intoxication syndrome, activated blood catalase and superoxide dismutase, and decreased lipoperoxidation [47, 48].

Features of the Course of Stroke on the Background of COVID-19. Many studies have been published on the

characteristics of the course of stroke in patients with COVID-19. Thus, a study by Siegler et al. [49] at the very beginning of the pandemic analyzed a series of measures in patients with stroke and COVID-19 and the results were compared with data from the prepandemic period. The authors showed that patients with COVID-19 had a more severe course of stroke, though there was no significant influence on the outcome. Large vessel thromboses were also more frequently diagnosed in COVID-19. Another study described five cases of severe IS with occlusion of a major vessel in patients less than 50 years old with COVID-19 with no CVRF [50]. Sparr and Bieri [51] described four patients with IS and COVID-19 with atypical infarcts of the posterior part of the corpus callosum. Bengner et al. [52] described five patients with COVID-19 and HS aged 41–64 years without significant CVRF. Kvernland et al. [53] found that of 4071 COVID-19 patients, 19 (0.5%) were diagnosed with HS, while three had nonaneurysmal subarachnoid hemorrhage, the main cause of which was, in the authors' view, severe coagulopathy, apparent as high INR and APTT, D-dimer, C-reactive protein, and fibrinogen levels; most patients were receiving anticoagulant therapy because of diagnoses of COVID-19 before onset of stroke, and mortality was 89%. Severe COVID-19, prolonged periods in the resuscitation department, and long periods of mechanical ventilation of the lungs were risk factors for microhemorrhages and leukoencephalopathy [31]. Apart from focal neurological symptomatology and general cerebral and meningeal symptoms, individual patients with stroke showed the symptoms of COVID-19 which worsened the course of stroke and had significant influence on the potential for rehabilitation. Thus, 36% of patients with severe COVID-19 had executive functional impairment syndrome, with severe impairments to attention and the inability to carry out tasks [54, 55]. COVID-19 patients frequently developed severe depressive or anxiety disorders [56].

The main complaints presented by patients in the acute phase of COVID-19 and those who had had infection were diffuse, bursting-type headache, aggravated in the mornings, vertigo of nonsystemic nature, nausea, loss of appetite, "brain fog," reduced consciousness, slowed thinking, and word-finding difficulty. Cognitive impairments were found in elderly patients suffering from diabetes mellitus, ischemic heart disease, hypertension, and lung diseases, and were accompanied by feelings of anxiety, fear, restlessness, sleeplessness, or anxiety, interrupted sleep, apathy, and low mood [57].

Organization of Medical Care for Patients with COVID-19 and Stroke. Specialized medical care for these patients is provided in compliance with Russian Ministry of Health Order No. 928n of 2012 and Temporary Methodological Guidelines for the Management of Patients with aCVA in the COVID-19 Pandemic (Version 2 of April 16, 2020). The drug therapy of aCVA when needing to be provided simultaneously with treatment for COVID-19 takes account of the severity of the viral infection and antiviral

drugs being used [58]. From the onset of the pandemic, a decrease in the number of hospital admissions for stroke was recorded, probably because of patients' fear of becoming infected in hospital [59]. The key point in providing care to stroke patients in the COVID-19 pandemic is ensuring the safety of both medical staff and the patient. In accordance with international guidelines, any patient with aCVA at both the prehospital stage and in hospital should be regarded as potentially infected with SARS-CoV-2 virus and should undergo detailed history-taking seeking to identify signs of infection during the period leading up to the consultation [60]. On admission of stroke patients with suspected COVID-19, some authors recommend using separate facilities, including separate CT and ultrasound scan diagnostic cabinets [61]. Where required, resuscitation measures, including intubation, should preferably be carried out in a specialized facility where a negative pressure atmosphere can be produced [62]. Neuroimaging studies of patients with stroke and suspected COVID-19, especially those put forward for thrombolytic therapy or mechanical thrombus extraction, should be performed by standard protocols, including native CT/CT angiography/CT perfusion or native MRI/MR angiography/MR perfusion [60]. When indications are present, thrombolytic therapy should be provided within the therapeutic window of up to 4.5 h in compliance with clinical guidelines, without considering the presence of COVID-19. In patients in whom the time of onset of focal neurological symptomatology is unknown, management should be guided by neuroimaging results. It should be noted that young patients not infrequently develop thrombosis of major arteries in COVID-19, leading to massive stroke, so provision of thrombolytic therapy is critically important. Provision of maximal mechanical thrombus extraction is indicated in patients with IS and COVID-19 with large vessel occlusion. Thrombus extraction results may be unsatisfactory, because of the pathogenesis of COVID-19 producing secondary thrombi, rethrombosis, and thrombus fragmentation followed by higher embolization [63]. There are as yet no large studies assessing the efficacy and safety of x-ray-guided endovascular treatment methods for IS in COVID-19 patients. There are occasional publications with small numbers of patients. Thus, thrombus extraction with complete recanalization was performed in a 62-year-old female patient with acute right-sided hemiparesis and aphasia, though the patient was readmitted after 10 days in a severe state with signs of HS [64]. Ten patients with acute large cerebral artery occlusion underwent mechanical thrombus extraction and nine developed rethrombosis in the post-operative period; six died and the remainder showed no significant regression of focal neurological deficit [65]. Other studies have also reported ambiguous results.

