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POST-COVID-19 COGNITIVE IMPAIRMENTS (LITERATURE REVIEW)

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ПОСТКОВИДНЫЕ КОГНИТИВНЫЕ НАРУШЕНИЯ (ОБЗОР ЛИТЕРАТУРЫ)

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Post-COVID-19 condition (PCC) is a condition that occurs in patients with a history of SARS-CoV-2 infection 3 months after the onset of COVID-19 with symptoms that last at least 2 months and are not explained by any other diseases. PCC affects from 17 % to 28 % of patients and includes a wide range of clinical manifestations, including cognitive dysfunction. Cognitive dysfunctions can be manifested by a wide range of symptoms, such as memory impairment, attention deficit, executive dysfunction, and reduced information processing speed. Risk factors for developing PCC, with or without cognitive impairment, include late adulthood, pre-existing medical conditions, and severity of acute illness. The underlying mechanisms remain unclear, but suspected factors include neuroinflammation, hypoxia, vascular damage and latent reactivation of the virus,

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this does not exclude the possibility of direct viral central nervous system invasion. The analysis of retrospective cohort studies showed that the risk of cognitive deficits, dementia, psychotic disorders and seizures remained elevated even 2 years after the infection of SARS-CoV-2. It is interesting to note that there were no differences in the risks of neurological and psychiatric outcomes between infections caused by Omicron (B.1.1.529) or Delta (B.1.617.2) variants. Recent researches show that cognitive deficits after infection of SARS-CoV-2 persist for two years after the infection and were the greatest in individuals with more severe SARS-CoV-2 infection [2]. COVID-19 can impair the function of the interoceptive network of the brain selectively, while exteroceptive brain processing remains undamaged [3].
Keywords. Post-COVID-19 condition, cognitive impairment, post-COVID disorders.

Изучены последние данные литературы о постковидных когнитивных нарушениях. Post-COVID-19 condition (PCC) – это состояние, которое возникает у пациентов с инфекцией SARS-CoV-2 в анамнезе через 3 месяца после начала COVID-19 с симптомами, длящимися не менее 2 месяцев и не объясняющимися никакими иными заболеваниями. PCC поражает от 17 до 28 % пациентов и включает в себя широкий спектр клинических проявлений, в том числе когнитивную дисфункцию. Когнитивные дисфункции могут проявляться в виде широкого спектра симптомов, включая ухудшение памяти, дефицит внимания, исполнительную дисфункцию и снижение скорости обработки информации. Факторы риска развития PCC, с когнитивными нарушениями или без них, включают пожилой возраст, ранее существовавшие заболевания и тяжесть острого заболевания. Лежащие в основе механизмы остаются неясными, но предполагаемые факторы включают нейровоспаление, гипоксию, повреждение сосудов и латентную реактивацию вируса, не исключая возможности прямой вирусной инвазии в центральную нервную систему.
Анализ ретроспективных когортных исследований привел к выводу, что риск когнитивного дефицита, слабоумия, психотических расстройств и судорог оставался повышенным даже через 2 года после заражения SARS-CoV-2. Интересно также то, что не наблюдалось различий в рисках неврологических и психиатрических исходов между инфекциями, вызванными вариантами «Омикрон» (B.1.1.529) или «Дельта» (B.1.617.2). Последние исследования подводят к выводу, что когнитивный дефицит после заражения SARS-CoV-2 сохранялся через два года после заражения и был наибольшим у лиц с более тяжелой инфекцией SARS-CoV-2, а также показывают, что COVID-19 может избирательно нарушать функцию интероцептивной сети мозга, оставляя нетронутой экстероцептивную обработку мозга.
Ключевые слова. COVID-19, post-COVID-19 condition, когнитивные нарушения.

INTRODUCTION

The new coronavirus infection has led to long-term consequences in the form of cognitive impairment in the working population, since vaccination against SARS-CoV-2 was not a completely reliable protection against the post-COVID-19 condition (PCC). Today, there is still insufficient data on what causes cognitive dysfunction in patients with PCC, and even less is known about the most effective rehabilitation measures [1; 2]. The latest foreign data on cognitive impairment associated with SARS-CoV-2 infection and their prevalence in the population were analyzed through the PubMed® search engine. The novelty (2022–2023) was the main criteria for selecting articles. The following queries were entered into the search: cognitive dysfunction in post-COVID-19; the effects of COVID-19 on cognitive; persistent symptoms after COVID-19; post-COVID syndrome; main symptoms of long-COVID.

