Post-covid syndrome: a review of pathophysiology, neuropsychiatric manifestations and treatment perspectives

Khasanova D.R.[1, 2], Zhitkova Yu.V.[2], Vaskaeva G.R.[1]
[1]Kazan State Medical University, Ministry of Health of Russia, Kazan;
[2]Interregional Clinical Diagnostic Center, Ministry of Healthof the Republic of Tatarstan, Kazan
[1]49, Butlerov St., Kazan 420012, Russia; [2]12a, Karbyshev St., Kazan 420101, Russia

In the context of the COVID-19 pandemic, healthcare is faced with several new problems, one of which is a post-covid syndrome. Symptoms in many COVID-19 survivors can persist for a long time, significantly affecting the quality of life and work performance. All of the above makes post-covid syndrome a socially significant disease, requires dynamic follow-up of such patients, and rehabilitation programs development. We are currently at the stage of accumulating knowledge about the SARS-CoV-2 pathophysiology and morphogenesis and its long-term consequences. This article discusses neuropsychiatric aspects of the post-covid syndrome: pathogenetic hypotheses, clinical features, and potentially promising treatment strategies.

Keywords: *COVID-19; post-covid syndrome; neuropsychiatric manifestations; pathophysiology; treatment strategies.*
Contact: *Yulia Vladimirovna Zhitkova;* ***zhitkova@mail.ru***
For reference: *Khasanova DR, Zhitkova YuV, Vaskaeva GR. Post-covid syndrome: a review of pathophysiology, neuropsychiatric manifestations and treatment perspectives. Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics. 2021;13(3):93–98. DOI: 10.14412/2074-2711-2021-3-93-98*

In December 2019, an outbreak of a new coronavirus infection (COVID-19) occurred in Wuhan, China, caused by the new SARS-CoV-2 virus. This infection has become a pandemic, and the number of cases of COVID-19 infection worldwide, as well as the number of deaths, continues to grow. In this regard, the fight against COVID-19 has become a priority task for world healthcare today. Along with the number of people infected with SARS-CoV-2, understanding of the features of this new infection is growing, and clinical guidelines for the management of patients with COVID-19 are constantly being updated. Nevertheless, SARS-CoV-2 poses a problem for neuroscientists and clinicians due to its insufficiently understood pathomorphogenesis.

According to the data available today, the complex of pathogenetic mechanisms caused by the SARS-CoV-2 virus leads to the development of multi-organ pathology of varying severity: from asymptomatic to fatal forms. In February 2020, the World Health Organization (WHO) reported that the time from disease onset to clinical recovery in mild cases is approximately 2 weeks, while recovery in patients with severe or critical illness takes 3 to 6 weeks. Over time, however, it became clear that a number of symptoms could persist for weeks or even months, and in some patients the symptoms did not go away. At the same time, prolonged damage to many organs or systems, including the lungs, heart, brain, kidneys and vascular system, has been documented even in patients with mild COVID-19. One of the first reports on this topic was received on July 9, 2020 and included 143 patients from Italy who were followed up for 2 months after discharge [1]. 87% of patients in this observation had at least one persistent symptom (most often fatigue and shortness of breath), and a decrease in the quality of life was observed in 44.1% of patients [1]. Two more recent reports gave similar results: a telephone survey conducted from April to June 2020 in 13 US states showed that 35% of COVID-19 patients did not return to their normal state of health [2]. In a Dutch three-month follow-up of 126 patients stratified by the initial severity of COVID-19, even 27 patients with mild disease and 51 patients with moderate infection showed a set of symptoms of the same severity as patients with severe and critical forms of COVID-19 [3]. Despite the small sample size, these studies, as well as many subsequent studies of the distant manifestations of COVID-19, are extremely novel and help to solve an acute medical problem based on actively collected data. However, it is already clear today that we will need years of experience in monitoring COVID-19 survivors to fully understand the implications associated with the disease.

Thus, a new term has appeared – «post-COVID-19 syndrome» (PCS; synonym: long COVID, post-COVID-19 syndrome and post-acute COVID-19 syndrome), describing the signs and symptoms that develop during or after the disease COVID-19, last more than 12 weeks (and in 2.3% of cases – longer), occur in waves or constantly and do not have an alternative diagnosis (there is no consensus definition yet). PCS received the official status of a disease and was included in the new edition of the International Classification of Diseases, revision 10, where it is designated as a «post-COVID-19 condition» under the code U09.9.

