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ABSTRACT

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NEUROCOGNITIVE AND NEUROLOGICAL DISORDERS ASSOCIATED WITH COVID-19: A REVIEW OF PATHOPHYSIOLOGY, DIAGNOSIS, AND TREATMENT

Relevance. Post-COVID syndrome (PCS), especially its neurological and neurocognitive manifestations, has become one of the main challenges for global health after the COVID-19 pandemic. Affecting 10% to 30% of people who have had even mild forms of the disease, post-COVID syndrome places a significant burden on the healthcare system and causes socio-economic losses due to the prolonged incapacity of millions of people.

Objective. To systematize and summarize current data on clinical manifestations, pathophysiological mechanisms, and means of diagnosis and treatment of neurological and neurocognitive disorders in post-COVID syndrome.

Materials and methods. A review of the literature was conducted. Publications were searched for in English in the PubMed, Cochrane Library, and Scopus databases for the period 2020–2025. Key terms were used: post-COVID syndrome, neurocognitive disorders, brain fog, pathophysiology of brain fog in COVID-19. The analysis included randomized controlled trials, systematic reviews, meta-analyses, and large cohort studies. Studies with a high risk of bias were excluded from further consideration.

Results. Post-COVID syndrome is considered a complex multisystem condition characterized by brain fog, persistent headache, post-COVID neuropathies, psychiatric disorders, and dysautonomia (e.g., POTS). The leading clinical manifestation remains “brain fog” - a complex of cognitive impairments such as decreased attention, memory, and executive functions. The pathophysiology is multifactorial and includes: direct neurotropic effects of SARS-CoV-2 (via the olfactory bulb or hematogenous route), chronic systemic inflammation, neuroinflammation with microglial activation, endothelial dysfunction, microthrombosis, and autoimmune reactions. Diagnosis is based on

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clinical history, neuropsychological testing (MoCA, MMSE scales), and instrumental studies (MRI, fMRI, PET), which can reveal structural, functional, and metabolic changes. There is no standardized treatment. The therapeutic approach should be individualized and multidisciplinary, with an emphasis on non-pharmacological measures (cognitive rehabilitation, gradual physical activity) and symptomatic pharmacotherapy.

Conclusions. Post-COVID syndrome is a global medical and socioeconomic problem diagnosed in 10% to 30% of patients after COVID-19, even in mild cases. Neurological consequences include brain fog, persistent headaches, post-COVID neuropathies, psychiatric disorders, and dysautonomia (e.g., postural orthostatic tachycardia syndrome, POTS). Cognitive impairment in PCS is multifactorial in nature, caused by the synergy of the direct neurotropic effect of SARS-CoV-2, chronic neuroinflammation with cytokine activation of microglia and endothelial dysfunction with microthrombosis, as well as mechanisms of tau protein dysregulation common to Alzheimer's disease. Diagnosis of PCS is complicated by the lack of a universal biomarker and the variety of symptoms. Treatment is currently not standardized and is based on an individual approach. It includes cognitive rehabilitation, physical activity with consideration of the risk of post-exertional malaise, psycho-emotional support, and symptomatic pharmacotherapy.

Keywords: post-COVID syndrome, cognitive impairment, brain fog, pathophysiology, SARS-CoV-2, neuroinflammation.

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НЕЙРОКОГНІТИВНІ ТА НЕВРОЛОГІЧНІ ПОРУШЕННЯ АСОЦІЙОВАНІ ІЗ COVID-19: ОГЛЯДОВИЙ АНАЛІЗ ПАТОФІЗІОЛОГІЇ, ДІАГНОСТИКИ ТА ЛІКУВАННЯ

Актуальність. Постковідний синдром (ПКС), особливо його неврологічні та нейрокогнітивні прояви, став одним із головних викликів для глобальної охорони здоров'я після пандемії COVID-19. Уражаючи від 10 % до 30 % осіб, які перенесли навіть легкі форми захворювання, постковідний синдром значно навантажує систему охорони здоров'я та завдає соціально-економічних втрат через тривалу непрацездатність мільйонів людей.

Мета. Систематизувати та узагальнити сучасні дані про клінічні прояви, патофізіологічні механізми, засоби діагностики та лікування неврологічних і нейрокогнітивних порушень при постковідному синдромі.

Матеріали й методи. Проведено оглядовий аналіз літератури. Пошук публікацій здійснювався англійською мовою в базах даних PubMed, Cochrane Library та Scopus за період 2020–2025 року. Застосовано ключові терміни: постковідний синдром, нейрокогнітивні розлади, мозковий туман, патофізіологія мозкового туману при COVID-19. До аналізу включено рандомізовані контрольовані дослідження, систематичні огляди, мета-аналізи та великі когортні спостереження. Роботи з високим ризиком упередженості були виключені з подальшого розгляду.

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Результати. Постковідний синдром розглядається як складний мультисистемний стан, для якого характерними є «мозковий туман», стійкий головний біль, постковідні нейропатії, психіатричні розлади та дизавтономія (наприклад, POTS). Провідним клінічним проявом залишається «мозковий туман» - комплекс когнітивних порушень, таких як зниження уваги, пам'яті та виконавчих функцій. Патофізіологія є багатофакторною та включає: прямий нейротропний вплив SARS-CoV-2 (через нюхову цибулину або гематогенний шлях), хронічне системне запалення, нейрозапалення з активацією мікроглії, ендотеліальну дисфункцію, мікротромбози та автоімунні реакції. Діагностика базується на клінічному анамнезі, нейропсихологічному тестуванні (шкали MoCA, MMSE) та інструментальних дослідженнях (МРТ, фМРТ, ПЕТ), які можуть виявити структурні, функціональні й метаболічні зміни. Стандартизованого лікування не існує. Терапевтичний підхід має бути індивідуальним та міждисциплінарним, з акцентом на немедикаментозні заходи (когнітивна реабілітація, поступове фізичне навантаження) та симптоматичну фармакотерапію.

