DOI 10.1007/s11055-022-01324-1
Neuroscience and Behavioral Physiology, Vol. 52, No. 7, September, 2022

Neurological Signs of Postcovid Syndrome

P. R. Kamchatnov,[1] R. A. Cheremin,[2] L. A. Skipetrova,[2] and A. V. Chugunov[1]

Translated from Zhurnal Nevrologii i Psikhiatrii imeni S. S. Korsakova, Vol. 122, No. 3, Iss. 1, pp. 7–15, March, 2022. Original article submitted February 15, 2022. Accepted February 23, 2022.

The challenge of postcovid syndrome (PCS) is of great interest due to its wide distribution and variety of clinical signs. The main neurological signs of PCS are discussed. Data on the presumptive mechanisms forming PCS are presented. The potential for using the drug Mexidol to treat patients with PCS is addressed.

Keywords: COVID-19, postcovid syndrome, cognitive impairments, chronic cerebral ischemia, Mexidol, treatment.

The exclusively wide distribution of COVID-19 in the population, often producing persistent complaints and objective derangement of health in patients who have had acute illness, provides grounds for studying status after experiencing coronavirus infection with SARS-CoV-2. The term "postcovid syndrome" (PCS) was initially proposed to describe the symptom complex developing during or immediately after COVID-19 infection, lasting more than 12 weeks, and not being explicable in terms of other alternative diagnoses [1]. This term includes both the signs of symptomatic persistent COVID-19 and post-COVID-19 syndrome itself. Subsequently, the term post-acute sequelae of SARS-CoV-2 infection/COVID-19 (PASC) was proposed to discriminate long-lasting COVID-19 and PCS [2]. The WHO proposed characterizing this state using the following definition: "The post-COVID-19 state develops in people with histories of likely or confirmed infection with SARS-CoV-2, generally within three months from the onset of COVID-19, and is characterized by symptoms for at least two months which cannot be explained by any other diagnosis. These symptoms include fatigue, breathlessness, cognitive dysfunction, and various others, which generally have consequences for everyday functioning. Onset of symptoms can occur after a healthy period following acute COVID-19 infection or persistence of symptoms from the moment of initially contracting the disease. In addition, periodically arising or recurrent symptoms over time can occur" [3].

Prevalence and Clinical Signs of PCS. The clinical signs of PCS are exclusively diverse, and the process involves different body systems; neurological and neuropsychiatric manifestations, including cognitive impairments, autonomic disorders, and asthenic and anxiety disorders, are of particular importance, as they are linked with significant reductions in patients' quality of life, not infrequently with slowing of the recovery process and restrictions to work activity [4, 5]. These and other manifestations of PCS are seen in a large proportion of patients who have had COVID-19. Thus, about one third of patients show increases in fatigue and constant feelings of tiredness, while more than a fifth display cognitive impairments for 12 or more weeks after the acute stage of illness [6]. This type of abnormality is seen in patients with COVID-19 with different types of course and severity. In contrast to other neurological disorders, which can regress spontaneously with time (for example, anosmia, dysgeusia) [7], tiredness (fatigue) and cognitive impairments can persist over prolonged periods of time, subsequently not only failing to settle, but also increasing in some patients for at least six months [8].

Overall, the combination of increased fatigue and cognitive impairments in PCS has a series of similarities in the clinical manifestations with postinfection fatigue syndrome (postinfection asthenia), as well as myalgic encephalopathy/chronic fatigue syndrome, which are not infrequently associated with experiencing infectious diseases [8, 9]. Comparable indicators of persistent tiredness and increased fatigue and significant decreases in measures of quality of

[1] Pirogov Russian National Research Medical University, Russian Ministry of Health, Moscow, Russia; e-mail: pavkam7@gmail.com.
[2] Speech Pathology and Neurorehabilitation Center, Moscow Health Department, Moscow, Russia.

life have been recorded in patients after infectious diseases due to variety of coronaviruses, including severe acute respiratory and Middle East respiratory syndromes [10, 11]. Furthermore, it has been suggested that some of the clinical manifestations of encephalitis lethargica (von Economo's encephalitis), outbreaks of which were documented in the 1920s (fatigue, cognitive impairment, headache) and are presumptively associated with the Spanish flu of 1918, may have similarity with the signs of PCS [12].

The relationship between the severity of the acute period of COVID-19 and the nature and extent of PCS has repeatedly been studied. Results from the largest cohort study of survivors of hospitalization for COVID-19 to date (Wuhan, China) provided evidence that at six months, these or other manifestations of PCS or their combinations are seen in more than 80% of patients, and a relationship was established between their extent and the severity of COVID-19, particularly as defined by the need for respiratory support [13].

A relationship between the rate and completeness of regression of symptoms six months from the onset of illness and the outcome of severe COVID-19 was demonstrated in results from a series of studies in different parts of the world. Complete recovery is found to occur in 20–30% of hospitalized patients [13, 14], while the number of patients treated as out-patients (not needing hospital admission) recovering reaches 70–90% at three months [15]. The severity of persistent symptoms for at least six months after hospitalization for COVID-19 was significantly greater in patients admitted with community-acquired pneumonia and needing hospitalization for more than three weeks [16].

It is entirely expected that the nature of the course of acute COVID-19 is associated with the subsequent risk of developing PCS, such that when patients show at least five predictor symptoms in the first week (assessed using the original addendum of the COVID Symptom Study for long-term questionnaires), the odds ratio for PCS is 3.53 (2.76–4.50). Studies of the value of this predictor, developed in a set of 2149 patients, entirely confirmed the effectiveness of its use during subsequent testing in a group of 2472 patients with positive SARS-CoV-2 tests [15].

