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НЕЙРОКОГНИТИВНЫЕ РАССТРОЙСТВА У ПАЦИЕНТОВ С COVID-19: СПОРНЫЕ И НЕРЕШЕННЫЕ ВОПРОСЫ

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Neurocognitive Disorders in COVID-19 Patients: Controversed and Unresolved Issues

Резюме

Новая коронавирусная инфекция (НКВИ, COVID-19) — инфекционное заболевание, вызываемое коронавирусом тяжелого острого респираторного синдрома-2 (SARS-CoV-2). С 2019г. появилось большое количество исследований, посвященных когнитивным нарушениям на фоне НКВИ, и в том числе «длительного COVID-19» (long COVID). В несистематическом обзоре, основанном на исследованиях за 2019-2022гг., представлена информация о выраженности изменений когнитивных функций пациентов, перенесших НКВИ, методах диагностики, позволяющих выявлять эти нарушения, и долгосрочных нейропсихических и когнитивных последствиях, которые могут стать серьезной проблемой общественного здравоохранения.

Ключевые слова: *новая коронавирусная инфекция, когнитивные нарушения, длительный COVID-19, постковидный синдром, SARS-CoV-2, поражение центральной нервной системы*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

New Coronavirus Infection (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2). Since 2019, a large number of studies on cognitive impairment in the background of COVID-19 have emerged, and "long COVID" is among them. A non-systematic review based on 2019-2022 studies provides information on the severity of cognitive changes in patients with COVID-19, diagnostic methods that can detect these cognitive impairment and long-term neuropsychiatric and cognitive outcomes that may pose a serious public health challenge.

Key words: *new coronavirus infection, cognitive impairment, long COVID, post-COVID-19 syndrome, SARS-CoV-2, central nervous system lesions*

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BP — blood pressure, HIV — human immunodeficiency virus, NCVI — novel coronavirus infection, ARDS — acute respiratory distress syndrome, FDG 18F PET — positron emission tomography with 18F-fludeoxyglucose, MCI — mild cognitive impairment, CNS — central nervous system, APOE4 — apolipoprotein E4, COVID-19 — novel coronavirus infection, MMSE — Mini-Mental Status Examination, MoCA — Montreal Cognitive Assessment, SARS-CoV-2 — severe acute respiratory syndrome coronavirus-2

Introduction

The novel coronavirus infection (COVID-19, NCVI) is an infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). COVID-19 appeared in December 2019 in Wuhan (China). The World Health Organisation (WHO) announced COVID-19 pandemic on 11 March 2020 due to the lasting global spread of this disease.

Patients infected with the novel coronavirus had confirmed central nervous system (CNS) involvement with cognitive disorders as a result of neurotropic and neuroinvasive features of the virus as well as inflammatory processes and secondary systemic disorders.

There is information on the presence of mental and/or cognitive disorders in 36 % of patients 3 months after recovery from COVID-19 [1]. Thus, the term "long COVID-19" introduced by the WHO assumes the presence of cognitive disorders.

In a majority of studies of cognitive disorders in NCVI, special attention is paid to memory, regulatory functions and attention [2, 3].

The objective of this non-systematic review was accumulation of information on cognitive disorders associated with past NCVI, including in post-COVID syndrome.

Nervous System Involvement in COVID-19

SARS-CoV-2 is transmitted from person to person mostly via airborne and contact routes. Its genome encodes proteins participating in replication and the four structural proteins — spike glucoprotein, nucleocapsid, membrane and wall proteins. The viral nucleocapsid is surrounded by a membrane with glycoprotein spikes, called S-proteins. The interaction between S-proteins and host receptors, in particular angiotensin converting enzyme 2 (ACE2), has the most important role to play in SARS-CoV-2 virulence and invasion. The receptor is expressed on various nervous system components. It has uneven distribution in brain stem, motor cortex, glutamatergic neurons and plexus chorioideus [4].

Neuropathological studies in humans revealed high ACE2 expression all over the CNS, especially in pons cerebelli, medulla, substantia nigra, caudate nuclei, spine, hypothalamus, hippocamp, middle temporal gyrus, tonsil, cingulate cortex, frontal cortex and olfactory bulb. Considering that medulla has respiration centers of the brain, its involvement can partially explain predisposition of a lot of COVID-19 patients to severe respiratory distress [5].

