Management tactics in patients with chronic cerebral ischemia during COVID-19 pandemic

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The article describes the current state of evidence of hypertension and diabetes mellitus roles in the pathophysiology of chronic cerebral ischemia (CCI). CCI is mediated by cerebral microangiopathy, which develops due to vascular remodeling, increased arterial stiffness, endothelial dysfunction, impaired cerebrovascular reactivity, and neuroinflammation. All those mechanisms lead to white matter lesions and cognitive impairment. Arteriolosclerosis is the primary morphological process that damages perforating arteries and arterioles. COVID-19 pandemic can modify CCI progression due to similar pathophysiology. In particular, COVID-19-associated coagulopathy can lead to silent lacunar infarctions and lacunar stroke development. Treatment features of patients with CCI during the COVID-19 pandemic are reviewed. It is concluded that special attention in this group of patients should be paid to primary and secondary cardiovascular prevention issues, an essential element of which is the use of dipyridamole since it has a pleiotropic effect.

Keywords: *chronic cerebral ischemia; cerebral microangiopathy; lacunar stroke; COVID-19; dipyridamole.*
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Chronic cerebral ischemia (CCI), or discirculatory encephalopathy, is one of the most common diagnoses in Russian neurological practice. In foreign literature, this condition is usually referred to as vascular cognitive impairment (CI), which most often develop against the background of pathology of small cerebral arteries (cerebral microangiopathy – CMA) [1–3]. Clinical manifestations of CMA are determined by the severity of the pathological process and may include, in addition to a decrease in cognitive functions (dysregulatory and neurodynamic disorders), emotional, postural and urinary disorders [4, 5]. From the point of view of etiology, there are: 1) sporadic non-amyloid CMA, which usually develops against the background of arterial hypertension (AH) and type 2 diabetes mellitus (DM); 2) associated with cerebral amyloid angiopathy; 3) hereditary. Neuroimaging markers of the disease vary depending on its pathogenesis and are represented by lacunae, lacunar infarctions, microinfarctions, white matter hyperintensity (WMH), enlargement of the perivascular spaces, cerebral microbleeds, intracerebral and hemorrhages [6–10]. The COVID-19 pandemic is making a negative contribution to the course of diseases of the circulatory system. At the same time, cardiovascular and metabolic pathology aggravates the course of an infectious disease and serves as a predictor of its poor outcome. This article discusses the relationship between COVID-19 and the course of CCI in the presence of CMA.

The role of hypertension and diabetes mellitus in the development of CCI. Hypertension is the main cause of damage to small cerebral arteries. Long-term uncontrolled course of the disease is associated with a violation of the mechanisms of autoregulation of cerebral circulation due to changes in myogenic tone and hypertrophic remodeling of arteries with an increase in the ratio of the thickness of the arterial wall and the lumen of the vessel [11, 12]. An important role in the remodeling of arteries belongs to angiotensin II, which, together with aldosterone, promotes the formation of free radical oxidation products – the most important mediator of cerebrovascular dysfunction. AH is also associated with an increase in the permeability of the blood-brain barrier (BBB) and, as a consequence, a violation of the homeostasis of the central nervous system [13].

The key pathomorphological phenomenon associated with hypertension is an increase of arterial stiffness. Arterial stiffness is associated with age, heart rate and mean arterial pressure (BP), as well as with the duration of the disease and the use of insulin in patients with hypertension and type 2 diabetes [14]. An important indicator reflecting the role of hypertension in brain damage is the pulsation index, which correlates with the severity of WMH in patients with minor ischemic stroke or transient ischemic attack (TIA) [15]. It is believed that a significant increase in the stiffness of the aorta in the elderly promotes the transfer of excess pressure and flow pulsation into the carotid circulation, which entails damage to small arteries, their remodeling with the development of CMA and CCI [14]. When assessing the role of hypertension in the development of CCI, one should also take into account the variability of blood pressure over short and long time intervals. BP variability acts as a predictor of vascular events, including stroke, myocardial infarction, and chronic heart failure, regardless of mean BP values [16].