Висновки. Постковідний синдром є глобальною медичною та соціально-економічною проблемою, що діагностується у 10–30 % пацієнтів після перенесеного COVID-19, навіть при легкому ступені перебігу. Неврологічні наслідки включають «мозковий туман», стійкий головний біль, постковідні нейропатії, психіатричні розлади та дизавтономію (наприклад, постуральна ортостатична тахікардія, POTS). Когнітивний дефіцит при ПКС має багатофакторну природу, зумовлену синергією прямого нейротропного впливу SARS-CoV-2, хронічного нейрозапалення з цитокіновою активацією мікроглії та ендотеліальної дисфункції з мікротромбозами, а також спільні з хворобою Альцгеймера механізми дисрегуляції тау-білка. Діагностика ПКС ускладнена через відсутність універсального біомаркера та різноманітність симптомів. Лікування наразі не стандартизоване, базується на індивідуальному підході. Включає когнітивну реабілітацію, фізичну активність з урахуванням ризику постнавантажувального виснаження, психоемоційну підтримку та симптоматичну фармакотерапію.

Ключові слова: постковідний синдром, когнітивні порушення, мозковий туман, патофізіологія, SARS-CoV-2, нейрозапалення.

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INTRODUCTION

The global COVID-19 pandemic has left a deep mark, affecting not only mortality rates but also creating a long-term medical problem in the form of post-COVID syndrome (PCS). This condition is currently one of the most acute threats to global health. According to large-scale studies, 10% to 30% of people who have had even a mild case of COVID-19 experience prolonged symptoms lasting more than three months after the acute stage of the disease [1]. Thus, millions of people around the world are experiencing the effects of the infection, which places a significant burden on health care systems and socio-economic structures.

Post-COVID syndrome, as defined by the World Health Organization, occurs in patients with possible or confirmed SARS-CoV-2 infection and is usually diagnosed three months after the end of the disease [2]. Symptoms persist for at least two months. This condition is characterized by a wide range of clinical manifestations. Medical professionals and scientists are particularly interested in neurological and neurocognitive disorders, which are among the leading symptoms of post-COVID syndrome. They have a

significant impact on patients' functionality and significantly impair their quality of life [3].

Neurological disorders in post-COVID syndrome cover a wide range of pathological conditions of the central and peripheral nervous system, while neurocognitive disorders are characterized by a deficit in higher mental functions such as memory, attention, information processing speed, and executive abilities. The main manifestation of these changes is the so-called "brain fog," characterized by difficulty concentrating, impaired working memory, and reduced multitasking ability. Combined with chronic fatigue, persistent headaches, autonomic dysregulation, and peripheral neuropathies, these symptoms constitute the main clinical picture in a significant number of patients [4].

The relevance of this topic is growing due to the rapid increase in the number of people who need neurological care due to the consequences of COVID-19. According to research, neurocognitive disorders can last for months after the illness, significantly affecting patients' professional lives and ability to integrate socially [5]. This creates long-term challenges for public health and the working capacity of the population, turning the problem into not only a medical but also a socio-economic threat.

Modern science is actively researching the pathophysiological mechanisms underlying these phenomena. Among the main hypotheses are the direct neurotropic effect of the virus through the nasal mucosa, chronic systemic inflammation with microglial activation, known as "neuroinflammation," endothelial dysfunction and microthrombus formation that disrupt cerebral microcirculation, as well as autoimmune reactions directed against nervous system tissues [6]. Important areas of research include the prolonged persistence of viral particles and blood clotting disorders, which may explain the persistent nature of neurological symptoms [7].

Despite significant progress in studying the pathogenesis of post-COVID neurological complications, a number of aspects remain understudied. This creates considerable difficulties for the development of uniform diagnostic standards and effective treatment methods, requiring an integrative approach to the analysis of available scientific information. The lack of unified diagnostic criteria and standardized treatment protocols significantly complicates the provision of care to patients with post-COVID neurological disorders.

The aim is to systematize and summarize current data on clinical manifestations, pathophysiological mechanisms, and methods of diagnosis and treatment of neurological and neurocognitive disorders in post-COVID syndrome.

MATERIALS AND METHODS

During our search for scientific papers, we consulted the PubMed, Cochrane Library, and Scopus databases. The following keywords were used for the search query: "post-COVID condition," "post-COVID syndrome," "neurocognitive disorders," "brain fog," "post-COVID memory impairment," and "pathophysiology of brain fog in COVID-19." The sample included publications from 2020 to 2025. The main types of studies selected were randomized controlled trials, systematic reviews, meta-analyses, and large cohort studies. Scientific articles were analyzed exclusively in English. Works with a high risk of bias were excluded from further consideration.

RESULTS

Post-COVID syndrome is a complex multisystem condition that develops in patients after illness caused by SARS-CoV-2. It includes a wide range of neurological, cognitive, and psychiatric symptoms. Current research confirms that even patients with mild COVID-19 may experience prolonged and significant nervous system disorders that negatively affect quality of life and social and professional functioning [8–10].

Neurocognitive dysfunction, widely known in scientific and medical literature as "brain fog," is one of the most common characteristics of PKS. According to studies, this condition is found in 10-40% of patients who have had COVID-19 [11, 12]. It is accompanied by a complex of cognitive disorders, including impaired ability to focus and concentrate, problems with working and long-term memory, slowed psychomotor reactions, and impaired executive function [8–10].