There are some evidences of SARS-CoV-2 spread in CNS and its damage in the form of direct neurotropy, aberrant immune response, local circulatory dysfunction and hypoxia, presence of inflammatory cytokines in spinal fluid (SF) and migration of infected monocytes/macrophages via hematoencephalic barrier (HEB) [6].

It is known that SARS-CoV-2 infects lymphocyte, granulocytes and monocytes and can be found in SF [7].

Unregulated host response called "cytokine storm" involves a higher level of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukins 6, 1-β, 18 (IL-6, IL-1β, IL-18), causing HEB damage, astrocyte dysfunction and microglia activation. In general, it can result in acute encephalopathy, hypoperfusion, hypoxia and impaired coagulation, amyelination, aberrant transmission of neural signals, cell damage and death. Moreover, cytokine storm is also associated with a higher level of ferritin, lactic dehydrogenase (LDH) and D-dimer, which, in turn, can result in hypercoagulation and an increased risk of cerebrovascular events [8].

It has been proven that higher cytokine levels, especially IL-6 levels, have positive correlation with COVID-19 severity and mortality and result in multiorgan failure [9].

Some authors note the similarity in pathogenesis of nervous system involvement between an infection caused by human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and COVID-19. Being a lymph neurotropic virus, HIV appears in CNS at early stages of the disease. Chronic HIV infection is associated with changes in HEB and an array of neuropathological changes, including vasculopathy, amyloid accu-

mulation and HIV-associated dementia even in young patients. Low lymphocyte count with a drastic reduction in CD4+ T-cells is associated with poor clinical outcome in COVID-19 patients, similar to HIV infection progression [10].

Anosmia is observed in a majority of cases of chronic rhinosinusitis, ageing, neurodegenerative diseases and in so-called post-virus olfactory disorder which is common in COVID-19 patients [11].

Meinhardt J., et al. (2021) conducted a regional mapping of olfactory tracts using necropsy materials from 33 COVID-19 patients and demonstrated that SARS-CoV-2 was present in the samples from nasopharynx and brain. The virus moved along neuroanatomic structures to cardiovascular regulatory centers in brain stem [12].

Neuroimaging studies demonstrated cerebral cortex atrophy after COVID-19 on MRI scans before and after the pandemic, thus showing the direct viral invasion of entorhinal areas of the CNS hippocampal formation [13].

Association Between Cognitive Disorders and Changes in Cerebral Metabolism in COVID-19 Patients

In one paper, patients who were complaining of cognitive disorders after COVID-19 had impaired episodic, visuospatial memory and regulatory functions, which could be related to abnormal hypometabolic regions in the anterior and anterior part of the callosal convolution recorded during positron emission tomography with 18F-fludeoxyglucose (FDG 18F PET). The anterior cingulate cortex receives information from the frontoorbital area, while the posterior cingulate cortex has outputs to hippocamp [14].

Cingulate cortex hypometabolism was observed in some neurological and mental disorders, including mild cognitive disorders in Alzheimer's disease, severe depression and Internet gaming addiction disorder [15].

There are reports on impaired frontoparietal cognitive functions associated with frontoparietal dominant cortex hypometabolism at FDG 18F PET in a group of patients with long-lasting COVID-19 [16].

At the same time, Guedj E., et al. (2021) reported the hypometabolism profile in limbic or paralimbic regions involving brain stem and cerebellum in patients with long-lasting COVID-19, who were examined approximately 3 months after first symptoms [17].

Mild cognitive impairment (MCI) is a diagnostic entity for identification of persons who are at the borderline between normal cognitive ageing and dementia.

In 2021, it was demonstrated that reduced glucose metabolism in neocortex seen at FDG 18F PET is significantly reversible, and it was associated with improved cognitive functions in patients with subacute NCVI to post-COVID syndrome. The authors observed marked improvement during cognitive function screening; however, results could be repeated for MCI [18].