AH is a universal factor that leads to damage to vessels of various sizes: large arteries (increased stiffness, remodeling,

hypertrophy, atherosclerosis), lenticulostriatic arteries (lipohyalinosis, microatheromatosis), penetrating arterioles (microatheromatosis) and pial arteries (remodeling, hypertrophy) [17]. The pial and penetrating arteries and arterioles are responsible for the pressure gradient between large arteries and capillaries, therefore they are the main target of the effects of chronic BP elevation [18, 19]. Hypertrophic and eutrophic remodeling are the main pathological processes that develop in small arteries under the influence of hypertension [12]. These vessels are also surrounded by the perivascular space, the expansion of which is one of the markers of CMA [20]. The small arteries and arterioles of the basal nuclei and deep white matter emanating from the first segment of the middle cerebral artery C the lenticulostriate arteries C are especially sensitive to the effects of hypertension [21]. Occlusion of at least one perforating artery leads to the development of lacunar infarction due to the absence of collaterals [20].

The main links in the pathogenesis of CMA against the background of hypertension are: endothelial dysfunction, including an unexpressed but diffuse lesion of the BBB [22], impaired cerebrovascular reactivity [23], increased intracranial arterial pulsation [24], white matter edema [25] and diffuse microstructural changes in white matter [26]. As a result, secondary distant cortical atrophy develops [27].

The development of CCI in type 2 diabetes is associated with cerebral hypoperfusion, impaired BBB, insufficient clearance of beta-amyloid, pericyte dysfunction, vascular damage with a decrease in regional and global vasoreactivity. Type 2 diabetes is also characterized by vascular remodeling, impaired angiogenesis, and activation of matrix metalloproteinases. The risk factors associated with the development of CI in type 2 diabetes include uncontrolled hyperglycemia, hypoglycemia, depression, duration of the disease, the presence of microvascular complications, dyslipidemia, and obesity [28]. Type 2 diabetes is an independent cause of the development of CMA, in particular, lacunar infarctions [29]. CMA in this disease causes the development of depressive symptoms [30]. Retinopathy in these patients can act as a marker of CMA [31, 32].

AH and type 2 diabetes are the main pathological processes associated with the development of arteriolosclerosis. The combination of hypertension, type 2 diabetes, obesity, and dyslipidemia is known as metabolic syndrome, which is also associated with cerebrovascular disease [33, 34]. Increased systolic blood pressure and hyperglycemia contribute to the imperceptible progression of carotid atherosclerosis, being at the same time a risk factor for intracranial atherosclerosis [18, 35, 36]. The resulting link in the pathogenesis of CCI against the background of hypertension and type 2 diabetes is lesion of the white matter with global dysfunction of neuronal networks [3, 37].

Impact of COVID-19 on the course of CCI in the presence of hypertension and type 2 diabetes. In conditions of COVID-associated coagulopathy and thrombosis of the microvasculature, it is possible to develop both asymptomatic lacunar infarctions and microinfarctions, and clinically manifest lacunar stroke. It is known that the severity of COVID-19 and the outcome of the disease are associated with age, hypertension, type 2 diabetes and other chronic diseases. There is a hypothesis according to which SARS-CoV-2, penetrating into the pulmonary capillaries and then interacting with the catalytic domain of the angiotensin-converting enzyme type 2 (ACE2), infects the endothelium. The virus causes endothelial damage by increasing the expression of pro-inflammatory cytokines and chemokines, as well as excessive activation of coagulation pathways. Further, the interaction of the virus with ACE2 compromises the ACE2-dependent degradation of antiotensin II, which leads to hyperstimulation of the renin-angiotensin system. These events exacerbate endothelial dysfunction and therefore vascular permeability. Damage to the endothelium of the distant vascular bed causes dysfunction of arteries of low resistance, in particular small arteries of the brain, which is realized in a decrease in perfusion and an increase in the risk of thrombosis. The presence of hypertension and type 2 diabetes, associated with premorbid endothelial dysfunction, enhances these negative effects [38].

With the most unfavorable development of this pathogenetic scenario, a COVID-associated stroke may occur. Three main mechanisms of its formation are discussed: COVID-associated coagulopathy, vasculitis, and cardiomyopathy [39–41]. The development of hypercoagulation is based on a cytokine storm, which leads to activation and damage of the endothelium, activation of coagulatory processes with an increase in the formation of thrombin, platelets and leukocytes, as well as the complement system, dysregulation of the natural mechanisms of anticoagulation and fibrinolysis, which is manifested by an increase in the concentration of D-dimer, degradation products fibrinogen, increased prothrombin time, mild thrombocytopenia and increased ferritin concentration [42].