Headache is one of the leading neurological symptoms that occur with PCS. According to various studies, the prevalence of this symptom among such patients is 25-50%, with persistent headaches sometimes appearing for the first time even 2 years after acute COVID-19 [13, 14]. It can manifest as paroxysmal or tension pain, characterized by both periodic and constant episodes. This condition is often accompanied by complications such as photosensitivity and hyperacusis, as well as poor sleep quality, which further complicates the patient's overall well-being [15, 16]. An important aspect is that post-COVID headaches are often resistant to standard analgesic therapy, requiring a comprehensive approach to treatment. Mechanistically, headaches may be associated with neurovascular disorders, activation of the trigeminal system, as well as an inflammatory response and changes in serotonergic pathways [15, 16]. A number of studies have noted that prolonged headaches are associated with cognitive impairment, dysautonomia, and chronic fatigue, forming a complex of symptoms that requires interdisciplinary treatment [16, 17, 26].

Dysautonomia is a relatively common manifestation of PCS, occurring in 2.5% of patients [18]. It may include postural orthostatic tachycardia syndrome (POTS), intolerance to standing, and impaired blood pressure regulation [19]. Patients often complain of palpitations, dizziness, weakness, and rapid fatigue when standing or exercising. The pathophysiology of dysautonomia is based on an imbalance of the sympathetic and parasympathetic nervous systems, impaired cardiovascular regulation, and chronic inflammation [18]. Such disorders not only reduce physical endurance but also exacerbate cognitive and psychoemotional symptoms, forming an interrelated multisystem syndrome [19].

Post-COVID neuropathies, diagnosed in 12–56% of patients [20, 21], are characterized by the appearance of various symptoms, among which the most common are smell disorders, such as anosmia, hyposmia, and parosmia, taste sensitivity disorders, pain syndromes, as well as numbness and paresthesia of the extremities [9, 22]. These manifestations can usually persist for a long time, sometimes even several months after the end of the acute period of the disease. The development of these pathological conditions is complex and multifactorial. They can be caused by direct damage to neurons by the virus, activation of inflammatory processes, impaired blood microcirculation, and damage to sensory nerve fibers. For example, disturbances in smell and taste can be explained by changes in the olfactory and gustatory nerve pathways, while peripheral paresthesias are usually associated with neuropathic damage to the spinal nerves or peripheral sensory fibers [9, 23].

Psychiatric symptoms associated with PCS are one of the most significant components of this complex condition. According to various studies, up to 47% of such patients have symptoms of mental disorders, with 2.1-8.5% of cases developing for the first time within 2 years after acute COVID-19 [24, 25]. These include anxiety, susceptibility to depression, and the development of post-traumatic stress disorder (PTSD), which can significantly affect the psycho-emotional state of patients [10, 23]. These disorders are often accompanied by cognitive deficits and manifestations of dysautonomia, which together have a significant negative impact on the overall quality of life of patients. A significant factor in the development of mental disorders is their dual nature: they can be the result of both psychological stress and anxiety caused by the pandemic and the disease, as well as neurophysiological changes in the body. The latter include inflammation of brain tissue, neurotransmitter imbalance, and hypoxic conditions that develop under the systemic influence of coronavirus infection [10, 23, 26].

In addition to psychiatric symptoms, patients with PCS often experience symptoms such as dizziness, chronic fatigue (asthenia), and significant sleep problems. These symptoms significantly limit both physical and cognitive performance, contributing to the overall exhaustion of the body. Asthenia, which is often accompanied by mental disorders and disturbances in the autonomic nervous system, forms a complex symptomatic complex that requires a carefully thought-out and multifaceted therapeutic approach. Special attention should also be paid to sleep disorders, as disorders such as insomnia or sleep fragmentation can exacerbate existing cognitive difficulties and emotional distress. This creates a vicious circle, where lack of rest causes further exhaustion and intensification of the psycho-emotional and physical manifestations of PCS [8, 16, 26].

Cognitive impairment in PCS has a multifactorial origin, caused by the direct neuroviral effect of SARS-CoV-2, prolonged neuroinflammation (activation of microglia, release of IL-6, TNF-a), and endothelial dysfunction [9, 15]. Microthrombosis, hypoxia [8, 10], and mechanisms of tau protein dysregulation common to Alzheimer's disease, leading to neuronal damage and synaptic dysfunction, play an important role [9, 23].

SARS-CoV-2 is capable of directly infecting CNS cells through several mechanisms. One of the most likely is penetration through the olfactory mucosa, where the virus interacts with angiotensin-converting enzyme 2 (ACE2) receptors and transmembrane serine protease type 2 (TMPRSS2), which are located in the cells of the olfactory epithelium and neuroepithelial structures [27, 28]. This route of infection explains the characteristic early symptoms, such as anosmia and hyposmia. Scientific studies have confirmed that SARS-CoV-2 is capable of spreading along the olfactory nerve, crossing the cribriform plate, and reaching the olfactory bulb, from where it can be transported to the structures of the frontal cortex and limbic system [28].

Another route is hematogenous dissemination - the penetration of the virus through the blood-brain barrier (BBB) by infecting endothelial cells or through the migration of infected leukocytes (“Trojan horse”) [27-29]. Auxiliary receptors play an important role in this process, in particular neuropilin 1 (NRP1), a transmembrane glycoprotein involved in vascular growth, nervous system development, and immune response regulation. NRP1 can bind to the SARS-Cov-2 S protein after its cleavage by the furin enzyme, which significantly facilitates the penetration of the virus into cells even under conditions of low ACE2 expression. High expression of NRP1 in the olfactory epithelium, olfactory neurons, and vascular endothelium of the brain explains the neurotropism of SARS-CoV-2 and its

ability to overcome the barrier structures of the brain [27]. Another auxiliary receptor is BASIGIN, a glycoprotein involved in intercellular interaction that may serve as an additional pathway for the virus to attach to the target cell. By interacting with these receptors, the virus causes damage to the endothelium, increases the permeability of the vascular wall, and creates conditions for further invasion of neuronal structures [27, 28].