Wang C., et al. (2021)pointed at the cause-and-effect relationship between the risk factor for Alzheimer's disease, apolipoprotein E4 (APOE4) and COVID-19. In the experiment, neurons and astrocytes with APOE4 demonstrated high susceptibility and response to SARS-CoV-2 infection vs. neutral cells with apolipoprotein E3 (APOE3) [7].

On the other hand, lack of APOE4 together with better vision/oflaction, larger hippocamp is a predictor of reversion (recovery to the normal cognitive functions) [19].

Screening Diagnostics of Cognitive Disorders in COVID-19

The Montreal Cognitive Assessment (MoCA) is a cognitive assessment tool developed for MCI identification [3].

MoCA assesses several cognitive areas: memory, speech, regulatory functions, visual-spatial skills, counting, abstract thinking, attention, concentration and orientation. MoCA is a more sensitive method for mild cognitive impairments than the Mini-Mental Status Examination (MMSE); it is a handy screening tool for diagnosing a wide range of cognitive disorders. MMSE was criticised as a screening test for its non-sensibility for identification of impaired visual-spatial and regulatory functions [2].

Differences between MMSE and MoCA values can be a result of higher sensitivity of MoCA in identification of mild changes in cognitive functions, as can be seen in an Italian study of post-COVID-19 patients [20].

In the study by Pistarini C., et al. (2021), a majority of patients in COVID-19 group (20 subjects) had MMSE neuropsychologic deficit (35 %) vs. patients with post-COVID syndrome (20 subjects) — (5 %), whereas both groups (70–75 % of patients) had MoCA cognitive impairments. Patients with post-COVID syndrome had higher points for speech (MMSE), regulatory functions, speech and abstract thinking (MoCA) vs. COVID-19 patients. Both groups had impaired regulatory functions, shirt-term and long-term memory, visual-spatial functions, abstract thinking and orientation. Patients with post-COVID syndrome demonstrated improvements during a month-long follow-up in speech vs. COVID-19 patients; however, memory impairment was still significant [2].

Although MMSE and MoCA are commonly used in clinical practice, in Russia they have not been validated

properly. Currently, the Addenbrooke`s Cognitive Examination III (ACE-III) can be used in Russia; the Russian version of the method has undergone the first stage of validation [21].

Cognitive Disorders in post-COVID Period

In the study by Italian scientists there was a high level of cognitive deficit in post-NCVI patients 3 months later, irrespective of severity of the disease. Only 22 % of the population demonstrated good results of cognitive assessment. Most affected were regulatory functions and psychomotor coordination (impairments were observed in 50 % and 57 %, respectively). Problems with information processing, verbal fluency and temporary memory were recorded approximately in 30 % of the study population [22].

French scientists demonstrated that, on the average 110.9 days after NCVI, the most common symptoms were fatigue (55 %), shortness of breath (41.7 %), memory disorders (34.2 %), memory deficit (26.7 %) and sleep disorders (30.8 %) [23].

A small Spanish study with participation of 35 COVID-19 patients aged 20 to 60 years old, which was conducted 10–35 days after discharge from the hospital, demonstrated that patients who were complaining of headache, anosmia, dysgeusia, diarrhea, and also those who required oxygen therapy, had poorer cognitive functions (long-term episodic memory, temporary memory capacity, attention, regulatory functions, processing speed and naming) vs. asymptomatic patients [24].

Alemanno F., et al. (2021) analysed a group of 87 COVID-19 patients and demonstrated that in the subacute stage the majority of them (80 %) had significant cognitive impairments, including deficit of short-term and long-term memory, regulatory functions, abstract thinking, attention, speech and spacial and time orientation. One month after discharge from the hospital, 70 % of patients still had signs of cognitive dysfunction [3].

Provisional data obtained 7 months after NCVI for a group of 3762 patients confirm impaired memory, short-term memory and regulatory functions which affect the ability to get back to work [25].