The main stages of COVID-associated coagulopathy are as follows:

1) the penetration of SARS-CoV2 into the cell by interacting with ACE2 receptors, which leads to the activation of innate immunity. Direct infection of immune cells is accompanied by their dysregulation and release of cytokines;
2) activated monocytes, macrophages stimulate the JAK-STAT signaling pathways, which leads to an increase in the production of cytokines;
3) SARS-CoV2 directly infects endothelial cells, causing endothelial damage and promoting hypercoagulation;
4) activation of leukocytes and the subsequent cytokine storm lead to the development of hypercoagulable status due to such mechanisms as increased release of tissue coagulation factors, neutrophil extracellular traps (Neutrophil extracellular traps, NETs), platelet activation, inactivation of anticoagulation pathways and activation of the complement system;
5) dysregulation of the immune system with the development of endothelial dysfunction and hypercoagulability is realized in the form of widespread microthrombosis, venous thromboembolism and arterial thrombosis [43].

In recent years, factors have been identified that are involved in thrombosis, but do not play a role in maintaining hemostasis. These factors include NETs. Experiments have shown that NETs promote venous and arterial thrombosis due to the fact that they represent a negatively charged surface for the activation of factor XII, induce platelet activation and aggregation, and also activate the external coagulation pathway [44]. Studies [45–47] have demonstrated the importance of NETs in

the development of thrombosis in patients. The potentiation of the release of NETs is one of the mechanisms by which antiphospholipid antibodies induce thrombotic events in patients with antiphospholipid syndrome [48].

COVID-associated vasculitis (endotheliitis) is caused by the affinity of the virus for ACE2 receptors of the endothelium and manifests itself by occlusions of large arteries, their atypical localization and development in young patients without vascular risk factors [49, 50].

The etiological structure of stroke is dominated by atherothrombotic, cardioembolic, and cryptogenic subtypes; however, small artery occlusion develops in some patients [51–53]. A brain biopsy demonstrates evidence of thrombotic microangiopathy in patients with COVID-associated stroke. The lesion of small cerebral arteries in severe COVID-19 is indirectly indicated by thrombocytopenia, an increase in the concentration of D-dimer and the level of C-reactive protein [54].

Microthrombus formation is the most common cause of cardiac injury in COVID-19 [55, 56]. A third of COVID-19 patients have antiphospholipid antibodies. High antibody titer is associated with neutrophil hyperactivity, including the release of NETs, increased platelet count, and decreased glomerular filtration rate, which determines the prothrombogenic potential of antiphospholipid antibodies [57].

These facts suggest a high probability of CMA destabilization against the background of COVID-19 with the development of asymptomatic and clinically manifest lacunar infarctions (Fig. 1).

In a recent study by E. Keller et al. [50] Lacunar stroke was observed at an early stage of the disease in two out of eight patients with critically severe COVID-19. In addition, the authors have shown that microinfarctions associated with lesions of small arteries are typical for the late stage of the disease along with the accumulation of contrast by the wall of large arteries. A. Elshereye et al. [58] described a clinical case of multiple lacunar infarctions in a 75-year-old patient, which was regarded as the initial manifestation of COVID-19.

The clinical feature of lacunar stroke is the development of early deterioration in neurological status in 37% of patients [59]. Lacunar stroke can manifest itself as one of five lacunar syndromes: hemihypesthesia with hemiparesis, isolated hemihypesthesia, isolated hemiparesis, dysarthria-clumsy hand syndrome, and atactic hemiparesis [60].

According to STRIVE criteria (STandards for ReportIng Vascular changes on nEuroimaging), lacunar infarction is defined as a recent infarction in the area of the blood supply of one perforating arteriole, with the corresponding clinical symptoms occurring within several previous weeks, measuring <20 mm [10]. According to the CCS classification, lacunar stroke is characterized by a CT / MRI lesion in the area of blood supply of perforating arteries <20 mm in size, correlating with acute symptoms; in this case, there should be no pathology of the maternal artery [61]. The severity of neurological deficit in lacunar stroke depends on the localization of occlusion of the lenticulostriatic arteries: proximal occlusion is associated with more pronounced disorders [62].