According to the World Health Organization (WHO), PCC is a condition that

occurs in patients with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months after the onset of COVID-19, with symptoms that last at least 2 months and are not explained by any other diseases (World Health Organization. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021. Geneva, Switzerland). PCC includes a wide range of clinical manifestations affecting multiple organ systems. In most people with PCC, symptoms gradually resolve over time, but in some patients, they persist for many months or even years after SARS-CoV-2 infection and have a significant impact on quality of life [1].

Long-term cognitive dysfunction is one of the most common impairments in PCC, affecting 17 to 28 % of people more than 12 weeks after infection and persisting for several years in some cases [3]. Cognitive dysfunction can be manifested as a wide range of symptoms, including memory impairment, attention deficit, executive dysfunction, and reduced information processing speed. Risk factors for developing PCC, with or without cognitive impairment, include late adulthood, pre-existing medical conditions, and severity of acute illness. The underlying mechanisms remain unclear, but suspected factors include neuroinflammation, hypoxia, vascular damage and latent reactivation of the virus, this does not exclude the possibility of direct viral central nervous system invasion [1].

The most common symptoms in PCC are fatigue, memory problems, decreased concentration, and impaired attention. Large meta-analyses by F. Ceban et al. and Q. Han et al. summarize that the overall proportion of individuals with cognitive impairment is 19–22 %. Cognitive impairment is also accompanied by sleep disturbances, anxiety, and depression [3; 4].

In the study by Rija Aziz et al. patients reported that the most common symptoms of PCC were fatigue (89 %), forgetfulness or "brain fog" (89 %), and difficulty concentrating (77 %). The Montreal Cognitive Assessment (MoCA) showed that 46 % had mild cognitive dysfunction. And in a study by Jedsada Khieukhajee, the prevalence of cognitive impairment after COVID-19, defined as a total MoCA score below 25 points, was 61.76 % [5; 6]. Testing the health of patients who had recovered from the new coronavirus infection using the PHQ-9 (Patient Health Questionnaire) in a study by Rija Aziz et al. showed that 42 % had moderate to severe depression. Moderate to severe anxiety was also detected in 38 % of COVID-19 survivors, as assessed by the General Anxiety Disorder-7 (GAD-7) test. Symptom severity was similar across gender, age, and initial disease severity. Patients with PCC presenting to an academic hospital after COVID-19 experienced multiple multisystem symptoms and functional impairments, regardless of initial COVID-19 disease severity [5].

Mihaela-Camelia Vasile et al. [7] assessed COVID-19-related neuropsychiatric disorders in a prospective study using the Mini-Mental State Examination (MMSE) and

MoCA questionnaires, which were administered to hospitalized COVID-19 patients who had experienced moderate to severe forms of the disease. Tests were performed at discharge and re-evaluated after 6 and 12 months. Baseline cognitive dysfunction was detected in 12.4 % of patients according to the MMSE test and in 19.7 % according to the MoCA scale. Overall cognitive dysfunction in COVID-19 normalized after 6 months, but some symptoms were quite severe, such as impaired concentration, short-term memory, and task performance skills. Male gender and the degree of hypoxia associated with the severity of COVID-19 infection were associated with cognitive dysfunction in the study group [7].

An analysis of retrospective cohort studies led M. Taquet et al. to the conclusion that the risk of cognitive deficit, dementia, psychotic disorders and seizures remained elevated even 2 years after SARS-CoV-2 infection [8]. It is interesting to note, that no differences in the risks of neurological and psychiatric outcomes were observed between infections caused by the Omicron (B.1.1.529) or Delta (B.1.617.2) variants [1]. Given that attentional functions define the fundamental basis of cognitive processes, they are crucial for managing our daily lives. Impaired attentional functions, even in cases of mild changes, directly affect performance in both daily tasks and professional activities.

Fatigue is a characteristic symptom in both acute COVID-19 and PCC. The prevalence rates of post-COVID fatigue range from 32 to 46 % in different studies, and from 18 to 39 % in a meta-analysis of one-year follow-up. In neurological conditions, decreased attention, slower processing speed, and tiredness were associated with the feeling of fatigue, but also showed a significant correlation with depression and sleep disturbances [5].