There are many pathogenetic hypotheses of PCS, however, currently there is no unified pathogenetic theory. All existing hypotheses do not contradict each other, and the factors considered in them can contribute to the formation of PCS. There is no doubt that the pathogenesis of PCS is associated with the basic mechanisms of development and course of COVID-19. The pathogenic effect of SARS-CoV-2 on the nervous system can be caused by the following mechanisms:

1. Neurotropism and neurovirulence – the ability to directly penetrate nerve cells and cause a disease of the nervous system. The tropism of SARS-CoV-2 to human cells is provided by receptors for angiotensin converting enzyme 2 (ACE2), which are expressed by neurons, glial cells, endothelial cells, respiratory epithelium, lung parenchyma, kidneys, and small intestine. Neuroinvasion of SARS-CoV-2 probably occurs in two ways: a) neuronal; b) hematoencephalic.

The neuronal pathway implies that during intranasal infection, the virus penetrates directly into the olfactory nerve and then spreads in the central nervous system (CNS), reaching the medulla oblongata. In a study by P. Kumari et al. [4], after intranasal infection of K18-hACE2 mice, the SARS-CoV-2 virus antigen was detected in all parts of the brain, including the cortex, cerebellum, and hippocampus. The peak virus titers in the brain were about 1000 times higher than the peak titers in the lungs, indicating the high replicative potential of SARS-CoV-2 in the brain. These data suggest that the brain is the primary target of SARS-CoV-2 infection.

Hematoencephalic SARS-CoV-2 neuroinvasion occurs through the damaged endothelium of the cerebral vessels and through the migration of leukocytes across the blood-brain barrier (BBB). Despite the fact that viral RNA was not always detected in the brain tissue and cerebrospinal fluid during the autopsy of patients with neurological manifestations of COVID-19, neurotropic nature of SARS-CoV-2 finds more and more confirmation. Probably, there were false negative results or insufficient viral load of the cerebrospinal fluid to detect the virus by polymerase chain reaction [5]. Long-term presence of the virus and persistent viremia with a weak immune response are considered one of the pathogenetic hypotheses of PCS.

2. «Cytokine storm» – a systemic hyperinflammatory response of the immune system associated with the activation of macrophages, mast cells, leukocytes, endothelial cells with the release of a large number of proinflammatory cytokines and chemokines. Excessive production of inflammatory mediators leads to damage or destruction of the BBB, changes in cerebral perfusion, activation of microglia and astrocytes, imbalance of neurotransmitters and neuroplastic changes. Damage to the BBB seems to be extremely important in terms of neuropsychiatric consequences of COVID-19, since increased BBB permeability in the experiment was associated with some severe mental disorders, such as schizophrenic spectrum disorders, major depression, bipolar disorder [6]. The key role in the alteration of the nervous tissue is played by inflammatory changes in astrocytes – the main population of glial cells involved in synaptogenesis, control of the release and uptake of neurotransmitters, production of trophic factors necessary for the differentiation and survival of neurons, formation and functioning of the neurovascular unit and the BBB, as well as the glymphatic system, which eliminates toxic products, including virus particles. Astroglial reactions induced by SARS-CoV-2 can contribute to the onset of neuropsychiatric symptoms, manifestation or aggravation of symptoms of neurodegenerative diseases.

3. Pathogenic immune response with autoaggression as a result of hyperactivation and depletion of microglia with impairment of the systemic antiviral response of T-cells, inducing neuronal damage and demyelination.

4. Indirect effect of the virus associated with organ damage, such as encephalopathy, myopathy, neuropathy of critical conditions.