A study by Chinese scientists evaluated a year-long trend of cognitive changes in elderly people who had COVID-19. 3233 patients at the age of 60 years old and older were studied. Exclusion criteria were as follows: pre-infection cognitive disorders, concomitant nervous disorders or a family history of dementia, as well as severe heart diseases, hepatic and renal disorders, cancer. The cognitive status was followed up for 6 and 12 months. After screening, the study group comprised 1438 post-COVID-19 patients. The control group included 438 subjects. As a result, cognitive trends were divided into 4 categories: stable cognitive development, early cognitive impairment, late cognitive impairment and progressive cognitive impairment. Approximately 3.3 % of post-COVID-19 patients had dementia, 9.1 % were diagnosed with mild cognitive impairment 12 months after discharge from the hospital. It is worth mentioning that dementia and MCI were observed in 15 % and 26.15 % of patients with severe NCVI, respectively. The incidence of dementia and MCI did not differ in subjects with mild NCVI and non-infected controls [26].

The heterogeneity of the data on the assessment of cognitive functions in post-COVID patients is of certain interest. A Spanish study of 179 patients who were healthy before the disease (22 to 81 years of age) who underwent evaluation of cognitive functions approximately 2 months after discharge demonstrated that over a half (58 %) had MCI in at least one out of four cognitive domains (more often in aptitude for learning and verbal fluency) [27].

At the same time, in an Australian group of 78 patients who were tested 2–3 months after NCVI (only 12 % of them required hospitalisation for severe NCVI), objective cognitive impairments were observed in 10 % of patients (most often in a test for the speed of psychomotor abilities) [28].

Based on neuropsychologic data, Moretta P., et al. (2022) identified that 44 % of post-NCVI patients had reduced cognitive efficiency (RCE). Patients with RCE did not significantly differ from patients with normal cognitive efficiency (NCE) in demographics and a number of clinical parameters, however, they had a longer bed regime and D-dimer levels. Also, this group had more severe NCVI, clinically more significant symptoms of posttraumatic stress disorder and more complaints of daily cognitive disorders (poor attention concentration, difficulty with choice of words in speech, reduced ability to remember and process new information). Besides, patients with RCE had significantly higher levels of anxiety and usually demonstrated lower EuroQol-5D scores (EQ-5D, European Quality of Life Questionnaire). Of note, patients with RCE more frequently had changes in circadian blood pressure (BP) (non-dipper), confirming the association between cognitive impairments and changes in circadian BP rhythm [29].

Nersesjan V., et al. (2022) found statistically significant reduction in MoCA scores in patients after mild COVID-19 vs. subjects who were not infected with SARS-CoV-2 [30]. Although the absolute difference in MoCA scores of 0.8 score between cases and controls after 6 months may seem insignificant [30], an earlier Swedish population demonstrated that this difference

equaled to cognitive ageing of 8 years for people of 60 years of age [31]. Taking into account pandemic nature of NCVI, it can result in significant cognitive impairments globally.

Comorbidities, Cognitive Status and Post-COVID Syndrome

A recent Chinese study added new information on dynamic changes in cognitive functions in COVID-19. Severe COVID-19 was associated with a higher risk of early, late and progressive reduction in cognitive functions, while mild COVID-19 was associated with a higher risk of early cognitive impairment adjusted for the age and comorbidity, which were risk factors for cognitive disorders [26].

Yelin D., et al. (2022) included 1027 subjects with post-COVID symptoms into an analysis. A majority of subjects had mild COVID-19 (n=763, 74.3 %). They identified six patterns of symptoms: cognitive, pain-related, pulmonary, cardiac, anosmia-dysgeusia and isolated headache (Fig. 1). The cognitive pattern was the main pattern of symptoms accounting for 26.2 % of dispersion; the remaining patterns accounted for 6.5–9.5 % of dispersion. The cognitive pattern was higher in patients who were treated in outpatient settings during the acute period of the disease. The nature of pain syndrome was associated with severity of primary disease; it was higher in female subjects and increased with the age. The pulmonary pattern was related to the underlying disease and severe acute onset of COVID-19. Just 6 factors account for 64.6 % of differences between recovered patients [32].

Cognitive impairments in survivors of acute respiratory distress syndrome (ARDS) vary from 70 % to 100 % upon discharge from hospital, from 46 % to 80 % in 1 year and 20 % in 5 years [33].