As demonstrated by results from a multicenter, prospective, long-term study in the UK (PHOSP-COVID, $n = 1077$), the probabilities that the recovery process will be slowed to six months after discharge from hospital in patients with COVID-19 and of developing PCS are linked with a number of risk factors, including female sex, age, at least two comorbid diseases, and more severe course of acute-phase illness [17]. The authors noted that throughout the observation period most patients had symptoms of one kind or another evidencing the lack of complete recovery; 20% developed disability and 19% of the two thirds who worked before onset of COVID-19 had to change their work activities (including transfer to lighter work) after recovery. In addition, after the acute phase of COVID-19, the further course of illness and changes in individual clinical manifestations could differ, such that while changes in the physical and mental components of health were tightly connected, impairments to cognitive status were to a significant extent independent of other manifestations of PCS. The results suggested heterogeneity in the mechanisms of development of the different manifestations of PCS, which probably supports stratification of patients for therapeutic-prophylactic measures.

The fact that SARS-CoV-2 syndromes affecting organs and body systems of different severities have different degrees of linkage with the risk of subsequently developing PCS, and particularly the formation of neurological, mental, and cognitive impairments, is of undoubted interest. The extent of acute lung damage largely determines the level of respiratory support needed in the acute phase of illness; it is therefor unsurprising that measures of lung function and patients' physiological status at six months are associated with the severity of the acute illness [17]. However, this relationship is absent for markers of heart or kidney failure (both clinical and laboratory). This observation may be evidence that despite the existence of a link between the risk of developing PCS and admission to the intensive care unit, its formation also involves other mechanisms determining not only the risk of developing PCS, but also the nature of the subsequent course of illness [18].

There are also other examples of the noncorrespondence of the course of the acute period of illness and its long-term outcomes. Thus, despite the higher incidence and mortality, severe COVID-19 and a greater risk of cardiovascular and respiratory complications after discharge from hospital in ethnic minorities [19, 20], there are no reports of any increase in the risk of developing PCS in these patients. Establishment of these mechanisms will provide an explanation for the development of PCS in patients with mild COVID-19 who have received out-patient treatment.

Considering the heterogeneity of the clinical manifestations of PCS, different variants of recovery of COVID-19 patients should be noted. Thus, for example, external respiration, physical exercise tolerance (walking), and health-related measures of quality of life have been fund to be significantly worse in patients requiring mechanical ventilation. At the same time, the extent of manifestations such as breathlessness, fatigue, pain, anxiety, and depression, and their influences on health status were not associated with the severity of the acute-phase illness [15].

There are serious methodological problems with studies addressing the early and late sequelae of COVID-19, including PCS. It has repeatedly been noted that most studies on this problem have included patients treated in hospital, including intensive care units, i.e., these studies have used the most severe patients; the reference groups, including out-patients, often do not fully reflect the ratio of patients with different severities of illness [21]. In this situation it is quite hard to determine the influences on the development of PCS of COVID-19 itself and comorbid diseases and

pathological states (impairments to the functioning of various organs and body systems, multiorgan failure, alimentary derangements, etc.) and treatment provided to patients with the severe form of the disease and able to influence the rate and completeness of recovery processes. In this regard, it should be noted that PCS-typical impairments such as breathlessness and fatigue are also seen in patients with other, non-coronavirus, infectious diseases [22, 23] and in patients with various severe somatic diseases requiring prolonged treatment in the intensive care unit (post-ICU syndrome) [24].

No less difficult is the problem of discriminating asthenic impairments (not infrequently described by researchers as weakness, elevated fatigue, etc.) in the framework of post-viral fatigue syndromes (commentary G93.3, International Classification of Diseases, 10th edition) or similar states and manifestations of mental illnesses, including major depressive disorder [25]. Finally, a serious limitation of most studies, hindering interpretation of results and correct meta-analysis, is the wide use of screening tools (the MMSE and MoCA questionnaires) to assess the state of cognitive functions, which may have limited sensitivity to decreases in cognitive functions in young respondents [26]. It should be noted that a proposed solution for this latter task is use of more sensitive tools, particularly a screening questionnaire for cognitive impairments in psychiatry, and others [26, 27].

Mechanisms of Development of PCS. Many experimental and clinical studies have significantly expanded our concept of the mechanisms forming PCS. An important outcome was establishment of signs of changes in the state of the brain matter using state-of-the-art methods for static and functional neuroimaging. In this regard, results from investigations of two patients (aged 45 and 47 years, with no history of neurological/mental diseases) with COVID-19 in whom native brain MRI and contrast MRI showed no structural changes are of interest. ^{18}F-Phosphodeoxyglucose (^{18}FPDG) positron emission tomography of the brain in both cases revealed areas of hypometabolism in the cingulate gyrus [28]. Clinical observations and neuropsychological testing in both patients demonstrated increased fatigue, slowed thought processes, and decreased memory and memorization ability, along with elements of anxiety and depressive disorders and dyssomnia, which correspond to the clinical picture of so-called brain fog.

More severe and widespread signs of cortical hypometabolism were seen in the patient in whom the course of COVID-19 infection was more severe, such that he required respiratory support for several days (changes were recorded in the cingulate gyrus, precuneus, and several other cortical zones), as compared with the second patient, with less severe illness (out-patient treatment for two weeks). Considering the difference in the course of illness and the absence of changes on the native MRI, the changes detected cannot be linked with hypoxia, acute cerebrovascular events, or focal inflammatory brain lesions. The authors suggested that there was a relationship between the developing cognitive impairments and regional changes in metabolism with neuroinflammatory processes, though this suggestion has not been confirmed, as CSF laboratory tests were not performed.

It is interesting that previous studies showed that the anterior and posterior cingulate cortex take part in realizing the emotions, and the functioning of this structure is linked with the processes forming memory, regulating emotional state, and decision-taking [29]. Overall, data obtained from PET studies are consistent with results from neuropsychological testing and link the disorders of episodic memory found in patients and impairments to executive functions with dysfunction of the cortex of the cingulate gyrus. Similar functional neuroimaging results were obtained in patients with cognitive impairments in Alzheimer's disease and depressive disorders [30, 31].