Potential for Use of Drugs with Complex Neuroprotective and Antioxidant Mechanisms. Considering the key pathophysiological mechanisms of COVID-19 and stroke, associated primarily with the development of deep

and prolonged ischemia with a dual mechanism of development due to circulatory impairment and changes in oxygen-transporting function, along with hypercoagulation, cytokine storm, and activation of inflammatory processes, a number of investigators advise using drugs with complex neuroprotective mechanisms of action [4]. Only a few studies have as yet been published on the use of neuroprotectors in COVID-19. Thus, Roncati et al. [66] evaluated the potential use of palmitoylethanolamide (PEA), a substance belonging to the endogenous fatty acid amides class. PEA has a polymodal action due to its ability to bind a number of receptors (PPAR- α , NR1C1, VR1, and GPR55) and has anti-inflammatory, antinociceptive, neuroprotective, and anti-convulsant effects. Two clinical trials have now been started addressing the efficacy of PEA in COVID-19 [67, 68]. Ginkgolic acid, the main component of the plant *Ginkgo biloba*, has been shown to have neuroprotective and antiviral efficacy in relation to the neurotropic viruses Epstein-Barr, Zika, and cytomegalovirus. The authors suggested that this substance may also be effective in COVID-19 [69].

The Russian drug Mexidol, which has multimodal actions, has demonstrated its high efficacy in IS. A large number of studies have been reported, including double-blind, placebo-controlled studies compliant with international GCP standards in which the efficacy of Mexidol in stroke was confirmed using an evidence-based medicine approach [70].

The EPIKA study assessed the efficacy and safety of prolonged sequential therapy with Mexidol in patients in the acute and early recovery periods of hemispheric IS. This study included 151 patients. Simple randomization was used to assign patients to two groups: patients of group 1 received Mexidol 500 mg/day by i.v. infusion for 10 days followed by one tablet (125 mg) three times daily for eight weeks; patients in group 2 received placebo by the same regimen. Study participation lasted 67–71 days. Group 1 showed a significantly more marked (as compared with placebo) improvements in viability as measured on the Modified Rankin Scale (MRS). Levels of viability assessed at the end of the study were significantly greater than in group 1. Recovery corresponding to 0–2 points on the MRS were noted in 96.7% of patients in group 1 and 84.1% of those in group 2 ($p = 0.039$). At the end of treatment, neurological deficit on the NIHSS was significantly lower in patients receiving Mexidol than in those given placebo. Mexidol produced positive effects in patients with concomitant diabetes mellitus. A majority of patients in the study group had no problems with movement, self-care, or the activities of daily living and had no pain or discomfort, anxiety, or depression [71].