An important clinical sign of lacunar stroke is capsular warning syndrome, which manifests itself as a recurrent transient motor or sensorimotor lacunar syndrome involving two of the three body parts (face, arm, leg) and full recovery between episodes [63].

CMA causes 9 out of 10 lacunar strokes, but in every tenth patient the disease is associated with other mechanisms, the leading of which is intracranial atherosclerosis [64]. The pathogenesis of lacunar stroke against the background of CMA, taking into account the possible influence of COVID-19, is shown in Fig. 2

Treatment of patients with CCI with hypertension and type 2 diabetes during the COVID-19 pandemic. The main principle of treatment of patients with CCI associated with CMA is the control of cardiovascular risk factors and diseases. The leading role belongs to smoking cessation, cessation of alcohol abuse, regular physical activity, effective treatment of AH, type 2 diabetes and atrial fibrillation [1]. The most important direction for the prevention of vascular CI against the background of CCI is the normalization of blood pressure on the basis of antihypertensive therapy. The positive effect of antihypertensive scratching in reducing the risk of developing CI was demonstrated in the clinical studies SPRINT (Systolic Blood Pressure Intervention Trial) MIND [65] and PROGRESS (Perindopril Protection Against Recurrent Stroke Study) [66]. According to the consensus of Russian experts, antihypertensive therapy has been shown to be effective in reducing the risk of developing CI and dementia. The

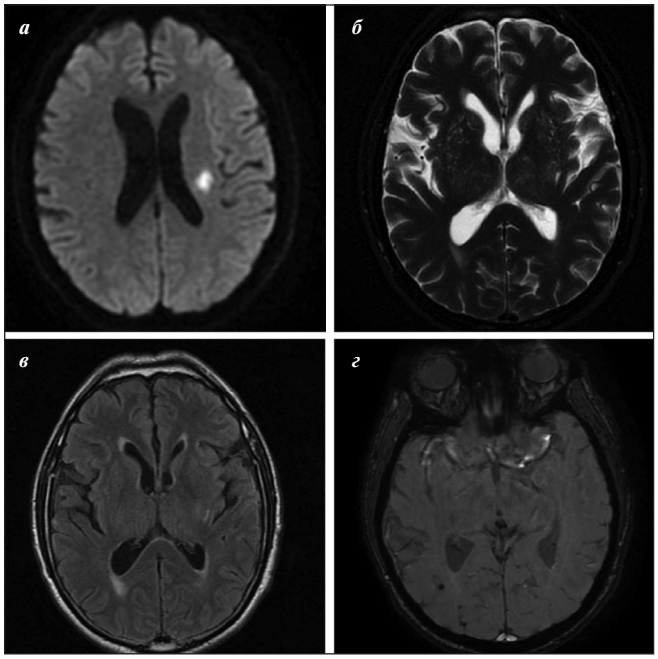

Fig. 1. *Case report of a lacunar stroke associated with COVID-19. A 62-year-old male has long-term treated and controlled hypertension. In the middle of March 2021, the patient suffered from COVID-19-associated viral pneumonia (CT-1). He received standard treatment in the outpatient department. 09.04.2021 around 11 a.m., acute numbness in the right extremities developed. The patient was admitted to the neurology department. During the examination, the diagnosis of lacunar stroke was established with the localization of the lacunar infarction in the region of left corona radiata (a – DWI MRI) secondary to mild sporadic cerebral microangiopathy (b – enlarged perivascular spaces in the deep white matter of the brain hemispheres, T2 MRI; c – white matter hyperintensities, Fazekas I, FLAIR MRI; d – a single cerebral microbleed in the white matter of the right temporal lobe, SWAN MRI)*