Recent ^{18}FDG PET results in 35 patients with PCS were compared with data from studies of 44 patients of the same age and sex (control group) [32]. PCS patients showed bilateral decreases in metabolism in the orbital cortex (including the olfactory gyrus), the right temporal lobe (amygdaloid body and hippocampus, spreading to the thalamus), the pons, the medulla oblongata, and the cerebellum on both sides (voxel analysis demonstrated statistically significant differences on comparison with the control group regardless of corrections). Differences in energy metabolism in the two groups were sufficiently marked to allow patients and healthy subjects to be discriminated with accuracy of 100%. The patterns of hypometabolism corresponded to the numerous complaints and focal symptomatology (stem and cerebellar impairments, hyposmia/anosmia, impairment to memory and other cognitive functions, dysosmia). It is interesting to note that in the frontal lobes, particularly the olfactory gyrus, measures of energy metabolism were lower in seven patients receiving angiotensin converting enzyme inhibitors for arterial hypertension ($p = 0.032$) and higher in three patients using nasal anti-edema sprays ($p < 0.001$). The study authors took the view that the characteristics of the distribution of areas of hypometabolism in patients with PCS, particularly the olfactory gyrus and associated limbic/paralimbic areas, and spreading to the brainstem and cerebellum, may be linked with the clinical manifestations of PCS, and may also be able to support the involvement of the olfactory analyzer in the process of CNS infection by SARS-CoV-2. It should be noted that the authors did not report neuroimaging, serological, or CSF signs of brain or meningeal damage in the patients studied.

With the aim of explaining the development of acute and delayed impairments to the central nervous system in COVID-19, several attempts have been made to seek evidence for a direct action of SARS-CoV-2 on brain matter. The results of these studies, which included patients with different forms of the illness, both with and without CNS damage, showed the absence or minimal severity of cere-

brospinal fluid (CSF) changes typical of neurotropic viruses (pleocytosis, markers of blood–brain barrier damage) [33, 34]. Increases in CSF neurospecific protein levels seen by various investigators in COVID-19 patients may be evidence of damage to brain cells, but do not allow the nature of the pathological process to be assessed (hypoxic, ischemic, inflammatory, etc.) and do not confirm SARS-CoV-2-induced encephalitis. COVID-19 patients also showed, regardless of the presence of neurological and/or mental impairments, no pathological intrathecal synthesis of immunoglobulins [33]. Direct effects of SARS-CoV-2 (its RNA) in the CSF are seen very rarely, and results from most studies have not supported the suggestion that there is a high frequency of specific CNS lesions in either the acute stage of COVID-19 or in the development of PCS [35, 36]. The results of these studies made the suggestion that CNS damage in COVID-19 patients is a direct consequence of virus infection unlikely. It is also important that studies using neuromorphology diagnostic methods and CSF diagnostics included patients with the most severe forms of disease, in whom the course of COVID-19 was accompanied by severe respiratory failure and multiorgan failure, while it has been well established that PCS develops quite frequently in patients in whom the course of COVID-19 was not severe.

Immunological studies of the brain (including the brainstem and olfactory bulb) in patients dying from severe COVID-19 identified significant immune activation in the CNS with a diversity of morphological manifestations, including astrocytosis, axon damage, and impairments to the blood–brain barrier in patients in whom virus antigen was detected in cells positive for angiotensin-converting enzyme receptors [37]. The authors interpreted these results as supporting a severe neuroinflammatory reaction with activation of the mechanisms of innate and adaptive immunity due to the actions of SARS-CoV-2 virus. It should, however, be noted that the patients included in the study did not have severe COVID-19 with progressive multiorgan failure, severity inflammatory reactions, hypoxic brain damage, or cerebral edema, which to some extent hinders interpretation of the results.

Considering that the most severe course of COVID-19 is seen in patients with multiple comorbid pathologies and cardiovascular risk factors, it seems obvious that they will have different forms of cerebrovascular pathology, including chronic cerebral ischemia (CCI, dyscirculatory encephalopathy). The acute infectious disease in those with hypoxia and systemic inflammatory reactions due to endothelial dysfunction, activation of neuroinflammatory processes, and other factors may be accompanied by worsening of the course of vascular brain damage [38, 39]. These mechanisms are probably linked with a number of the clinical manifestations of PCS, including cognitive disorders and motor impairments.

It has been suggested that many of the clinical manifestations of PCS are mediated by dysfunction of the autonomic nervous system. This suggestion is of undoubted interest, as to a significant extent it allows many of the somatic manifestations (instability of systemic pressure, heart rhythm and conduction abnormalities, motor disorders in the gastrointestinal tract, etc.) seen in the absence of confirmed internal organ pathology to be explained [40]. Furthermore, considering the absence of morphological confirmation of direct SARS-CoV-2-induced structural impairments to the autonomic nervous system or damage mediated by other mechanisms, autonomic dysfunction can only be seen as one component of a complex mechanism forming PCS. It has been suggested that chronic activation of the autonomic nervous system and its associated endocrine and other functions (the neuroendocrine and neuroimmune systems) increase the risk of developing PCS [41]. The clinical manifestations may include myalgic encephalomyelitis, chronic fatigue syndrome, and postural orthostatic tachycardia syndrome [42, 43]. Studies of the role of the autonomic nervous system in the pathogenesis of PCS are entirely prospective, considering the possibility that emotional state can act on it and, conversely, the autonomic support of emotional, cognitive, and behavioral functions [44]. It is of note that cognitive impairments of the "brain fog" type can also occur in Lyme disease and influenza, and in infections due to Western Nile and ebola viruses [45, 46]. These data suggest that neuropsychological sequelae of several infectious diseases may have a similar pathogenesis. A chronic proinflammatory process in the CNS may thus be supported by stable activation of a population of circulating T and B lymphocytes cross-reactive with viral epitopes and ultimately targeting microglial cells in the brain [42]. Analysis of the clinical manifestations of PCS, particularly the nature of autonomic manifestations, and the results of a number of experimental studies led to the suggestion that the long-term pathological sequelae of SARS-CoV-2 infection with CNS involvement arise as a result of the immune response, leading to neuroinflammation with mitochondrial and microglial dysfunctions [38, 39]. Despite the fact that there are as yet no convincing data for the dysimmune nature of autonomic impairments in COVID-19 and other infectious diseases, this suggestion is extremely interesting in relation to future research.