The “Trojan horse” mechanism involves the indirect penetration of SARS-CoV-2 into the CNS through infected immune system cells - mainly monocytes, macrophages, and T lymphocytes, which act as “transport carriers” for the virus. These cells can express ACE2 and other auxiliary receptors, including NRP1 and CD147, which allows the virus to attach to them during viremia. After infection, these cells adhere and diapedesis through the endothelial cells of the brain vessels, passing through the BBB. This activates intercellular adhesion molecules - ICAM-1 (Intercellular Adhesion Molecule) and VCAM-1 (Vascular Adhesion Molecule), which are located on the surface of endothelial cells and ensure the “adhesion” of leukocytes to the vessel wall. Integrins are activated on the leukocytes themselves, in particular LFA-1 (Lymphocyte Function-Associated Antigen-1), which binds to ICAM-1, forming a stable “endothelium-leukocyte” contact. This binding allows immune system cells to “crawl” along the endothelium and penetrate through the vascular wall into the brain parenchyma. The conditions of systemic inflammation in COVID-19, in particular the increase in the levels of cytokines IL-1 and TNF-a, significantly increase the expression of ICAM-1 and VCAM-1, facilitating the passage of infected cells through the BBB. Once in the perivascular space of the brain, these cells can release viral particles or inflammatory mediators (IL-6, TNF-a, reactive oxygen species), triggering local neuroinflammation and microglia activation. This pathway provides “hidden” transport of the virus, as it is masked within the cells of the immune system, avoiding neutralization by antibodies. This explains why in some cases viral RNA is found in brain tissue but is absent in cerebrospinal fluid. In addition, infected leukocytes that have entered the brain tissue remain active sources of cytokines and maintain a chronic inflammatory process even after viremia has disappeared [28, 29].

One of the key mechanisms of damage is a cytokine storm, manifested by excessive activation of the immune system and the release of large amounts of pro-inflammatory cytokines, such as IL-1, IL-6, TNF-a, and interferon-γ [16, 30, 31]. An excess of these mediators causes systemic inflammation, endothelial damage, and increases the permeability of the BBB, allowing toxic metabolites to penetrate brain tissue.

Chronic hypercytokinemia provokes neuro-inflammation, activation of microglia and astrocytes, which produce additional pro-inflammatory mediators, intensifying the destruction of neurons [16, 32]. Patients with PCS have elevated levels of IL-6 and TNF-a in their blood and cerebrospinal fluid, which correlates with cognitive impairment [16]. This prolonged inflammatory process contributes to the development of post-COVID encephalopathy, which is accompanied by chronic neurometabolic changes [16].

Microglia, which are resident immune cells of the central nervous system, play a key role in the development of neuroinflammation. Studies have shown that SARS-CoV-2 is capable of infecting or overactivating microglial cells. This leads to the release of cytokines, reactive oxygen species, and glutamate, which cause synaptic plasticity disorders and neuronal dysfunction [31, 32]. Prolonged activation of microglia causes neurodegenerative processes similar to the mechanisms of Alzheimer's disease, including increased expression of phagocytosis genes and accumulation of phosphorylated tau protein [16, 27, 32]. In addition, reactive astrocytes together with microglia form a pro-inflammatory microenvironment that reduces the level of brain-derived neurotrophic factor (BDNF). This protein is essential for maintaining neuron survival and regulating the formation of new synapses. BDNF deficiency is often associated with cognitive decline and the phenomenon of “COVID fog” [31, 32].

The virus directly affects the endothelial cells of blood vessels through ACE2 receptors, leading to endotheliopathy - damage to the walls of blood vessels with increased permeability, edema, and microthrombus formation [27, 29]. Virus replication is accompanied by a rupture of intercellular contacts and platelet activation, leading to hypoperfusion and ischemia of brain tissues [16, 29]. Neuroimaging studies of patients with PCS show reduced blood flow in the frontal and temporal regions of the brain, which is associated with cognitive impairment [30]. The release of von Willebrand factor, elevated D-dimer levels, and the formation of microthrombi confirm the vascular nature of post-COVID encephalopathy [16, 29].

SARS-CoV-2 is capable of initiating autoimmune reactions through the phenomenon of molecular mimicry, which consists in the similarity between viral antigens and human proteins [30, 31]. Antibodies to NMDA receptors, glial proteins, and phospholipids have been detected in patients with COVID-19. Due to damage to the BBB, these antibodies penetrate the central nervous system, provoking the development of

autoimmune encephalitis, demyelinating pathologies, and Guillain-Barré syndrome [30].

Some patients who have had COVID-19 develop new chronic autoimmune syndromes that persist for several months, including autoimmune encephalopathy and polyradiculoneuropathy [31]. This pathophysiological mechanism clearly indicates the key role of the humoral link of the immune system in the onset and development of post-COVID neurological diseases.

Studies show that the SARS-CoV-2 virus can persist in body tissues even after the acute symptoms of the disease have disappeared. This is especially true for the central nervous system, endothelial cells, and immune system cells. Residual viral antigens and RNA were detected in brain tissue, olfactory bulbs, and choroid plexus several months after infection. Such persistence is associated with low-level chronic inflammation and cytokine production, as confirmed by relevant data [29, 31].

The persistence of the virus in tissues is accompanied by the activation of the NLRP3 inflammasome (an intracellular protein complex of the innate immune system), which is an intracellular protein complex that stimulates the release of interleukins-1β and -18, contributing to the maintenance of a prolonged inflammatory process [16]. In addition, the biomarkers GFAP (glial fibrillary acidic protein) and NFL (neurofilament light chain) remain elevated for several months after the disease, indicating damage to glial cells and neurons [16]. The chronic presence of SARS-CoV-2 may also cause the activation of neurodegenerative processes similar to the early stages of pathologies such as Parkinson's and Alzheimer's diseases [32, 33].