5. Thrombus formation (arterial and venous thrombosis, micro- and macro-) in patients with COVID-19 can be caused by endothelial dysfunction and endotheliitis, «cytokine storm», hypoxic damage, hypercoagulability and / or increased platelet activity. A special concept of microthrombosis in situ was introduced. To date, the role of chronic inflammation (primarily endotheliitis – vasculitis with microthrombosis and microcirculatory disorders) and other immune reactions is considered the main theory of the pathogenesis of PCS. It is emphasized that even the so-called «silent» hypoxia in asymptomatic COVID pneumonia and, of course, in combination with a «cytokine storm» can trigger an aggressive autoimmune process and be a precursor of the subsequent development of neurodegenerative brain diseases. Increased thrombus formation is associated with a high incidence of thrombotic cerebral complications of COVID infection caused by an increase in procoagulation factors such as fibrinogen, D-dimer, prothrombin time [7]. On the other hand, damage to the BBB in combination with an increase in the level of angiotensin 2 and arterial hypertension leads to hemorrhagic complications [7]. All this determines the complexity of the selection of medical pathogenetic therapy for this viral infection, in particular the use of anticoagulants, due to the risk of cerebral hemorrhagic complications, both in the acute period of the disease, and after it – in the form of delayed ischemic and hemorrhagic strokes.

The white matter of the brain is especially susceptible to ischemic damage in COVID-19. Confirmation of long-term changes in the brain substance in individuals with neurological consequences of SARS-CoV-2 is neuroradiological evidence of microstructural damage and impaired functional integrity of the brain after 3 months of follow-up in patients who recovered from COVID-19 [8]. There is evidence that hypoperfusion of the brain accelerates the accumulation of beta-amyloid and is associated with the pathology of tau protein, TDP-43 and alpha-synuclein [9]. In this regard, accelerated aging, cerebrovascular diseases and age-related neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease have been considered long-term consequences of COVID-19.

Thus, the direct effect of SARS-CoV-2 on neuronal function and survival, glial reactivity, excessive cytokine response, antineuronal antibodies, and the consequences of cerebrovascular disorders may contribute to the pathophysiology of PCS. However, the question remains: is PCS a complication of COVID-19 or an ongoing pathological process?

Neuropsychiatric manifestations of PCS

Patients with PCS have a number of long-term multisystem symptoms with no proven organ damage and with normal physical and laboratory parameters. PCS can manifest clinically 3 months or more after «recovery» and is more common in women than in men (ratio 4: 1). Studies of PCS included young and middle-aged patients, who showed a decrease in working capacity of varying severity, up to its complete loss. Cognitive impairments (CI), which were equally represented in all age groups [10, 11], were often the reason for decreased working capacity and ability to perform everyday activities. Most of the studies initially showed a predominantly regulatory character of CI associated with PCS [7, 9]. For example, a study by V. Beaud et al. [12] evaluated cognitive functions of

patients (mean age 64.8 years) who recovered from acute respiratory distress syndrome associated with COVID-19. The authors identified two CI profiles: 1) patients with a normal Montreal Cognitive Assessment (MoCa) score, but with a tendency to a decrease in executive functions compared with other cognitive domains; 2) patients with MoCa and the Frontal Assessment Battery (FAB) test deficiency from mild to severe, with predominant impairment of executive functions, attention, memory, visual-spatial impairments, with relative preservation of orientation and speech functions. Moreover, in all patients, CI was combined with anxiety and depression and did not correlate with the duration of mechanical ventilation and the length of stay in the intensive care unit, i.e., with the severity of the infection in the acute period, with the exception of delirium, which was strongly associated with severe cognitive deficits [12]. However, in studies conducted on a much younger population of patients using specialized scales for assessing short-term memory sensitive to moderate (predementia) CI, primary memory deficit was revealed in young people (mean age 42.2 years) who had mild and moderate forms of COVID-19, in comparison with the control group of the same age (mean age – 38.4 years) [9]. Similar results were obtained by J.P. Rogers et al. [13]: 19.9% of patients had impaired attention and 18.9% had memory impairment. Thus, there is a need to develop standardized cognitive screening tools that are sensitive to subclinical and moderate CI, including those in young people.