Data have been obtained indicating the efficacy of Mexidol in viral infections. Thus, Mexidol was shown to have marked antioxidant actions in patients with viral infections, decreasing malondialdehyde levels and increasing antioxidant defense and SOD [72]. SOD, catalase, glutathione peroxidase, and glutathione reductase activities, the reduced glutathione concentration, and levels of secondary lipid per-

oxidation products were assessed within the first 24 h of the onset of symptoms in a study including 51 patients with acute carotid IS. Levels of antioxidant defense enzymes were significantly higher on the background of Mexidol treatment than in the placebo group. The activity of enzymes characterizing the intensity of cell oxygenation – mitochondrial succinate dehydrogenase and α -glycerophosphate dehydrogenase – were suppressed in patients receiving placebo, while measures of cellular respiration were significantly higher in patients receiving Mexidol [73]. Mexidol was shown to have efficacy in patients with chronic cerebral ischemia and COVID-19 – in sequential long-term treatment, Mexidol (i.v. injections of Mexidol 500 mg/day for 14 days with subsequent transfer to the tableted form of Mexidol FORTE 250 at a dose of 250 mg three times daily for two months) normalized cognitive functions, cured asthenia syndrome, normalized sleep, and improved patients' quality of life [74]. Mexidol was shown to be effective in 62 patients aged over 18 years with confirmed COVID-19 with severe and moderate courses. As compared with the control group, patients treated with Mexidol showed significantly more marked reductions in body temperature, a tendency to greater reductions in respiratory rate, and decreases in the severity of breathlessness. Analysis of the dynamics of laboratory changes showed that patients receiving Mexidol had essentially no change in SOD level, while the control group showed a tendency for this to decrease. At seven days of infusion therapy, the decrease in the C-reactive protein level in the Mexidol group was 2.2 times greater than that in the comparison group ($p = 0.09$). Mexidol promoted a reduction in the creatinine concentration, while this increased in the comparison group ($p = 0.031$). A tendency to a faster reduction in the ferritin level in the Mexidol treatment group was noted. Treatment had positive influences on the clinical signs and severity of inflammatory syndrome [75].

Conclusions. Thus, use of Mexidol in patients with stroke and COVID-19 is advised, considering its high efficacy both in stroke and in SARS-CoV-2 infection. Regardless of the duration of illness – in both the acute phase and the early and late recovery phases – Mexidol could potentially produce significant improvements in patient status and the subsequent prognosis. The principle of the continuity of treatment should be followed, treatment starting with i.v. administration of Mexidol at a dose of 500–1000 mg/day for 14 days with subsequent use of the oral form, Mexidol FORTE 250, at a dose of 250 mg three times daily for two months.

The authors declare no conflict of interest.