The diagnosis of PCS remains challenging due to the wide range and nonspecific nature of symptoms. A comprehensive clinical and neurological examination, including a thorough medical history, assessment of the patient's neurocognitive status, and instrumental diagnostics, is crucial for confirming the diagnosis [34].

When diagnosing PCS, in order to rule out symptoms that may indicate a concomitant pathology in the patient, it is necessary to establish a laboratory-confirmed history of COVID-19. Symptoms characteristic of PCS occur 3 months after the onset of COVID-19 and last for at least 2 months [2].

To accurately identify neurocognitive disorders, it is important to use standardized neuropsychological tests such as the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). They help to quantitatively assess the level of impairment and monitor the dynamics of PCS [9].

However, it should be noted that the diagnosis of PCS is based on an analysis of the clinical picture and medical history, not just on the results of individual tests. Even normal MoCA or MMSE scores do not rule out a diagnosis of PCS if characteristic symptoms are present.

The MMSE scale is a more common tool for assessing cognitive status. However, it has limited sensitivity to minor executive function impairments, which may reduce its diagnostic value in cases of mild cognitive complaints, such as “brain fog,” which is common in patients with PCS who show normal test results. Despite these limitations, the MMSE remains an effective method for primary screening and detection of severe dementia or significant cognitive impairment. Interpretation of MMSE results: a score below 24 out of a maximum of 30 is considered pathological [35]. However, normal MMSE results do not rule out the possible presence of neurocognitive effects in patients with PCS.

The MoCA scale covers a wide range of cognitive functions, making it particularly useful for diagnosing manifestations such as “brain fog.” In particular, this test assesses: executive functions, attention and concentration, language skills, visuospatial analysis, memory, and orientation. Test results are evaluated on a total score, with a maximum value of 30. A score below 26 is defined as an indicator of cognitive impairment and requires further clarification. In cases of PCS, patients most often receive lower scores on tasks involving attention (serial subtraction), concentration (visual tracking), and working memory (delayed word recall), which is consistent with their main complaints of cognitive difficulties [9].

Studies clearly demonstrate that MoCA is a significantly more sensitive tool for detecting mild cognitive impairment following COVID-19 than MMSE. The advantage of MoCA lies in its ability to assess in more detail the higher cognitive functions that are most often impaired by PCS, such as executive functions, cognitive speed, and attention span.

Although the diagnosis of neurocognitive disorders in PCS remains largely clinical, modern instrumental research methods play an important role in confirming impairments, conducting differential diagnosis, and identifying pathophysiological mechanisms. Studies show that a significant proportion of patients with long-standing complaints of cognitive impairment have nonspecific but statistically significant changes.

Magnetic resonance imaging (MRI) of the brain remains a key neuroimaging method for the objective assessment of patients with suspected neurocognitive consequences of PCS. Although standard scanning modes do not reveal gross structural changes in most patients, detailed analysis using 1.5 T magnetic field induction tomographs and specialized protocols allows

for the identification of a number of characteristic abnormalities.

Among the most common findings are focal or diffuse changes in the white matter signal, which may indicate the development of gliosis (proliferation of glial cells) or microangiopathy (damage to small blood vessels). These changes are most often found in the frontal and temporal lobes of the brain, regions that are important for cognitive function, attention, working memory, and behavioral control. A large-scale study by Douaud et al. (2022), based on UK Biobank data, demonstrated a significant reduction in white matter integrity after infection compared to pre-disease levels. This reduction correlated with cognitive decline. Pathophysiologically, these changes may be related to damage to the endothelial layer of microvessels, leading to disruption of the blood-brain barrier, microthrombosis, ischemia, and ultimately axonal degeneration [36].

One of the significant observations is the detection of mild cerebral atrophy - a reduction in the volume of the cerebral cortex compared to the control group, which does not correspond to normal age-related changes. A study by Hellgren et al. (2023) recorded a decrease in gray matter volume in the orbitofrontal cortex and hippocampus seven months after COVID-19. The hippocampus, which plays a key role in long-term memory formation, is particularly vulnerable. This may explain the persistent impairment of episodic memory and learning abilities in patients with COVID-19. Potential mechanisms for this phenomenon include direct viral infection via ACE2 receptors, prolonged neuroinflammation, or metabolic stress [37].

Functional magnetic resonance imaging (fMRI), which assesses the metabolic activity of different areas of the brain by measuring changes in blood flow, provides even more detailed and meaningful data. It allows the detection of subtle disturbances in the structure and efficiency of large-scale neural networks.

Dysfunction of the default mode network (DMN) is one of the key aspects. This network of brain structures is activated mainly at rest, when a person is not engaged in specific cognitive tasks. It is responsible for self-referential thinking, memories, and “wandering” thoughts. A study by Hugon et al. (2023) pointed to increased connectivity within the DMN in patients with post-TBI conditions, indicating the inefficiency of this network. This can manifest as an inability to effectively “turn off” the DMN when performing tasks that require attention and concentration, resulting in increased distractibility, feelings of “brain fog,” and difficulty concentrating.

Disruption of the connections between the frontal and temporal regions of the brain is also a significant problem. The frontal lobes are actively involved in executive functions, language organization, and behavior regulation, working in close connection with the temporal regions. Using fMRI, it was possible to detect a decrease in functional connectivity between these important areas of the brain. This disconnect may explain patients' complaints of slow thinking, difficulty with planning, initiating actions, and problems with finding words [38].