Results from a number of experimental and clinical studies provide grounds for proposing that oxidative stress plays an important role both in the development of acute tissue damage in COVID-19 and in forming PCS. Activation of the innate immune system by SARS-CoV-2 due to increased formation of cytokines, chemokines, and other biologically active substances in conditions of severe inflammatory reactions accompanied by suppression of the intrinsic antioxidant systems of the body are accompanied by sharp increases in free radical formation, i.e., oxidant stress [47]. Data have been obtained indicating that the formation of excessive quantities of free radicals mediates a number of pathophysiological processes, including impairment to the blood–brain barrier, infiltration of the brain matter by

activated resident immunocompetent cells, and secondary brain damage.

Oxidant stress can induce dysfunction of neurons themselves, particularly as a result of impairment to energy metabolism and synaptic dysfunction. In addition, an exclusively important role is played by free radical oxidation in the development of endothelial dysfunction leading to progression of dyshemic disorders in COVID-19 patients. This is exclusively important, as, along with other pathological processes, difficulty in delivery of blood to particular parts of the brain and impaired gas exchange processes are significant pathogenic mechanisms in the development of acute brain damage and, probably, the formation of PCS [48]. There are reports that excessive formation of proinflammatory cytokines persists after acute COVID-19, resulting in long-lasting low-intensity inflammation, one important consequence of which is endothelial dysfunction [49]. This mechanism of impairment of local blood flow regulation may play a key role in the development of PCS, especially in patients with pre-existing brain damage due to cerebrovascular pathology, particularly in patients with CCI. Activation of the mechanisms of programmed cell death, especially apoptosis of neurons, astrocytes, and other nervous system cells, in response to excessive quantities of free radicals, may be the main mechanism of brain damage and persistent neurological (neuropsychological) dysfunction [50].

Thus, oxidant stress and its consequences can be regarded as an important pathogenic mechanism of acute and long-term nervous system damage and dysfunction in patients infected with SARS-CoV-2. Oxidant stress and developing lipid peroxidation (LPO) cannot be regarded as pathological mechanisms specific for COVID-19, though their exclusive role in realizing the diverse mechanisms of cell damage and death allow the use of antioxidants, along with drugs activating the intrinsic mechanisms eliminating excess radicals, to be considered as an important therapeutic direction in these patients.

Approaches to the Treatment of PCS Patients. Despite the difficulty of studying the pathogenesis and clinical manifestations of PCS, the need to develop treatment methods for these patients is beyond doubt. There are also arguments for a differential approach to treatment selection depending on patient's condition. Previous studies developed interventions in chronic fatigue syndrome or postviral fatigue syndrome, though it remains unknown whether these interventions were effective in patients after COVID-19 [51, 52]. It is of note that these apparently grounded guidelines for the treatment of patients with the sequelae of viral infections, such as dosed increases in the volume of physical exercise, were inappropriate for patients with PCS because of poor tolerance. Furthermore, despite the existence of many similarities in the clinical manifestations of PCS and chronic fatigue syndrome, one report published by the UK National Institute for Health and Care Excellence (NICE) emphasized that guidelines for the treatment of patients with chronic fatigue syndrome [53] should not be applied to the treatment of patients with postcovid fatigue [54, 55]. Selection of effective methods of dosed and nondrug treatment methods suitable for patients, particularly use of optimum levels of physical exercise, will undoubtedly be the subject of further research.

A means of treating patients with neurological and other manifestations of PCS includes a wide range of physiological methods, the volume and nature of which are determined by a multidisciplinary team of medics taking account of indications and contraindications [56]. Relaxation methods including meditation and respiratory exercises are advised in in patients with respiratory impairments. Patients with distress syndrome, post-traumatic stress disorder, and anxiety and depressive disorders require specialist consultations. It should be emphasized that there are still insufficient results from clinical trials which would allow the efficacy of these approaches to be determined, so guidelines remain based on results from analyses of case series and experts' opinions.

Given the established role of cerebrovascular pathology in forming PCS in at least a significant proportion of patients, it is advisable to use a number of approaches whose efficacy has been demonstrated in the treatment of patients with CCI [57, 58]. There is significant interest in the possibility of using the original Russian drug 2-ethyl-6-methyl-hydroxypyridine succinate (Mexidol), which has powerful antioxidant and antihypoxic effects: it suppresses LPO and significantly increases the activity of antioxidant enzymes (superoxide dismutase, glutathione peroxidase). It has direct antioxidant activity due to the fact that the molecule contains a mobile hydrogen atom, bound to an oxygen atom, which improves mitochondrial respiration and restores energy processes in the Krebs cycle, increasing the intensity of oxidative phosphorylation and ATP synthesis. Experimental studies have shown that the drug has membrane-stabilizing actions, apparent as the ability to stabilize membrane structures in erythrocytes and platelets, decreasing the probability of developing hemolysis and decreasing the severity of the signs of glutamate excitotoxicity [59, 60]. These properties of Mexidol are responsible for its clinical effects as a nootropic and antiamnestic, though it also has anxiolytic and antiasthenic actions, which are of exclusive importance for the treatment of patients with CCI and elderly patients with comorbidities. An important role in the decision to prescribe Mexidol is played by its good tolerance and the absence of excessive sedative and myorelaxant effects [61, 62].