REFERENCES

1. *Global Health Estimates*, WHO, Geneva (2012), https://www.who.int/healthinfo/global_burden_disease/en.
2. E. I. Gusev, V. I. Skvortsova, L. V. Stakhovskaya, and N. Yu. Airiyan, "Epidemiology of stroke in Russia," *Zh. Nevrol. Psikiatr.*, **8**, 4–9 (2003).
3. S. Barker-Collo, D. A. Bennett, R. V. Krishnamurthi, et al., "Sex differences in stroke incidence, prevalence, mortality and disability-adjusted life years: Results from the Global Burden of Disease Study 2013," *Neuroepidemiology*, **45**, No. 3, 203–214 (2015), <https://doi.org/10.1159/000441103>.
4. G. E. Ivanova, E. V. Mel'nikova, O. S. Levin, et al., "Current challenges in the rehabilitation of patients with stroke on the background of the new coronavirus infection (COVID-19). Resolution of the Council of Experts," *Zh. Nevrol. Psikiatr.*, **120**, No. 8, Iss. 2, 81–87 (2020), <https://doi.org/10.17116/jnevro202012008281>.
5. A. E. Merkle, N. S. Parikh, S. Mir, et al., "Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza," *JAMA Neurol.*, **77**, No. 11, 1366–1372 (2020), <https://doi.org/10.1001/jamaneurol.2020.2730>.
6. C. Qin, L. Zhou, Z. Hu, et al., "Clinical characteristics and outcomes of COVID-19 patients with a history of stroke in Wuhan, China," *Stroke*, **51**, No. 7, 2219–2223 (2020), <https://doi.org/10.1161/STROKEAHA.120.030365>.
7. A. I. Qureshi and I. William, "Acute ischemic stroke and COVID-19," *Stroke*, **52**, No. 3, 905–912 (2021), <https://doi.org/10.1161/STROKEAHA.120.031786>.
8. S. Nannoni, R. de Groot, S. Bell, and H. S. Markus, "Stroke in COVID-19: A systematic review and meta-analysis," *Int. J. Stroke*, **16**, No. 2, 137–149 (2021), <https://doi.org/10.1177/1747493020972922>.
9. S. Shahjouei, "SARS-CoV-2 and stroke characteristics. A report from the Multinational COVID-19 Stroke Study Group," *Stroke*, **52**, No. 5, 117–130 (2021), <https://doi.org/10.1161/STROKEAHA.120.032927>.
10. R. Ornello, D. Degan, C. Tiseo, et al., "Distribution and temporal trends from 1993 to 2015 of Stroke subtypes: a systematic review and meta-analysis," *Stroke*, **49**, 814–819 (2018), <https://doi.org/10.1161/STROKEAHA.117.020031>.
11. T. J. Oxley, J. Mocco, S. Majidi, et al., "Large-vessel stroke as a presenting feature of COVID-19 in the young," *N. Engl. J. Med.*, **382**, e60 (2020), <https://doi.org/10.1056/NEJMc2009787>.
12. J. E. Siegler, M. E. Heslin, L. Thau, et al., "Falling stroke rates during COVID-19 pandemic at a comprehensive stroke center: cover title: falling stroke rates during COVID-19," *J. Stroke Cerebrovasc. Dis.*, **29**, 104953 (2020).
3. B. M. Kissela and K. Alwell, "Age at stroke," *Neurology*, **79**, 1781–1787 (2012).
14. Y. W. Kim, M. F. Lawson, and B. L. Hoh, "Nonaneurysmal subarachnoid hemorrhage: an update," *Curr. Atheroscler. Rep.*, **14**, 328–334 (2012), <https://doi.org/10.1007/s11883-012-0256-x>.
15. B. R. Kummer, E. Klang, L. K. Stein, et al., "History of stroke is independently associated with in-hospital death in patients with COVID-19," *Stroke*, **51**, 3112–3114 (2020).
16. Y. Zhao, Z. Zhao, Y. Wang, et al., "Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCoV," *bioRxiv*, 2020.01.26.919985, <https://doi.org/10.1101/2020.01.26.919985>.
17. S. Hernández-Durán, C. Salfelder, J. Schaeper, et al., "Mechanical ventilation, sedation and neuromonitoring of patients with aneurysmal subarachnoid hemorrhage in Germany: Results of a nationwide survey," *Neurocrit. Care*, **34**, No. 1, 236–247 (2021).
18. P. Kaushik, M. Kaushik, S. Parveen, et al., "Cross-talk between key players in patients with COVID-19 and ischemic stroke: A review on neurobiological insight of the pandemic," *Mol. Neurobiol.*, **57**, No. 12, 4921–4928 (2020).
19. J. W. Wright and J. W. Harding, "The brain renin-angiotensin system: a diversity of functions and implications for CNS diseases," *Pflugers Arch.*, **465**, 133–151 (2013).
20. E. Stenman and L. Edvinsson, "Cerebral ischemia enhances vascular angiotensin AT1 receptor-mediated contraction in rats," *Stroke*, **35**, 970–974 (2004).
21. A. H. Newton, A. Cardani, and T. J. Braciale, "The host immune response in respiratory virus infection: balancing virus clearance and immunopathology," *Semin. Immunopathol.*, **38**, No. 4, 471–482 (2016).