Attempts have been made to identify risk factors for post-COVID CI in the acute period of the disease. In particular, in the study by M. Almeria et al. [14], the presence of neurological symptoms, such as headache, anosmia and dysgeusia, during the acute period of infection, as well as the need for oxygen support and diarrhea were associated with the development of persistent CI after recovery. Data have been obtained on the role of diabetes mellitus as a predictor of post-COVID dementia, especially in certain ethnic groups (African Americans, Hispanics) [15], who, apparently, have a generally high risk of neurological complications of COVID-19 [16]. The relationship between the inflammatory profile (for example, the level of C-reactive protein) and post-COVID CI was studied, which positively correlated [17]. In addition, it was found that ApoE4 genotype creates a preposition for the development of CI in PCS due to its association with increased BBB permeability and pericyte degeneration, small vessel disease and cerebral amyloidosis [18]. Also, individuals with ApoE4 have low ACE2 activity [19], and the prevalence of COVID-19 is generally higher among carriers of this genotype [20]. Thus, according to recent data, dementia and COVID-19 are likely to share common risk factors such as old age, gender, hypertension, diabetes mellitus, obesity, elevated C-reactive protein and ApoE4-genotype [9]. These findings have significant predictive value, especially for older adults who are more susceptible to severe cognitive outcomes of COVID-19.

PCS is no less often associated with affective disorders. The risk of a newly diagnosed mental disorder in the United States approximately doubled within 14–90 days after the COVID-19 outbreak [21], and a high percentage of severe anxiety-depressive conditions was recorded among hospitalized patients with COVID-19 [22]. This was expected in the face of frightening uncertainty, large-scale quarantine measures and isolation, fear for life, health and economic consequences of the pandemic. However, over the past two decades, evidence has accumulated supporting the hypothesis that neuroinflammation contributes to the onset of depression and that the immune system as a whole plays a significant role in the pathophysiology of mood disorders [23]. According to modern literature data, newly-onset depression can be initiated by the release of cytokines (eg, interleukin-6) during the active phase of COVID-19 and decreases as the level of cytokines normalizes, regardless of the use of antidepressants [24]. This suggests that the use of drugs that reduce the activity of cytokines can reduce the likelihood of affective manifestations of PCS, but further research is required to better understand this process [24].

The growing body of evidence for the CNS effects of SARS-CoV-2 raises key questions about identifying risk factors for subsequent cognitive decline, Alzheimer's disease and other types of dementia, and affective disorders. The scientific community of 30 countries, together with the Alzheimer's Association and WHO leadership, have formed the International Multidisciplinary Consortium to collect and evaluate the short- and long-term effects of SARS-CoV-2 on the central nervous system. This program will include 22 million clinical cases, bring together research groups from all over the world, and will address the delayed impact of COVID-19 on cognition and cognitive functioning, including the biology of infection contributing to the manifestation of Alzheimer's disease and other dementias. [25]. In addition, the World Federation of Neurology (WFN) is creating an international register of neurological manifestations of COVID-19. Large-scale studies have also begun to assess the prevalence of depression, anxiety, delirium and post-traumatic stress disorder in patients with COVID-19 [26].

General principles of patient management and treatment prospects

Currently, management protocols for patients with COVID-19 are under development. Of course, there is an urgent need for a unified guidance on rehabilitation, though in practice the basic principles based on the experience of rehabilitation of patients after infections, stroke and other diseases are applied. Respiratory rehabilitation aimed at reducing the symptoms of shortness of breath and psychological support begins in the acute period of infection. After stabilization of the patient's condition on the basis of clinical assessment (physical examination, imaging, laboratory data, lung function, concomitant diseases, etc.) and assessment of the rehabilitation potential, a personalized rehabilitation program is developed, including respiratory, cardiovascular, physical, cognitive and psychological rehabilitation, as well as measures to improve the household and professional adaptation of the patient [27, 28]. During the implementation of rehabilitation measures, the activity of the cardiovascular and respiratory systems, body temperature and oxygen saturation are monitored.

To date, there are no proven drug treatments for PCS. Approaches to the treatment of PCS are symptomatic and based on the available evidence and recommendations for the treatment of syndromes that make up the clinical picture of the disease. Based on the understanding of the pathogenesis of PCS and the mechanism of action of drugs, it can be assumed that certain drugs may be useful. One of the promising drugs in the