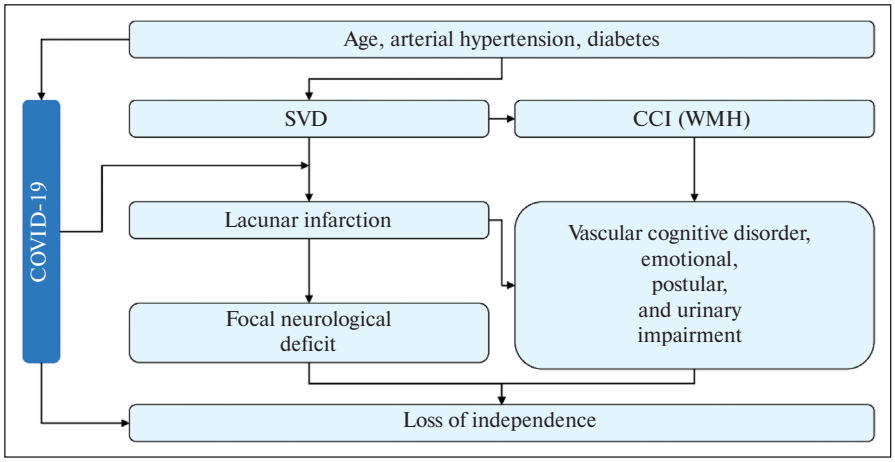

Fig. 2. *Hypothesis of the COVID-19 impact on the course of cerebral microangiopathy and CCI*

most promising is the use of blockers of the renin-angiotensin-aldosterone system, dihydropyridine calcium antagonists and diuretics [67].

For patients with CCI, the recommendations for primary and secondary prevention of stroke should be fully followed [68]. Antiplatelet therapy plays a special role in this. Currently, a patient who has had a non-cardioembolic stroke or TIA can be prescribed one of the following antiplatelet therapy regimens: acetylsalicylic acid, its combination with extended-release dipyridamole, clopidogrel, as well as a combination of acetylsalicylic acid with clopidogrel or ticagrelor in minor streoke or TIA [69, 70]. The efficacy and safety of dual antiplatelet therapy consisting of acetylsalicylic acid and dipyridamole has been demonstrated in four randomized clinical trials (ESPS-1, ESPS-2, ESPRIT and PRoFESS) [71–74].

Currently great interest of researchers and doctors cause recently described pleiotropic effects of classical dipyridamole antiplatelet drug (CurantilË) [75]. Dipyridamole inhibits the enzyme phosphodiesterase in platelets and, therefore, increases intra-platelet levels of cyclic adenosine monophosphate and cyclic guanosine monophosphate, thereby inhibiting platelet aggregation and enhancing the inhibitory effect of prostacyclin on platelets [76]. The drug also has anti-inflammatory activity, including a decrease in nuclear translocation of nuclear factor ?B (decrease in the expression of matrix metalloproteinase 9 and the level of proinflammatory cytokines), which is realized in reducing nonspecific inflammation and improving endothelial function [77, 78]. These effects may determine the advantage of dipyridamole over other antiplatelet agents in the treatment of patients with CCI associated with CMA.

Recent evidence also suggests pathogenetically substantiated benefits of the drug in patients with COVID-19. It has been shown that selective agonism to adenosine A2A receptors suppresses netosis (NETosis) associated with exposure to antiphospholipid antibodies. Therefore, dipyridamole, by increasing the concentration of adenosine, is a way to suppress immunothrombosis [48]. In a recent study by X. Liu et al. [79] showed that the administration of dipyridamole (150 mg/day for 14 days) in severe COVID-19 is associated with a significant level of D-dimer concentration, increased lymphocyte and platelet recovery, and a better clinical outcome. This effect can be explained by the fact that dipyridamole binds the Mpro protease of the SARS-CoV-2 virus and inhibits viral replication *in vitro*. In addition, dipyridamole is an inducer of interferon synthesis, which enhances its antiviral effect [80].

Conclusion. An increase in the number of patients with AH and type 2 diabetes in the population allows predicting an increase in the incidence of CMA and, consequently, CCI, the main negative consequence of which is an increase in the number of patients with dementia. The COVID-19 pandemic can serve as a factor destabilizing the course of CCI and its phenotypic modification with the development of acute manifestations of CMA, in particular lacunar infarctions, which carry the risk of patient disability. Modern knowledge about the pathogenesis of CMA, namely, the idea of a significant role in its development of endothelial dysfunction, inflammatory and thrombotic mechanisms, suggest the particular vulnerability of the latter in patients with COVID-19. Therefore, during a pandemic, special attention should be paid to the issues of primary and secondary cardiovascular prophylaxis in patients with CCI, an important drug element of which, in the light of pleiotropic effects, is the use of dipyridamole (Curantil®).

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