22. H. Wang, X. Tang, H. Fan, et al., "Potential mechanisms of hemorrhagic stroke in elderly COVID-19 patients," *Aging (Albany NY)*, **12**, No. 11, 10022–10034 (2020).
23. R. C. Becker, "COVID-19 update: COVID-19-associated coagulopathy," *J. Thromb. Thrombolysis*, **50**, No. 1, 54–67 (2020).
24. F. A. Klok, M. J. H. A. Kruip, N. J. M. van der Meer, et al., "Incidence of thrombotic complications in critically ill ICU patients with COVID-19," *Thromb. Res.*, **191**, 145–147 (2020).
25. R. Beyrouti, M. E. Adams, L. Benjamin, et al., "Characteristics of ischaemic stroke associated with COVID-19," *J. Neurol. Neurosurg. Psychiatry*, **91**, No. 8, 889–891 (2020).
26. Z. Varga, A. J. Flammer, P. Steiger, et al., "Endothelial cell infection and endotheliitis in COVID-19," *Lancet*, **395**, 1417–1418 (2020), [https://doi.org/10.1016/S0140-6736\(20\)30937-5](https://doi.org/10.1016/S0140-6736(20)30937-5).
27. G. Tsvigoulis, L. Palaiodimou, R. Zand, et al., "COVID-19 and cerebrovascular diseases: a comprehensive overview," *Ther. Adv. Neurol. Disord.*, **13**, 175–180 (2020), <https://doi.org/10.1177/1756286420978004>.
28. K. Dakay, G. Kaur, E. Gulko, et al., "Reversible cerebral vasoconstriction syndrome and dissection in the setting of COVID-19 infection," *J. Stroke Cerebrovasc. Dis.*, **29**, No. 9, 105011 (2020).
29. A. N. Kochi, A. P. Tagliari, G. B. Forleo, et al., "Cardiac and arrhythmic complications in patients with COVID-19," *J. Cardiovasc. Electrophysiol.*, **31**, No. 5, 1003–1008 (2020).
30. S. Fan, M. Xiao, F. Han, et al., "Neurological manifestations in critically ill patients With COVID-19: A retrospective study," *Front. Neurol.*, **11**, No. 1, 806 (2020).
31. S. Agarwal, R. Jain, S. Dogra, et al., "Cerebral microbleeds and leukoencephalopathy in critically ill patients with COVID-19," *Stroke*, **51**, No. 9, 2649–2655 (2020).
32. R. Cecchini and A. L. Cecchini, "SARS-CoV-2 infection pathogenesis is related to oxidative stress as a response to aggression," *Med. Hypotheses*, **143**, 110102 (2020), <https://doi.org/10.1016/j.mehy.2020.110102>.
33. Hui Li, Liang Liu, Dingyu Zhang, et al., "SARS-CoV-2 and viral sepsis: observations and hypotheses," *Lancet*, **395**, No. 10235, 1517–1520 (2020), [https://doi.org/10.1016/S0140-6736\(20\)30920-X](https://doi.org/10.1016/S0140-6736(20)30920-X).
34. P. Mehta, D. F. McAuley, and M. Brown, "COVID-19: consider cytokine storm syndromes and immunosuppression," *Lancet*, **395**, 28–31. EDN: GWYQPO (2020).
35. K. Effenberger-Neidnicht and M. Hartmann, "Mechanisms of hemolysis during sepsis," *Inflammation*, **41**, 5–10 (2018).
36. J. Jerzy, L. Philip, E. Pretorius, et al., "Unusual clotting dynamics of plasma supplemented with iron (III)," *Int. J. Mol. Med.*, **33**, 367–372 (2014).
37. E. Pretorius, J. Bester, and N. Vermeulen, "Oxidation inhibits iron-induced blood coagulation," *Curr. Drug Targets*, **14**, No. 1, 13–19 (2013).
38. J. M. Connors and J. H. Levy, "COVID-19 and its implications for thrombosis and anticoagulation," *Blood*, **27**, 45–49 (2020).
39. J. Nanduri, G. Yuan, and G. K. Kumar, "Transcriptional responses to intermittent hypoxia," *Respir. Physiol. Neurobiol.*, **164**, 277–281 (2008).
40. O. Ademowo, H. Dias, and D. Burton, "Lipid (per)oxidation in mitochondria: an emerging target in the ageing process?" *Biogerontology*, **18**, 859–879 (2017).
41. J. Wu, "Tackle the free radicals damage in COVID-19," *Nitric Oxide*, **102**, 39–41 (2020), <https://doi.org/10.1016/j.niox.2020.06.002>.
42. H. B. Suliman, "Prevention of influenza-induced lung injury in mice overexpressing extracellular superoxide dismutase," *Am. J. Physiol. Lung Cell. Mol. Physiol.*, **280**, No. 1, 69–78 (2001).
43. R. Bonetta, "Potential therapeutic applications of MnSODs and SOD-mimetics," *Chemistry*, **24**, No. 20, 5032–5041 (2018).
44. L. Ran, "Extra dose of vitamin C based on a daily supplementation shortens the common cold: a meta-analysis of 9 randomized controlled trials," *BioMed. Res. Int.*, **5**, 65–71 (2018).