treatment of patients in the post-COVID period, especially in combination with stroke, is cerebrolysin, the main multimodal effect of which is aimed at the main pathogenetic mechanisms of the development of degenerative processes and recovery processes after injury. It has been shown that cerebrolysin protects nerve cells from neurodegeneration caused by hypoxia, ischemia, toxic effects of glutamate and beta-amyloid [29], has a pronounced neuroimmunotrophic effect and thereby reduces the development of inflammatory phenomena («cytokine storm») in the tissue, prevents the death of neuronal structures and protects the BBB [30, 31]. Cerebrolysin protects cells from structural degradation in ischemic brain damage by increasing the pool of neuronal cytoskeletal protein (microtubule associated protein 2, MAP2), which is considered an indicator of the primary stage of neuronal damage [32]. The antioxidant systemic effect of cerebrolysin was demonstrated in some studies [33, 34]. The drug can stimulate the process of neurogenesis and slow down apoptosis, which has been shown in experimental studies of Japanese and American scientists [13, 35]. There is a large evidence base of clinical studies on restoration of impaired functions (CARS, ECOMPASS studies) after stroke and reduction of asthenia phenomena [36–38], as well as improvement of cognitive functions [39], which made it possible to introduce cerebrolysin into clinical guidelines for stroke rehabilitation in a number of countries. Thus, despite the fact that targeted clinical studies will be required, such mechanisms of cerebrolysin as neuroprotective action, reduction of neuroinflammation, BBB permeability, activation of neurogenesis and neuroplasticity, form the pathogenetic rationale and determine the prognostic efficiency of its use in the treatment of patients with neurological manifestations of COVID-19, including those complicated by stroke.

REFERENCES

1. Carfì A, Bernabei R, Landi F, et al. Persistent Symptoms in Patients after Acute COVID-19. *JAMA*. 2020 Aug 11;324(6):603-5. doi: 10.1001/jama.2020.12603

2. Tenforde MW, Kim SS, Lindsell CJ, et al. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network – United States, March–June 2020. *MMWR Morb Mortal Wkly Rep*. 2020 Jul 31;69(30):993-8. doi: 10.15585/mmwr.mm6930e1

3. Van den Borst B, Peters JB, Brink M, et al. Comprehensive health assessment three months after recovery from acute COVID-19. *Clin Infect Dis*. 2020 Nov 21;ciaa1750. doi: 10.1093/cid/ciaa1750. Online ahead of print.

4. Kumari P, Rothan HA, Natekar JP, et al. Neuroinvasion and Encephalitis Following Intranasal Inoculation of SARS-CoV-2 in K18-hACE2 Mice. *Viruses*. 2021 Jan 19;13(1):132. doi: 10.3390/v13010132

5. Алексеева НТ, Соколов ДА, Никитюк ДБ и др. Молекулярные и клеточные механизмы повреждения центральной нервной системы при COVID-19. *Журнал анатомии и гистопатологии*. 2020;9(3):72-85. [Alekseyeva NT, Sokolov DA, Nikityuk DB, et al. Molecular and cellular mechanisms of damage to the central nervous system in COVID-19. *Zhurnal anatomii i gistopatologii*. 2020;9(3):72-85 (In Russ.)].

6. Futtrup J, Margolinsky R, Benros ME, et al. Blood-brain barrier pathology in patients with severe mental disorders: a systematic review and meta-analysis of biomarkers in case-control studies. *Brain Behav Immun Health*. 2020 Nov;90:364-80. doi: 10.1016/j.bbi.2020.08.028. Epub 2020 Sep 3.

7. Wang Z, Yang Y, Liang X. COVID-19 Associated Ischemic Stroke and Hemorrhagic Stroke: Incidence, Potential Pathological Mechanism, and Management. *Front Neurol*. 2020 Oct 27;11:571996. doi: 10.3389/fneur.2020.571996. eCollection 2020.

8. Lu Y, Li X, Geng D, et al. Cerebral Micro-Structural Changes in COVID-19 Patients An MRI-based 3-month Follow-up Study. *EClinicalMedicine*. 2020 Aug;25:100484. doi: 10.1016/j.eclinm.2020.100484. Epub 2020 Aug 3.

9. Miners S, Kehoe PG, Love S. Cognitive impact of COVID-19: looking beyond the short term. *Alzheimer's Res Ther*. 2020 Dec 30;12(1):170. doi: 10.1186/s13195-020-00744-w

10. Carvalho-Schneider C, Laurent E, Lemaignen A, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect*. 2021 Feb;27(2):258-63. doi: 10.1016/j.cmi.2020.09.052. Epub 2020 Oct 5.

11. Garrigues E, Janvier P, Kherabi Y, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect*. 2020 Dec;81(6):e4-e6. doi: 10.1016/j.jinf.2020.08.029. Epub 2020 Aug 25.