Electroencephalography is also considered an effective method for detecting non-specific changes in brain activity. It has revealed changes that may include a slowing of the main electrical rhythms and the appearance of theta waves in the frontal areas. Such deviations indicate a disturbance in the functioning of the cerebral cortex and partially correlate with the degree of cognitive deficit. This allows for a more detailed assessment of the patient's neurological status [39].

In cases where structural MRI does not show significant changes, but the clinical manifestations of the pathology remain pronounced, functional neuroimaging methods become particularly important. These approaches provide the ability to assess the physiological activity of brain tissues. Among the most important methods are positron emission tomography (PET) and single photon emission computed tomography (SPECT), which allow the detection of abnormalities at the molecular and cellular levels long before structural changes become apparent.

PET is one of the most informative methods for assessing the metabolic activity of the brain. The basic principle of this method is based on the use of radioactive tracers - biologically active substances labeled with isotopes that emit positrons. The most commonly used study is FDG-PET, where fluorodeoxyglucose (FDG) is used as a tracer. Since glucose is the main source of energy for neurons, its absorption level directly reflects the functional state of brain tissue.

A large-scale study conducted by Guedj and co-authors in 2021, which included patients with prolonged neurocognitive complaints after COVID-19, revealed a clear and consistent trend: diffuse hypometabolism in certain areas of the brain. The most commonly affected areas were:

- the frontal lobes, particularly the prefrontal cortex, which is responsible for executive functions such as planning, decision-making, and behavior control;
- the anterior cingulate gyrus, which plays an important role in attention and emotion regulation networks;
- the temporal lobes, including the hippocampus, a structure important for long-term memory formation.

This pattern of hypometabolism correlated with the severity of patients' cognitive complaints, such as “brain

fog," memory impairment, and decreased ability to concentrate.

This suggests that even in the absence of obvious macroscopic changes on MRI, there is a persistent decrease in energy processes in neurons in the brain. This is the basis for both the subjective symptoms and objective cognitive impairments observed in such patients [40].

According to the results of another study, patients with persistent subjective cognitive impairments after a mild course of COVID-19 showed concomitant hypometabolism on PET and patterns of EEG slowing in the frontal lobes. FDG-PET analysis revealed significant clusters of hypometabolism in the frontal, temporal, and parietal lobes, as well as in the left occipital lobe. EEG analysis showed a significant increase in relative power in the delta and theta ranges, as well as a noticeable decrease in alpha range power in the frontal, temporal, and central regions [41].

SPECT is another important functional method for assessing cerebral perfusion. This approach is based on the use of tracers that accumulate in brain tissue in proportion to the intensity of regional cerebral blood flow. A study by Morand et al. (2022) clearly demonstrated that patients with post-COVID syndrome have reduced perfusion in the same anatomical areas where PET data revealed hypometabolism - in the frontal and temporal lobes, as well as in the cingulate gyrus [40].

This finding is particularly important because it indicates a systematic pathophysiological process: microcirculation and perfusion disorders → insufficient oxygen and glucose supply → decreased metabolic activity of neurons → cognitive dysfunction. This cascade of events may be caused by endothelial dysfunction, microthrombosis, or autonomic neuropathy resulting from SARS-CoV-2 infection.

Currently, there is no single specific biomarker for determining neurocognitive disorders associated with PCS. However, active research on this issue demonstrates a consistent correlation between cognitive impairment and signs of systemic inflammation or direct damage to neurons. Analysis of such markers in peripheral blood opens up prospects for non-invasive diagnosis and a deeper understanding of the pathophysiology of these processes.

One such marker of axonal damage, neurofilament light chain (NfL), has a directly proportional correlation with the level of neurocognitive impairment in PCS.

Neurofilaments form the basis of the cytoskeleton of neurons, with NfL being their most mobile and dynamic part. In the event of damage or degeneration of axons, NfL is released into the intercellular fluid, subsequently entering the cerebrospinal fluid and from there into the peripheral blood. Thus, elevated serum NfL levels are considered a sensitive and specific indicator of axonal damage. This marker is found in many neurological diseases, such as multiple sclerosis and Alzheimer's disease.

In a study, Gutman and co-authors (2024) analyzed the relationship between NfL levels and the cognitive consequences of PCS. They found that patients with PCS who complained of persistent cognitive symptoms had statistically elevated serum NfL levels compared to control groups who had COVID-19 without complications. In addition, a correlation was found between high NfL levels and poorer results on memory and executive function tests [42].

This suggests that even after acute infection, the active process of nerve fiber degeneration may continue, which largely explains the development of some neurocognitive symptoms. Possible mechanisms for these damages may include direct cytopathic effects of the virus, microthrombosis in the cerebral vessels, or prolonged neuroinflammation.

To establish PCS with neurocognitive impairment, it is necessary to carefully exclude other pathological conditions that may have similar clinical symptoms.

Cognitive impairment in PCS often resembles the early stages of the neurodegenerative process characteristic of mild cognitive impairment and Alzheimer's disease. A distinguishing criterion in this case is the medical history - the symptoms of PCS are clearly linked in time to a previous SARS-CoV-2 infection. MRI neuroimaging in PCS usually does not show significant hippocampal atrophy, which is characteristic of Alzheimer's disease. According to PET results, hypometabolism in PCS can be either more diffuse or concentrated in the frontal lobes of the brain, whereas in Alzheimer's disease it mostly begins in the temporal-parietal regions [36].

Asthenia, difficulty concentrating, and brain fog are typical symptoms of both depression and PCS. At the same time, in the case of depression, cognitive complaints are usually secondary and may decrease with antidepressant therapy. PCS is more likely to have specific executive function and attention problems, which is confirmed by MoCA test results, even if there's no obvious depression [38].