One of the early studies of the efficacy of Mexidol addressed its effects on LPO, emotional state, and the severity of asthenia in patients with CCI (dyscirculatory encephalopathy) [63]. The authors established that short (15 days) courses of treatment in patients produced statistically significant reductions in the extent of low density lipoprotein oxidation in vivo. Subsequent treatment (to 60 days) led to significant decreases in the severity of asthenic and anxiety

disorders (assessed using the MFI-20 questionnaire and the Hamilton scales). Patients simultaneously showed significant improvements in the state of cognitive functions, as evidenced by the statistically significant improvements in performance on the Schulte and Wechsler tests.

A number of studies have been conducted in recent years addressing the efficacy and tolerance of treatment with sequential use of Mexidol (i.v., 500 mg, once daily, 14 days) and Mexidol Forte 250 (p.o., 250 mg t.i.d., 60 days) in patients with CCI [64]. The authors found that by the end of the study, patients showed significant increases in performance on the MoCA (24.0 ± 2.4 and 27.2 ± 2.0 points, $p < 0.05$), the extent of the positive effect increasing during treatment. There was a simultaneous reduction in the extent of asthenia (on the asthenia assessment scale MFI-20 before and after: 65.4 ± 3.5 and 32.0 ± 4.1 points respectively, $p < 0.05$). The treatment was accompanied by statistically significant reductions in anxiety and depressive disorders (assessed on the Hamilton NX AND Depression Scale, differences were also statistically significant). Apart from high efficacy, the authors noted high treatment compliance among the patients included in the study and a low frequency of adverse events.

Data from preliminary studies were supported by results obtained from an international, multicenter, randomized, double-blind, placebo-controlled study assessing the efficacy and safety of sequential therapy in patients with CCI using Mexidol and Mexidol Forte 250 (MEMO) [65]. Follow-up results were obtained from a representative cohort of 318 patients with CCI who were randomized into two groups (the study group received i.v. Mexidol (500 mg) once daily by i.v. infusion for 14 days followed by Mexidol Forte 250 p.o. 250 mg t.i.d. for 60 days; the reference group received placebo by the same regimen). At the end of the study, between-group differences on the MoCA were statistically significant ($p < 0.000001$), evidencing significantly greater recovery of cognitive functions in patients of the study group. The study authors also noted recovery from the manifestations of asthenic syndrome and anxiety and depressive disorders. As in most previous studies, good tolerance was noted with Mexidol and Mexidol Forte, with no significant adverse events during treatment.

Because of its multimodal mechanism of action, treatment with Mexidol can act on the main components of the pathogenesis of COVID-19, with positive effects on the clinical manifestations and severity of laboratory inflammation syndrome in patients in the acute period of moderate and severe SARS-CoV-2, including on the background of CCI [66]. As a result of a study in the "red zone" of the Medical Rehabilitation Center, Semashko St. Petersburg City Hospital No. 38, patients were treated with i.v. Mexidol by infusion (500 mg (10 ml) for 14 days) followed by p.o. Mexidol Forte 250 (1 tablets (250 mg) t.i.d.) for two months. Use of Mexidol was started on days 3–14 (mean 5.4 ± 2.3) from onset of the first signs of COVID-19. Subsequent treatment with Mexidol and Mexidol Forte 250 for 75 days in patients with CCI and COVID-19 was accompanied by improvement in the state of cognitive functions (assessed on the MoCA), normalization of sleep (Spiegel scale), decreases in the severity of asthenic syndrome (MFI-20 scale), and improvements in measures characterizing quality of life (emotionality, social interaction, initiative, behavioral energy, communication); differences were significant compared with baseline and a reference group [67].

On the basis of clinical data, ethylmethylhydroxypyridine succinate (Mexidol) has been included in the methodological guidelines of the Russian Scientific Medical Society of Therapists (RSMST), "Features of the course of long covid infection. Therapeutic and rehabilitation measures" [68], which emphasizes that because of its antioxidant, antihypoxant, and membrane-protective effects, use of Mexidol is appropriate for patients with neurological symptoms of long covid.

Conclusions. PCS is a common condition developing in patients after COVID-19. Despite multidisciplinary studies of the mechanisms of development of PCS, very many questions need refinement, though the roles of neuroinflammation, intoxication, and activation of free radical oxidation in its formation can be regarded as established. The lack of a complete understanding of the mechanisms of development of PCS is one of the reasons for the paucity of rational approaches to the treatment of patients with PCS, which is to a significant extent empirical, based on clinical experience in curing the main neurological (neuropsychological) syndromes seen in patients with PCS (asthenic, anxiety disorders, cognitive dysfunction syndrome). Thus, there is significant interest in the possibility of using the multimodal drug Mexidol and Mexidol Forte in the treatment of patients with PCS.

The authors declare no conflict of interest.

REFERENCES

1. NICE guideline [NG188], *COVID-19 Rapid Guideline: Managing the Long-Term Effects of COVID-19*, publ. Dec. 18 2020, https://www.nice.org.uk/guidance/ng188.
2. "Fauci Introduces New Acronym for Long COVID at White House Briefing," *Medscape*, Feb. 24, 2021, https://www.medscape.com/viewarticle/946419.
3. "A clinical case definition of post-COVID-19 condition by a Delphi Consensus, 6 October 2021," WHO Ref. No. WHO/2019-nCoV/Post_COVID-19_condition/Clinical_case_definition/2021.1.
4. T. Rudroff, A. C. Fietsam, J. R. Deters, et al., "Post-COVID-19 fatigue: Potential contributing factors," *Brain Sci.*, **10**, No. 12, 1012–1020 (2020), https://doi.org/10.3390/brainsci10121012.
5. J. A. Frontera, A. Lewis, K. Melmed, et al., "Prevalence and predictors of prolonged cognitive and psychological symptoms following COVID-19 in the United States," *Front. Aging Neurosci.*, **13**, 690383 (2021), https://doi.org/10.3389/fnagi.2021.690383.
6. F. Ceban, S. Ling, L. M. W. Lui, et al., "Fatigue and cognitive impairment in Post-COVID-19 syndrome: A systematic review and meta-analysis," *Brain Behav. Immun.*, **101**, 93–135 (2021), https://doi.org/10.1016/j.bbi.2021.12.020.