A recent meta-analysis by Tsampasian et al. showed that female gender, age, high BMI, and smoking were associated with an increased risk of developing PCC symptoms. The presence of concomitant diseases and previous hospitalization, including admission to the intensive care unit, were found to be associated with an even higher risk of PCC developing. Markers of systemic inflammation are associated with persistent fatigue and cognitive symptoms with significant functional impairment. Most authors indicate a significant proportion (40–80 %) of hospitalized patients experiencing post-COVID consequences in the form of neuropsychiatric symptoms. In line with this, vaccination against SARS-CoV-2, which reduces the risk of severe COVID-19 for most people, appears to reduce the risk of developing PCC after infection [1].

The following pathophysiological mechanisms have been discussed to explain the persistence of symptoms after infection with the SARS-CoV-2 virus: direct brain injury during acute SARS-CoV-2 infection, low-level persistence of viral antigens to SARS-CoV-2 in the CNS, reactivation of latent herpes viruses, epigenetic response, central and peripheral hypoxia, ongoing

systemic inflammation, neuroinflammation and autoimmune response, microvascular inflammation and microthrombosis, glucose metabolism in the brain [1].

A study by Nathan J. Cheetham et al. found that cognitive deficits following SARS-CoV-2 infection were detected nearly two years after infection and were greatest in individuals with longer duration of symptoms, persistent symptoms, and/or more severe infection. However, no such deficits were found in individuals who reported full recovery from COVID-19 [2].

The results of Siri-Maria Kamp et al. show that COVID-19 can selectively disrupt the function of the brain's interoceptive network while leaving exteroceptive processing intact. Dysfunctional interoceptive processing may be associated with attention/concentration deficits and poor mental health outcomes such as depression and anxiety [9].

In a study by C. Gouraud et al., patients with persistent symptoms following COVID-19 underwent a multi-faceted assessment to describe their symptoms, provide medical reports (diagnoses and recommendations), and assess satisfaction with treatment. Among 286 patients (mean age: 44 years; 70 % women), the most common symptoms were fatigue (86 %), shortness of breath (65 %), joint/muscle pain (61 %) and cognitive dysfunction (58 %), with a mean duration of 429 days. Physical activity rehabilitation was recommended to 91 % of patients. The median patient satisfaction with the rehabilitation program was 8 out of 10. Most patients attending this program had long-term symptoms and severe impairment in quality of life, received a diagnosis of functional somatic disorder and reported high levels of satisfaction with the program [10].

A study by M. Jayasekera et al. examined 153 patients treated for COVID infection at the University Hospital, Kotelawala Defence University of Sri Lanka in July 2021. Of the patients, 92 (60.2 %) had severe disease, 43 (28.1 %) had moderate disease, and 18 (11.7 %) had mild disease. The mean age was 57.2 (± 16.3) years, of which 83 (54.2 %) were men. Cognitive impairment was detected in 26 patients (13 women, 13 men). The authors did not find any difference in gender and age, and no relationship with fatigue was found. The condition returned to normal within 3 months. According to this publication, patients diagnosed with cognitive impairment experienced difficulties with concentration, memory, speech perception, and executive functions. However, the authors concluded that it is impossible to judge cognitive impairment without clear evidence of patient's premorbid intelligence [11]. Disease severity and age over 60 years were risk factors for the development of post-COVID syndrome. According to the study results, vaccination reduced post-COVID symptoms. Quality of life and cognitive impairment improved after 12 weeks. This may indicate that at least 12 weeks are required to detect true dementia in patients after COVID-19 [11; 12].

PCC may also be of great concern in the pediatric population, even in patients who do not require hospitalization. D. Buonsenso et al. [13] reported that symptoms persisted 120 days after COVID-19 infection in more than half of the children, in 42.6 % of whom these disorders limited daily activities. Fatigue, muscle and joint pain, headache, insomnia, difficulty breathing and increased heart rate were particularly common. Cognitive disorders were recorded in 34.3 % of patients who had recovered from COVID-19 [14]. The authors emphasize the need to monitor children for several months after hospitalization to maintain their mental health. According to the authors, the inclusion of psychological assessment in the diagnosis of children with post-COVID syndrome is a practical necessity. In May 2023, an Italian prospective cohort study was conducted to identify risk factors for post-COVID syndrome in children, and the authors noted the following factors: age over 10 years, concomitant diseases, acute phase of novel coronavirus infection in the intensive care unit, multisystem inflammatory syndrome, recently diagnosed Kawasaki syndrome [15].