Chronic fatigue syndrome (myalgic encephalomyelitis) has symptoms that are very similar to PCS. These include constant fatigue that worsens after physical exertion (post-exertional malaise), cognitive impairment, and poor-quality, non-restorative sleep. Studies note similar manifestations of cerebral hypoperfusion according to SPECT data in patients with both conditions [40]. Currently, diagnosis is often based on clinical history, where acute SARS-CoV-2 infection acts as an obvious trigger for PCS.

Autoimmune diseases of the central nervous system, such as multiple sclerosis or vasculitis, can debut under the influence of infections, including COVID-19. Symptoms such as attention and vision disorders and other focal manifestations are often similar in nature. The decisive factor in the differentiation process is the detection of focal changes in white matter characteristic of multiple sclerosis on MRI, or the presence of positive laboratory markers of vasculitis.

The treatment of neurocognitive disorders in PCS is a complex task in which non-pharmacological methods often play a key role. Since there is no specific pharmacotherapy available yet, the main focus is on rehabilitation strategies. These include cognitive training, gradual restoration of physical activity, and psychological support to improve patients' quality of life.

“Brain fog” and related cognitive impairments require a targeted approach for correction. Cognitive rehabilitation and brain training are an effective basis for this.

The main goal is not simply to “cure” the brain, but to teach patients to use compensatory strategies, promote neuroplasticity, and restore the effectiveness of cognitive functions. To this end, compensatory strategies, computer-based cognitive training, and energy conservation strategies are used [43].

Physical activity is an effective method of rehabilitation, but in the case of postural weakness syndrome associated with PCS, it is often complicated by post-exertional weakness, when even minor exertion causes a sharp deterioration in the condition. Intense training in this case can be harmful. The method of gradually increasing activity offers a more cautious and controlled approach to gradually increasing physical activity [44].

As mentioned above, psychological state directly affects the intensity of neurocognitive symptoms. Anxiety, depression, and fear of uncertainty significantly weaken cognitive functions. Therefore, cognitive-behavioral therapy is recommended to alleviate these symptoms. This approach has been successfully used to overcome symptoms such as catastrophizing (the fear that symptoms are the result of irreversible damage), anxiety, and depression. Cognitive behavioral therapy (CBT) helps patients identify and correct dysfunctional thoughts and behavioral patterns associated with the disease, which helps them control their condition more effectively [45].

As of today, there is no approved specific pharmacological treatment for PCS, in particular its neurocognitive manifestations. Therefore, drug therapy is based mainly on a symptomatic approach aimed at alleviating the most pronounced symptoms that significantly affect the quality of life of patients. The treatment strategy should be individualized and developed after careful diagnosis.

Headache is one of the most common neurological symptoms of PCS, often presenting as tension headache or migraine. Standard nonsteroidal anti-inflammatory drugs (NSAIDs) are used to treat this condition. In cases that clinically resemble migraine, triptan drugs may be used.

During the COVID-19 pandemic, there were concerns about the use of NSAIDs due to the assumption that they could increase ACE2 expression, which in turn could contribute to SARS-CoV-2 infection. However, there is currently no reliable scientific data that would unequivocally rule out their use in the general population that may be infected with COVID-19, as well as in individuals with acute viral disease.

Another effective treatment for migraine status is the use of corticosteroids, which are potentially safe drugs for treating patients with prolonged headaches that do not respond to other treatments. Blockade of the greater occipital nerve may also be used to prevent migraine attacks in PCS [46].

A group of nootropics and neuroprotectors is of considerable interest for eliminating “brain fog” and improving cognitive functions. However, their effectiveness in cases of PCS needs to be confirmed by large-scale randomized studies.

Antidepressants are used to treat anxiety disorders and depression. Sertraline and escitalopram, which are serotonin reuptake inhibitors, are often considered the first-line drugs for treating depression and anxiety in patients with PCS due to their favorable safety profile. They can also reduce the intensity of autonomic symptoms. Venlafaxine, a serotonin and norepinephrine reuptake inhibitor, may be prescribed in cases where depression is accompanied by chronic pain syndrome or severe autonomic disorders [47].

The complexity and multifaceted nature of PCS manifestations make it impossible to provide effective care within the scope of a single medical specialty. The optimal approach to PCS treatment is considered to be an interdisciplinary strategy that involves close collaboration between specialists from different fields to create an individualized and comprehensive patient management program [48].

This significantly increases patient compliance with recommendations and improves treatment outcomes. As a result, a comprehensive rehabilitation strategy is developed that provides the best conditions for the rehabilitation of patients with PCS.

Table 1 – Differential diagnosis of neurocognitive disorders in PCS, MCI, dementia and other conditions