7. C. Hopkins, P. Surda, E. Whitehead, and B. N. Kumar, "Early recovery following new onset anosmia during the COVID-19 pandemic - an observational cohort study," *J. Otolaryngol. Head Neck Surg.*, **49**, No. 1, 26 (2020), https://doi.org/10.1186/s40463-020-00423-8.
8. L. A. Jason, M. Islam, K. Conroy, et al., "COVID-19 symptoms over time: Comparing long-haulers to ME/CFS," *Fatigue*, **9**, No. 2, 59–68 (2021), https://doi.org/10.1080/21641846.2021.1922140.
9. M. Taboada, A. Cariñena, E. Moreno, et al., "Post-COVID-19 functional status six-months after hospitalization," *J. Infect.*, **82**, No. 4, 31–33 (2021), https://doi.org/10.1016/j.jinf.2020.12.022.
10. M. H. B. Lam, Y. K. Wing, M. W. M. Yu, et al., "Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up," *Arch. Intern. Med.*, **169**, No. 22, 2142–2147 (2009), https://doi.org/10.1001/archinternmed.2009.384.
11. J. P. Rogers, E. Chesney, D. Oliver, 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*, **7**, No. 7, 611–627 (2020), https://doi.org/10.1016/S2215-0366(20)30203-0.
12. L. A. Hoffman and J. A. Vilensky, "Encephalitis lethargica: 100 years after the epidemic," *Brain*, **140**, No. 8, 2246–2251 (2017), https://doi.org/10.1093/brain/awx177.
13. F. Zhou, T. Yu, R. Du, et al., "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study," *Lancet*, **395**, No. 10229, 1054–1062 (2020).
14. Writing Committee for the COMEBAC Study Group, L. Morin, L. Savale, T. Pham, et al., "Four-month clinical status of a cohort of patients after hospitalization for COVID-19," *JAMA*, **325**, No. 15, 1525–1534 (2021), https://doi.org/10.1001/jama.2021.3331.
15. C. H. Sudre, B. Murray, T. Varsavsky, et al., "Attributes and predictors of long COVID," *Nat. Med.*, **27**, No. 4, 626–631 (2021), https://doi.org/10.1038/s41591-021-01292-y.
16. K. W. Wyrwich, H. Yu, R. Sato, and J. H. Powers, "Observational longitudinal study of symptom burden and time for recovery from community-acquired pneumonia reported by older adults surveyed nationwide using the CAP Burden of Illness Questionnaire," *Patient Relat. Outcome Meas.*, **6**, 215–23 (2015), https://doi.org/10.2147/PROM.S85779.
17. R. A. Evans, H. McAuley, E. M. Harrison, et al., "PHOSP-COVID Collaborative Group, "Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID, a UK multicentre, prospective cohort study," *Lancet Respir. Med.*, **9**, No. 11, 1275–1287 (2021), https://doi.org/10.1016/S2213-2600(21)00383-0.
18. Office for National Statistics, Updated Estimates of the Prevalence of Long COVID Symptoms, Jan. 2021, https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/adhocs/12788updatedestimatesoftheprevalenceoflongcovidsymptoms.
19. E. J. Williamson, A. J. Walker, K. Bhaskaran, et al., "Factors associated with COVID-19-related death using OpenSAFELY," *Nature*, **584**, No. 7821, 430–436 (2020), https://doi.org/10.1038/s41586-020-2521-4.
20. K. Ravi, "Ethnic disparities in COVID-19 mortality: are comorbidities to blame?" *Lancet*, **396**, No. 10243, 22–24 (2020), https://doi.org/10.1016/S0140-6736(20)31423-9.
21. R. A. Heckenberg, P. Eddy, S. Kent, and B. J. Wright, "Do workplace-based mindfulness meditation programs improve physiological indices of stress? A systematic review and meta-analysis," *J. Psychosom. Res.*, **114**, 62–71 (2018), https://doi.org/10.1016/j.jpsychores.2018.09.010.
22. H. Moldofsky and J. Patcai, "Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study," *BMC Neurol.*, **11**, 37–41 (2011), https://doi.org/10.1186/1471-2377-11-37.
23. J. G. Voss, "Predictors and correlates of fatigue in HIV/AIDS," *J. Pain Symptom Manage.*, **29**, 173–184 (2005), https://doi.org/10.1016/j.jpainsymman.2004.05.006.