In the pediatric cohort, cognitive impairment in the post-COVID syndrome is associated with asthenic syndrome. Common manifestations of cognitive impairment in children in the post-COVID period include: decreased concentration, visual gnosis, impaired visual-spatial perception, dynamic and kinesthetic praxis, and decline in thinking. Based on the concept of A.R. Luria, it can be assumed that the cognitive profile and nature of neurological complaints of children in the main group indicate that the temporo-parietal-occipital, mediobasal frontal-temporal regions of the brain, and the limbic-reticular complex are involved in the topic of disorders [16]. This requires a diagnostic algorithm and the development of correctional and educational programs for children with post-COVID cognitive impairment. According to K.S. Korotaeva et al., when examining children with the consequences of COVID-19, the most sensitive hematological indices were the degree of entropy of the leukocyte formula according to A.V. Gorelov, indicating a violation of the dynamic constancy of the leukocyte formula, indices of the ratio of neutrophils and monocytes, the ratio of lymphocytes and monocytes, showing the presence of a viral infection [17].

A study by M. Fotuhi et al. on the pathogenetic mechanisms of neurocognitive deficit caused by COVID-19 in adults divides the formation of neurological changes into three variants: 1) cytokine storm, but the brain is not affected; 2) cytokine storm causes inflammation of blood vessels; 3) cytokine storm damages the blood-brain barrier. In the first case, cognitive impairment does not seem to be observed. However, the emerging symptoms of COVID-19 include nausea, vomiting, sore throat, fever, anosmia and ageusia, the last two indicating damage to the peripheral nervous system. In the second variant, neurological impairment develops, leading

to partial hemiplegia, aphasia, brain fog, pain, blurred vision and ataxia. Working memory, attention deficit and cerebellar dysfunction are symptoms of cognitive impairment during this period. At this stage, COVID-19 symptoms include fatigue, body aches or discomfort, headache, insomnia, depression and/or anxiety. In the third and most severe variant of the disease, the patient develops encephalitis, coma, seizures and delirium. If the patient survives, motor functions, attention, memory, speech and executive functioning are significantly impaired. COVID-19 manifestations include chest discomfort, confusion, shortness of breath or difficulty breathing, and changes in blood pressure and heart rate [18].

Burak Yulug and other authors believe that SARS-CoV-2 may be a risk factor for Alzheimer's disease. The scientists compared 17 patients with COVID-19 with 20 control patients and assessed the impact of COVID-19 on overall cognitive performance, hippocampal volume and its connections. They showed that COVID-19 patients had significantly worse cognitive functioning and increased hippocampal connectivity, as evidenced by a strong correlation between hippocampal connectivity and cognitive performance. These findings of increased hippocampal connectivity in the absence of observable hippocampal morphological changes even in mild cases of COVID-19 infection may indicate a pre-structural compensatory mechanism to stimulate additional neural resources to combat cognitive dysfunction, as has been shown in the prodromal stages of degenerative cognitive disorders [19].

A systematic review and meta-analysis of 20 studies by Zoe Marjenberg et al. on the risks of prolonged manifestation of the main symptoms of COVID-19 after SARS-CoV-2 infection found that SARS-CoV-2 infection is associated with a significantly higher risk of memory problems and difficulty concentrating. However, the authors highlight that these risks are likely to change continually as vaccines, reinfections and new variants alter global immunity [20].

Conclusions

Long-term cognitive dysfunction is a common disorder affecting children and adults with PCC. Risk factors for the development of PCC in general include female gender, age, pre-existing medical conditions, and severity of acute illness, in pediatric practice – multisystem inflammatory syndrome, Kawasaki syndrome on the eve. Proposed mechanisms contributing to the development of PCC and cognitive impairment include neuroinflammation, hypoxia, vascular injury, latent viral reactivation, and direct viral invasion of the central nervous system. Treatment of cognitive dysfunction that persists for more than six months after the acute period of infection in PCC requires a multifaceted approach, including neuropsychological examination and individual rehabilitation, as well as systematic screening for early diagnosis of progressive brain pathologies. Further research on this

topic is needed to conduct evidence-based interventions specific to cognitive impairment associated with COVID-19.

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