12. Beaud V, Crottaz-Herbette S, Dunet V, et al. Pattern of cognitive deficits in severe COVID-19. *J Neurol Neurosurg Psychiatry*. 2021 May;92(5):567-8. doi: 10.1136/jnnp-2020-325173. Epub 2020 Nov 20.

13. Rogers JP, Chesney E, Oliver D, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry*. 2020 Jul;7(7):611-27. doi: 10.1016/S2215-0366(20)30203-0. Epub 2020 May 18.

14. Almeria M, Cejudo JC, Sotoca J, et al. Cognitive profile following COVID-19 infection: Clinical predictors leading to neuropsychological impairment. *Brain, Behav Immun Health*. 2020 Dec;9:100163. doi: 10.1016/j.bbih.2020.100163. Epub 2020 Oct 22.

15. Naughton SX, Raval U, Pasinetti GM. Potential Novel Role of COVID-19 in Alzheimer's disease and preventative mitigation strategies. *J Alzheimers Dis*. 2020;76(1):21-5. doi: 10.3233/JAD-200537

16. Pinna P, Grewal P, Hall JP, et al. Neurological manifestations and COVID-19: experiences from a tertiary care center at the frontline. *J Neurol Sci*. 2020 Aug 15;415:116969. doi: 10.1016/j.jns.2020.116969. Epub 2020 Jun 3.

17. Magoon R. Pulmonary vasculature in COVID-19: mechanism to monitoring! Korean J Anesthesiol. 2021 Apr;74(2):186-7. doi: 10.4097/kja.20536. Epub 2020 Oct 5.

18. Love S, Chalmers K, Ince P, et al. Development, appraisal, validation and implementation of a consensus protocol for the assessment of cerebral amyloid angiopathy in post-mortem brain tissue. *Am J Neurodegener Dis*. 2014 Mar 28;3(1):19-32. eCollection 2014.

19. Kehoe PG, Wong S, Mulhim NAL, et al. Angiotensin-converting enzyme 2 is reduced in Alzheimer's disease in association

with increasing amyloid-beta and tau pathology. *Alzheimers Res Ther.* 2016 Nov 25;8(1):50. doi: 10.1186/s13195-016-0217-7

20. Kuo CL, Pilling LC, Atkins JL, et al. APOE e4 Genotype Predicts Severe COVID-19 in the UK Biobank Community Cohort. *J Gerontol A Biol Sci Med Sci.* 2020 Oct 15;75(11):2231-2. doi: 10.1093/gerona/glaa131

21. Taquet M, Luciano S, Geddes JR, et al. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. *Lancet Psychiatry.* 2021 Feb;8(2):130-40. doi: 10.1016/S2215-0366(20)30462-4. Epub 2020 Nov 9.

22. Woo MS, Malsy J, Pöttgen J, et al. Frequent neurocognitive deficits after recovery from mild COVID-19. *Brain Commun*. 2020 Nov 23;2(2):fcaa205. doi: 10.1093/braincomms/fcaa205. eCollection 2020.

23. Lee Y, Subramaniapillai M, Brietzke E, et al. Anti-cytokine agents for anhedonia: targeting inflammation and the immune system to treat dimensional disturbances in depression. *Ther Adv Psychopharmacol.* 2018 Nov 19;8(12):337-48. doi: 10.1177/2045125318791944. eCollection 2018 Dec.

24. Alpert O, Begun L, Garren P, et al., Cytokine storm induced new onset depression in patients with COVID-19. A new look into the association between depression and cytokines – two case reports. *Brain Behav Immun Health*. 2020 Dec;9:100173. doi: 10.1016/j.bbih.2020.100173. Epub 2020 Nov 3.

25. De Erausquin GA, Snyder H, Carrillo M, et al. The chronic neuropsychiatric sequelae of COVID-19: The need for a prospective study of viral impact on brain functioning. *Alzheimer's Dement*. 2021 Jan 5. doi: 10.1002/alz.12255. Online ahead of print.

26. Shi J, Gao Y, Zhao L, et al. Prevalence of delirium, depression, anxiety, and post-traumatic stress disorder among COVID-19 patients: protocol for a living systematic review. *Syst Rev.* 2020 Nov 6;9(1):258. doi: 10.1186/s13643-020-01507-2

27. Barker-Davies RM, O'Sullivan O, Senaratneet KPP, et al. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. *Br J Sports Med.* 2020 Aug;54(16):949-59. doi: 10.1136/bjsports-2020-102596. Epub 2020 May 31.