Assessment criterion	**Post-COVID syndrome (PCS)**	**Mild cognitive impairment (MCI) and Alzheimer's disease (AD)**	**Vascular dementia**	**Depression**	**Chronic fatigue syndrome (CFS)**
Medical history and clinical course	A clear temporal link to a previous COVID-19 infection (onset 3 months later, duration from 2 months).	A slow, progressive course. Patients usually go through a stage of mild cognitive impairment before developing dementia.	Fluctuating course and stepwise progression. Presence of cerebrovascular pathology.	Psychotraumatic events, chronic stress. Reversible following treatment of the underlying condition.	Often manifests following viral infections.
Clinical presentation of cognitive impairment	«Brain fog», specific attention deficits, slowed reaction times and impaired executive function.	In MCI: objective cognitive impairment compared with baseline. In AD: hippocampal-type memory impairment (deficit in recall with a cue).	Frequent combination of cognitive impairments and focal neurological deficits. Fluctuations in condition and transient episodes of disorientation.	Cognitive complaints are secondary to depressed mood and apathy.	Cognitive impairments are closely associated with non-restorative sleep.
Ability to care for oneself (Activities of Daily Living)	Largely preserved, but limited due to rapid fatigue.	In MCI: ability to function independently is preserved. In AD: loss of daily living skills (assessed using the BADL scale).	Diminished skills, dependence on others. The degree correlates with the location of vascular events.	Reduced due to loss of motivation and apathy.	Significantly limited due to pronounced post-exertional exhaustion.
Laboratory markers	Elevated levels of neurofilament light chain (NfL) in the blood may be present as a sign of axonal damage.	Specific biomarkers in cerebrospinal fluid: amyloid (Aβ42, Aβ42/Aβ40) and tau protein (total tau, pTau).	There are no specific markers for AD. Lipid profile to assess the progression of atherosclerosis.	There are no specific biomarkers.	There are no specific biomarkers.
Neuroimaging findings (MRI/PET)	Diffuse frontal-temporal hypometabolism on PET. No significant hippocampal atrophy on MRI.	MRI: Regional atrophy, particularly of the medial temporal lobe. PET: Accumulation of amyloid and tau protein. Temporal-parietal hypometabolism.	The extent of vascular damage to the brain's white matter is assessed using the Fazekas scale on MRI. Doppler imaging is recommended to detect vascular abnormalities (stenosis, occlusion).	Usually without specific structural changes.	No specific macroscopic structural changes (hypo-perfusion on SPECT).
Psychiatric and behavioural disorders	Autonomic dysfunction, anxiety, persistent headache, loss of smell.	Depression, fear, agitation, wandering, psychosis (assessed using the NPI questionnaire).	Emotional lability, depressive symptoms.	Apathy, feelings of guilt, loss of interest in life, suicidal thoughts.	Marked physical asthenia.
Neuropsychological testing	The MoCA scale is significantly more sensitive than the MMSE for detecting impairments in executive function.	The short-form MMSE and MoCA tests are used as primary screening tools.	MMSE and MoCA (impairments in executive function). Tests of executive function (TMT, clock drawing, etc.)	Tests for detecting depression (Beck/Hamilton). The 'don't know' effect in responses. NPI for assessing mood.	Cognitive test results may vary depending on the level of fatigue.

Algorithm for the management of patients with suspected neurocognitive disorders following COVID-19:

1. Clinical verification of the diagnosis:
   - Confirmation of a history of laboratory-confirmed COVID-19;
   - Checking temporal criteria: onset of symptoms 3 months after the acute phase and their duration of at least 2 months.
2. Neuropsychological screening:
   - Use of the MoCA scale as a first-line tool. It is significantly more sensitive than the MMSE scale for detecting the executive function impairment and «brain fog» characteristic of PCS (a score <26 requires attention).
3. Differential diagnosis (process of «exclusion»):
   - Exclusion of other conditions (early stages of Alzheimer's disease, primary depression, chronic fatigue syndrome), based on Table 1.
4. Imaging studies (where indicated):
   - Brain MRI (preferably 1.5T) to rule out focal lesions (e.g., in multiple sclerosis) and assess white matter condition;
   - PET or SPECT (where possible) in cases of pronounced symptoms and the absence of changes on MRI to detect hypometabolism or hypoperfusion in the frontal lobe.

CONCLUSIONS

PCS is a global medical and socio-economic threat. It affects 10% to 30% of patients who have had COVID-19, even in mild form. The neurological and neurocognitive consequences of PCS include brain fog, headaches (which are resistant to traditional treatment), post-COVID neuropathies, psychiatric disorders, and dysautonomia (e.g., POTS).

The pathophysiology of neurocognitive disorders is a complex of interrelated mechanisms that reinforce each other and form a chronic pathological circuit. Penetration of the SARS-CoV-2 virus into the central nervous system through the olfactory nerve or disruption of the barrier functions of the blood-brain barrier, chronic systemic inflammation and cytokine storm, neuroinflammation with activation of microglia, which contributes to the deterioration of neuronal functions, endothelial dysfunction with the formation of microthrombi that disrupt cerebral blood flow, autoimmune reactions through the mechanism of molecular mimicry, prolonged presence of the virus in body tissues, causing a chronic immune response.

The diagnosis of PCS is greatly complicated by the lack of a universal biomarker that would allow a diagnosis to be made. That is why diagnostic approaches cannot be limited to a standard neurological examination. A comprehensive assessment of the condition is required: medical history with linking symptoms to the infection, neurocognitive testing (MoCA, MMSE if necessary), instrumental imaging (MRI, fMRI, PET, and SPECT), laboratory diagnostics, as well as the exclusion of other causes, including the onset of neurodegenerative and autoimmune diseases.

Treatment of PCS at this stage is not regulated by standardized protocols and requires a comprehensive approach that takes into account the individual needs and characteristics of the patient. The main treatment strategies are based on a combination of rehabilitation, psychotherapeutic, and symptomatic approaches. Individualized cognitive rehabilitation programs, phased physical activity taking into account the risk of post-exercise exhaustion, psycho-emotional support, correction of anxiety and depressive disorders, and symptomatic treatment of headaches have been shown to be effective.

PROSPECTS FOR FUTURE RESEARCH

The subject of debate is the differentiation of cognitive impairments in PCS from the early stages of neurodegenerative processes, due to the lack of a single, universally specific biomarker for neurocognitive impairments in post-concussion syndrome. Further research is needed to identify specific autoantibodies that damage the nervous system and determine their clinical significance. Their identification will lead to the development of targeted immunosuppression, which will reduce the severity of PCS. Since there are currently no universal biomarkers for PCS, it is necessary to develop a diagnostic panel of biomarkers and further determine the correlation of their levels with the severity of PCS. Given the complexity of the approach to comprehensive treatment of PCS, it is necessary to define the clinical forms of PCS, which will involve clustering patients according to their dominant symptoms. This approach will contribute to more effective personalized treatment.

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2. Drafting the work or revising it critically for important intellectual content;
3. Final approval of the version to be published;
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST

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