45. H. Lifang, W. Lang, T. Jianghong, et al., "High-dose vitamin C intravenous infusion in the treatment of patients with COVID-19," *Medicine (Baltimore)*, **100**, e25876 (2021), <https://doi.org/10.1097/MD.00000000000025876>.
46. A. C. Codo, G. G. Davanzo, L. B. Monteiro, et al., "Elevated glucose levels favor SARS-CoV-2 infection and monocyte response through a HIF-1 α /glycolysis-dependent axis," *Cell Metab.*, **32**, No. 3, 437–446.e5 (2020), <https://doi.org/10.1016/j.cmet.2020.07.007>.
47. T. A. Voronina, "Antioxidants/antihypoxants – the missing puzzle of effective pathogenetic therapies for patients with COVID-19," *Infekts. Bol.*, **18**, No. 2, 97–102 (2020), <https://doi.org/10.20953/1729-9225-2020-2-97-102>.
48. A. V. Shchul'kin and A. A. Filimonova, "The role of free-radical oxidation, hypoxia, and their correction in the pathogenesis of COVID-19," *Terapiya*, **5**, 187–194 (2020), <https://doi.org/10.18565/therapy.2020.5.187-194>.
49. J. E. Siegler, M. E. Heslin, L. Thau, et al., "Falling stroke rates during COVID-19 pandemic at a comprehensive stroke center," *J. Stroke Cerebrovasc. Dis.*, **29**, No. 8, 104953 (2020), <https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104953>.
50. T. J. Oxley, J. Mocco, S. Majidi, et al., "Large-vessel stroke as a presenting feature of COVID-19 in the young," *N. Engl. J. Med.*, **382**, No. 20, e60 (2020), <https://doi.org/10.1056/NEJMc2009787>.
51. S. A. Sparr and P. L. Bieri, "Infarction of the splenium of the corpus callosum in the age of COVID-19: A snapshot in time," *Stroke*, **51**, No. 9, 223–226 (2020), <https://doi.org/10.1161/STROKEAHA.120.030434>.
52. M. Bengler, O. Williams, J. Siddiqui, and L. Sztriha, "Intracerebral haemorrhage and COVID-19: Clinical characteristics from a case series," *Brain Behav. Immun.*, **88**, 940–944 (2020), <https://doi.org/10.1016/j.bbi.2020.06.005>.
53. A. Kvernland, A. Kumar, S. Yaghi, et al., "Anticoagulation use and hemorrhagic stroke in SARS-CoV-2 patients treated at a New York Healthcare system," *Neurocrit. Care*, **34**, No. 3, 748–759 (2021), <https://doi.org/10.1007/s12028-020-01077-0>.
54. S. Agarwal, R. Jain, S. Dogra, et al., "Cerebral microbleeds and leukoencephalopathy in critically ill patients with COVID-19," *Stroke*, **51**, No. 9, 2649–2655 (2020), <https://doi.org/10.1161/STROKEAHA.120.030940>.
55. S. Fridman, M. B. Bullrich, A. Jimenez-Ruiz, et al., "Stroke risk, phenotypes, and death in COVID-19: systematic review and newly reported cases," *Neurology*, **95**, 3373–3385 (2020), <https://doi.org/10.1212/WNL.0000000000010851>.
56. D. Giansanti, "WhatsApp in Mhealth: an overview on the potentialities and the opportunities in medical imaging," *Mhealth*, **6**, 19–23 (2020), <https://doi.org/10.21037/mhealth.2019.11.01>.
57. V. V. Konyaeva, "COVID-19-associated encephalopathy: experience of clinical observations in practical neurology," *Lechebnoe Delo*, **3**, 43–46 (2020), <https://doi.org/10.24412/2071-5315-2020-12255>.
58. E. I. Gusev, M. Yu. Martynov, A. N. Boiko, et al., "The new coronavirus infection (COVID-19) and nervous system damage: mechanisms of neurological disorders, clinical manifestations, and organization of neurological care," *Zh. Nevrol. Psikiatr.*, **120**, No. 6, 7–16 (2020), <https://doi.org/10.17116/jnevro20201200617>.
59. H. S. Markus and M. Brainin, "COVID-19 and stroke – A global World Stroke Organization perspective," *Int. J. Stroke*, **15**, No. 4, 361–364 (2020).
60. N. Venketasubramanian, C. Anderson, H. Ay, et al., "Stroke care during the COVID-19 pandemic: International Expert Panel Review," *Cerebrovasc. Dis.*, **50**, 245–261 (2021), <https://doi.org/10.1159/000514155>.
61. C. Baracchini, A. Pieroni, F. Viaro, et al., "Acute stroke management pathway during coronavirus-19 pandemic," *Neurol. Sci.*, **41**, No. 5, 1003–1005 (2020).