28. Demeco A, Marotta N, Barletta M, et al. Rehabilitation of patients post-COVID-19 infection: a literature review. *J Intern Med Res.* 2020 Aug;48(8):300060520948382. doi: 10.1177/0300060520948382

29. Deigner HP, Haberkorn U, Kinscherf R. Apoptosis modulators in the therapy of neurodegenerative diseases. *Expert Opin Investig Drugs.* 2000 Apr;9(4):747-64. doi: 10.1517/13543784.9.4.747

30. Alvarez XA, Lombardi VR, Fernandez-Novoa L, et al. Cerebrolysin reduces microglial activation in vivo and in vitro: a potential mechanism of neuroprotection. *J Neural Transm Suppl.* 2000;59:281-92. doi: 10.1007/978-3-7091-6781-6-30

31. Domzal T, Zaleska B. Cerebrolysin in treatment of acute ischemic stroke. *Neurol Neurochir Pol.* May-Jun 1995;29(3):325-31.

32. Schwab M, Antonow-Schlorke I, Zwiener U, et al. Brain-derived peptides reduce the size of cerebral infarction and loss of MAP2 immunoreactivity after focal ischemia in rats. *J Neural Transm Suppl.* 1998;53:299-311. doi: 10.1007/978-3-7091-6467-9-26

33. Бабенкова ИВ, Теселкин ОЮ, Макашова НВ, Гусева МР. Антиоксидантная активность гистохрома и некоторых лекарственных препаратов, применяемых в офтальмологии. *Вестник офтальмологии*. 1999;115(4):22-4. [Babenkova IV, Teselkin OYu, Makashova NV, Guseva MR. Antioxidative activity of histochrome and some other drugs used in ophthalmology. *Vestnik oftalmologii*. 1999;115:22-4 (In Russ.)].

34. Cruz R, Francis L, Diaz-Suarez CM, et al. Short-term effects of septohippocampal pathway transsection and cerebrolysin effects on glutathione-related enzymes in the rat brain. *Rev Neurol.* 1998 Apr;26(152):551-4.

35. Tatebayashi Y, Lee MH, Li L, et al. The dentate gyrus neurogenesis: a therapeutic target for Alzheimefs disease. *Acta Neuropathol.* 2003 Mar;105(3):225-32. doi: 10.1007/s00401-002-0636-3. Epub 2002 Nov 19.

36. Chang WH, Park CH, Kim DY, et al. Cerebrolysin combined with rehabilitation promotes motor recovery in patients with severe motor impairment after stroke. *BMC Neurol.* 2016 Mar 2;16:31. doi: 10.1186/s12883-016-0553-z

37. Montagne A, Nation DA, Sagare AP, et al. APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. *Nature*. 2020 May;581(7806):71-6. doi: 10.1038/s41586-020-2247-3. Epub 2020 Apr 29.

38. Muresanu DF, Heiss W-D, Hoemberg V, et al. Cerebrolysin and Recovery After Stroke (CARS). A randomized, placebo-controlled, double-blind, multicenter trial. *Stroke*. 2016 Jan;47(1):151-9. doi: 10.1161/STROKEAHA.115.009416. Epub 2015 Nov 12.

39. Guekht A, Moessler H, Novak PH, Gusev EI; Cerebrolysin Investigators. Cerebrolysin in vascular dementia: Improvement of clinical outcome in a randomized, double blind, placebo-controlled multicenter trial. *J Stroke Cerebrovasc Dis.* Jul-Aug 2011;20(4):310-8. doi: 10.1016/j.jstrokecerebrovasdis.2010.01.012. Epub 2010 Jul 24.

Received/Reviewed/Accepted
29.03.2021/2.05.2021/11.05.2021

Conflict of Interest Statement

This article has been supported by Ever Neuro Pharma. The conflict of interest has not affected the results of the investigation. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

Khasanova D.R. https://orchid.org/0000-0002-8825-2346
Zhitkova Yu.V. https://orchid.org/0000-0002-9851-4362
Vaskaeva G.R. https://orchid.org/0000-0001-6565-7642