24. H. Svenningsen, L. Langhorn, A. S. Ågård, et al., "Post-ICU symptoms, consequences, and follow-up: an integrative review," *Nurs. Crit. Care*, **22**, 212–220 (2017), https://doi.org/10.1111/nicc.12165.
25. M. Taquet, J. R. Geddes, M. Husain, et al., "6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records," *Lancet Psychiatry*, **8**, No. 5, 416–427 (2021), https://doi.org/10.1016/S2215-0366(21)00084-5.
26. R. S. McIntyre, N. Anderson, B. T. Baune, et al., "Expert consensus on screening and assessment of cognition in psychiatry," *CNS Spectr.*, **24**, No. 1, 154–162 (2019), https://doi.org/10.1017/S1092852918001189.
27. K. W. Miskowiak, S. Johnsen, S. M. Sattler, et al., "Cognitive impairments four months after COVID-19 hospital discharge: Pattern, severity and association with illness variables," *Eur. Neuropsychopharmacol.*, **46**, 39–48 (2021), https://doi.org/10.1016/j.euroneuro.2021.03.019.
28. J. Hugon, E. F. Msika, M. Queneau, et al., "Long COVID: cognitive complaints (brain fog) and dysfunction of the cingulate cortex," *J. Neurol.*, **269**, 44–46 (2022), https://doi.org/10.1007/s00415-021-10655-x.
29. S. D. Lichenstein, T. Verstynen, and E. E. Forbes, "Adolescent brain development and depression: a case for the importance of connectivity of the anterior cingulate cortex," *Neurosci. Biobehav. Rev.*, **70**, 271–287 (2016).
30. L. Su, Y. Cai, Y. Xu, et al., "Cerebral metabolism in major depressive disorder: a voxel-based metaanalysis of positron emission tomography studies," *BMC Psychiatry*, **14**, 321–330 (2014).
31. A. M. N. Coutinho, F. H. G. Porto, P. F. Zampieri, et al., "Analysis of the posterior cingulate cortex with [18F] FDG-PET and Naa/mI in mild cognitive impairment and Alzheimer's disease: correlations and differences between the two methods," *Dement. Neuropsychol.*, **9**, 385–393 (2015).
32. E. Guedj, J. Y. Campion, P. Dudouet, et al., "18F-FDG brain PET hypometabolism in patients with long COVID," *Eur. J. Nucl. Med. Mol. Imaging*, **48**, No. 9, 2823–2833 (2021), https://doi.org/10.1007/s00259-021-05215-4.
33. N. Kanberg, J. Simrén, A. Edén, et al., "Neurochemical signs of astrocytic and neuronal injury in acute COVID-19 normalizes during long-term follow-up," *EBioMedicine*, **70**, 103512 (2021), https://doi.org/10.1016/j.ebiom.2021.103512.
34. A. Edén, J. Simrén, R. W. Price, et al., "Neurochemical biomarkers to study CNS effects of COVID-19: A narrative review and synthesis," *J. Neurochem.*, **159**, No. 1, 61–77 (2021), https://doi.org/10.1111/jnc.15459.
35. Meppie, E, N. Peiffer-Smadja, A. Maury, et al., "Neurological manifestations associated with COVID-19: A multicentric registry," *Clin. Microbiol. Infect.*, **27**, 458–466 (2021).
36. J. Virhammar, A. Nääs, D. Fällmar, et al., "Biomarkers for central nervous system injury in cerebrospinal fluid are elevated in COVID-19 and associated with neurological symptoms and disease severity," *Eur. J. Neurol.*, **28**, No. 10, 3324–3331 (2021), https://doi.org/10.1111/ene.14703.
37. M. Schwabenland, H. Salie, J. Tanevski, et al., "Deep spatial profiling of human COVID-19 brains reveals neuroinflammation with distinct microanatomical microglia-T-cell interactions," *Immunity*, **54**, 1594–1610 (2021), https://doi.org/10.1016/j.immuni.2021.06.002.
38. V. V. Zakharov, "Postcovid syndrome through the eyes of a neurologist," *Poveden. Nevrol.*, **2**, 14–22 (2021), https://doi.org/10.46393/2712-9675_2021_2_14_22.
39. P. R. Kamchatnov, E. Yu. Solov'eva, D. R. Khasanova, and V. V. Fateeva, "Asthenic and cognitive disorders after COVID-19 infection,"