62. M. S. Smith, J. Bonomo, I. V. Knight, et al., "Endovascular therapy for patients with acute ischemic stroke during the COVID-19 pandemic. A proposed algorithm," *Stroke*, **51**, 1902–1909 (2020).
63. A. Wang, G. K. Mandigo, P. D. Yim, et al., "Stroke and mechanical thrombectomy in patients with COVID-19: technical observations and patient characteristics," *J. Neurointerv. Surg.*, **12**, No. 7, 648–653 (2020).
64. F. Saiegh, R. Ghosh, A. Leibold, et al., "Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke," *J. Neurol. Neurosurg. Psychiatry*, **91**, No. 8, 846–848 (2020).
65. S. Escalard, B. Maier, H. Redjem, et al., "Treatment of acute ischemic stroke due to large vessel occlusion with COVID-19," *Stroke*, **51**, 2540–2543 (2020).
66. L. Roncati, B. Lusenti, and F. Pellati, "Micronized/ultramicronized palmitoylethanolamide (PEA) as natural neuroprotector against COVID-19 inflammation," *Prostaglandins Other Lipid Mediat.*, **154**, 106–140 (2021), <https://doi.org/10.1016/j.prostaglandins.2021.106540>.
67. U.S. National Library of Medicine, *Micronized and Ultramicronized Palmitoylethanolamide in COVID-19 Patients*, ClinicalTrials.gov Identifier: NCT04568876.
68. U.S. National Library of Medicine, *Ultramicronized Palmitoylethanolamide (PEA) Treatment in Hospitalized Participants with COVID-19*, ClinicalTrials.gov Identifier: NCT04619706.
69. R. Borenstein, B. A. Hanson, R. M. Markosyan, et al., "Ginkgolic acid inhibits fusion of enveloped viruses," *Sci. Rep.*, **10**, 40–46 (2020), <https://doi.org/10.1038/s41598-020-61700-0>.
70. M. V. Zhuravleva, I. A. Shchukin, M. S. Fidler, et al., "Efficacy and safety of use of ethylmethyl hydroxypyridine succinate in pots with acute ischemic stroke," *Zh. Nevrol. Psikiatr.*, **120**, No. 12, Iss. 2, 60–66 (2020), <https://doi.org/10.17116/jnevro202012012260> EDN: CXZNOB.
71. L. V. Stakhovskaya, N. A. Shamalov, D. R. Khasanova, et al., "Results of a randomized double-blind multicenter placebo-controlled parallel-group study of the efficacy and safety of Mexidol in prolonged sequential therapy in patients in the acute and early recovery periods of hemispheric ischemic stroke (EPIKA)," *Zh. Nevrol. Psikiatr.*, **117**, No. 3, Iss. 2, 55–65 (2017), <https://doi.org/10.17116/jnevro20171173255-65> EDN: YTSZRV.
72. V. F. Pavelkina, *Clinical-Pathogenetic Aspects of Endogenous Intoxication and Its Correction in Viral and Bacterial Diseases: Dissert. for Doctorate in Med. Sci.*, Moscow (2010).
73. V. I. Skvortsova, L. V. Stakhovskaya, Ya. R. Nartsissov, et al., "A randomized double-blind, placebo-controlled study of the efficacy and safety of the drug Mexidol in the complex therapy of ischemic stroke in the acute phase," *Zh. Nevrol. Psikiatr.*, **106**, No. 18, 47–54 (2006).
74. V. V. Koval'chuk, I. I. Ershova, and N. V. Molodovskaya, "The possibility of increasing treatment efficacy in patients with chronic cerebral ischemia on the background of COVID-19," *Zh. Nevrol. Psikiatr.*, **121**, No. 3, Iss. 2, 60–66 (2021), <https://doi.org/10.17116/jnevro202112103260>.
75. E. K. Shavarova, E. R. Kazakhmedov, and M. V. Alekseeva, et al., "The role of antioxidant therapy in patients with the new coronavirus infection COVID-19 with moderate and severe courses," *Infekts. Bol.*, **19**, No. 1, 159–164 (2021), <https://doi.org/10.20953/1729-9225-2021-1-159-164>.