Ros. Med. Zh. Med. Obozr., **5**, No. 10, 636–641 (2021), https://doi.org/10.32364/2587-6821-2021-5-10-636-641.
40. M. Dani, A. Dirksen, P. Taraborrelli, et al., "Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies," *Clin. Med. (Lond.)*, **21**, No. 1, 63–67 (2021), https://doi.org/10.7861/clinmed.2020-0896.
41. D. S. Goldstein, "The extended autonomic system, dyshomeostasis, and COVID-19," *Clin. Auton. Res.*, **30**, No. 4, 299–315 (2020), https://doi.org/10.1007/s10286-020-00714-0.
42. G. B. Stefano, R. Ptacek, H. Ptackova, et al., "Selective neuronal mitochondrial targeting in SARS-CoV-2 infection affects cognitive processes to induce 'brain fog' and results in behavioral changes that favor viral survival," *Med. Sci. Monit.*, **27**, e930886 (2021), https://doi.org/10.12659/MSM.930886.
43. D. S. Goldstein, "The possible association between COVID-19 and postural tachycardia syndrome," *Heart Rhythm*, **18**, No. 4, 508–509 (2021), https://doi.org/10.1016/j.hrthm.2020.12.007.
44. L. Quadt, H. Critchley, and Y. Nagai, "Cognition, emotion, and the central autonomic network," *Auton. Neurosci.*, **238**, 102948 (2022), https://doi.org/10.1016/j.autneu.2022.102948.
45. C. B. Novak, V. M. Scheeler, and J. N. Aucott, "Lyme Disease in the Era of COVID-19: A delayed diagnosis and risk for complications," *Case Rep. Infect. Dis.*, **2021**, 6699536 (2021), https://doi.org/10.1155/2021/6699536.
46. D. S. Chertow, "Understanding long-term effects of Ebola virus disease," *Nat. Med.*, **25**, No. 5, 714–715 (2019), https://doi.org/10.1038/s41591-019-0444-0.
47. M. M. Almutairi, F. Sivandzade, T. H. Albekairi, et al., "Neuroinflammation and its impact on the pathogenesis of COVID-19," *Front. Med (Lausanne)*, **8**, 745789 (2021), https://doi.org/10.3389/fmed.2021.745789.
48. S. Najjar, A. Najjar, D. J. Chong, et al., "Central nervous system complications associated with SARS-CoV-2 infection: integrative concepts of pathophysiology and case reports," *J. Neuroinflammation*, **17**, No. 1, 231 (2020), https://doi.org/10.1186/s12974-020-01896-0.
49. B. Jarrott, R. Head, K. G. Pringle, et al., "'LONG COVID' – A hypothesis for understanding the biological basis and pharmacological treatment strategy," *Pharmacol. Res. Perspect.*, **10**, No. 1, e00911 (2022), https://doi.org/10.1002/prp2.911.
50. V. Murta, A. Villarreal, and A. J. Ramos, "Severe acute respiratory syndrome coronavirus 2 impact on the central nervous system: Are astrocytes and microglia main players or merely bystanders?" *ASN Neuro.*, **12**, 1759091420954960 (2020), https://doi.org/10.1177/1759091420954960.
51. G. B. Stefano, P. Büttiker, S. Weissenberger, et al., "Editorial: The pathogenesis of long-term neuropsychiatric COVID-19 and the role of microglia, mitochondria, and persistent neuroinflammation: A hypothesis," *Med. Sci. Monit.*, **27**, e933015 (2021), https://doi.org/10.12659/MSM.933015.
52. K. A. Rimes and T. Chalder, "Treatments for chronic fatigue syndrome," *Occup. Med. (Lond.)*, **55**, 32–39 (2005), https://doi.org/10.1093/occmed/kqi015.
53. "NICE cautions against using graded exercise therapy for patients recovering from COVID-19," *BMJ*, **370**, m2912 (2020), https://doi.org/10.1136/bmj.m2912.
54. National Institute for Health and Care Excellence, *Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (or Encephalopathy, Diagnosis and Management. Clinical Guideline [CG53]*, Aug. 22, 2007, https://www.nice.org.uk/Guidance/CG53.
55. *National Institute for Health and Care Excellence. Statement about Graded Exercise Therapy in the Context of COVID-19*, July, 2020, https://www.nice.org.uk/guidance/gid-ng10091/documents/interim-findings-2.
56. M. Nurek, C. Rayner, A. Freyer, et al., "Recommendations for the recognition, diagnosis, and management of long COVID: a Delphi study," *Br. J. Gen. Pract.* (2021), https://doi.org/10.3399/BJGP.2021.0265.
57. A. N. Belova, E. I. Bogdanov, I. A. Voznyuk, et al., "Therapy of moderate cognitive impairment in the early recovery period of ischemic stroke," *Zh. Nevrol. Psikhiatr.*, **121**, No. 5, 1–7 (2021), https://doi.org/10.17116/jnevro202112105133.
58. V. A. Parfenov, P. R. Kamchatnov, D. R. Khasanova, et al., "The randomized clinical trial results of the anxiety treatment in patients with somatoform dysfunction and neurotic disorders," *Sci. Rep.*, **1**, 24282 (2021), https://doi.org/10.1038/s41598-021-03727-5.
59. T. A. Voronina, " Antioxidants/antihypoxants: the missing puzzle piece in effective pathogenetic therapy for COVID-19," *Infekts. Bol.*, **18**, No. 2, 97–102 (2020), https://doi.org/10.20953/1729-9225-2020-2-97-102.
60. 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.
61. M. V. Zhuravleva, A. B. Prokof'ev, S. Yu. Serebrova, et al., "Efficacy and safety of ethylmethylhydroxypyridine succinate in patients with chronic cerebral ischemia," *Zh. Nevrol. Psikhiatr.*, **120**, No. 6, 119–124 (2020), https://doi.org/10.17116/jnevro2020120061119.
62. E. I. Chukanova and A. S. Chukanova, "Efficacy and safety of the drug Mexidol FORTE 250 in the framework of sequential therapy in patients with chronic cerebral ischemia," *Zh. Nevrol. Psikhiatr.*, **119**, No. 9, 39–45 (2019), https://doi.org/10.17116/jnevro201911909139.
63. S. N. Duma, "Possibilities of antioxidant therapy for asthenia and cognitive deficit in elderly patients with chronic cerebral ischemia," *Ter. Arkh.*, **85**, No. 12, 100–105 (2013).
64. L. A. Shchepankevich, Yu. A. Nikolaev, E. V. Taneeva, et al., "Efficacy and safety of Mexidol and Mexidol FORTE 250 in patients with chronic cerebral ischemia," *Zh. Nevrol. Psikhiatr.*, **121**, No. 10, 32–37 (2021), https://doi.org/10.17116/jnevro202112110132.
65. A. I. Fedin, V. V. Zakharov, M. M. Tanashyan, et al., "Results of an international multicenter, randomized, double-blind, placebo-controlled study assessing the efficacy and safety of sequential therapy with Mexidol and Mexidol FORTE 250 in patients with chronic cerebral ischemia," *Zh. Nevrol. Psikhiatr.*, **121**, No. 11, 7–16 (2021), https://doi.org/10.17116/jnevro20211211117.
66. E. K. Shavarova, E. R. Kazakhmedov, M. V. Alekseeva, et al., The role of antioxidant therapy in patients with moderate and severe COVID-19," *Infekts. Bol.*, **19**, No. 1, 159–164 (2021), https://doi.org/10.20953/1729-9225-2021-1-159-164.
67. V. V. Koval'chuk, I. I. Ershova, and N. V. Molodovskaya, "Possibilities of increasing the effectiveness of therapy in patients with chronic cerebral ischemia against the background of COVID-19," *Zh. Nevrol. Psikhiatr.*, **121**, No. 3, Iss. 2, 60–66 (2021), https://doi.org/10.17116/jnevro202112103260.
68. *Methodological Recommendations "Features of the Course of Long-COVID Infection. Therapeutic and Rehabilitation Measures*," *Terapiya*, Suppl. 1 (2022).