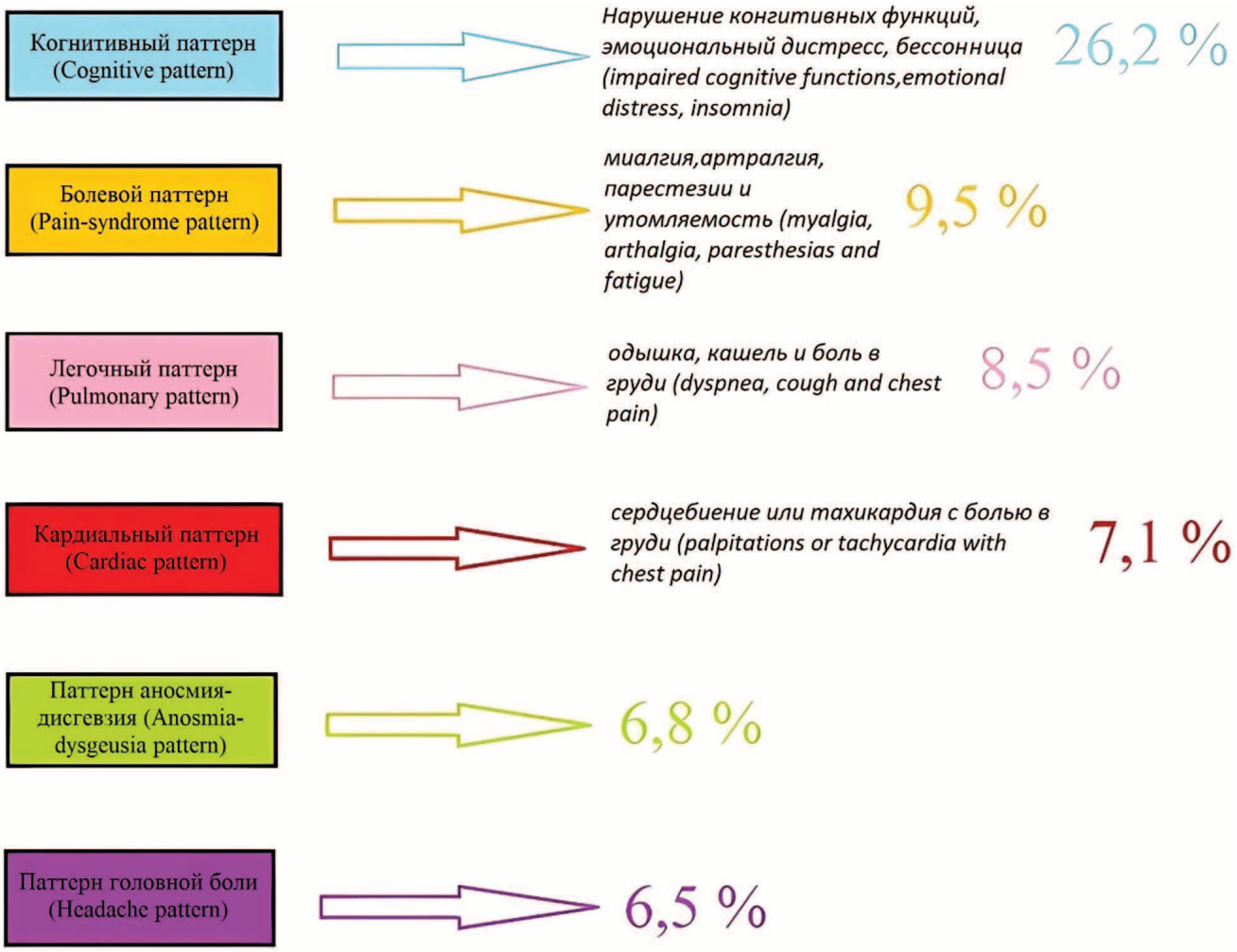

Figure 1. *Symptoms patterns of post-COVID-19 syndrome*

Note. Cognitive pattern combining impaired cognitive functions, emotional distress, insomnia (explaining 26.2 % of variance). Pain-syndrome pattern combining myalgia, arthralgia, paresthesias and fatigue (9.5 % of variance). Pulmonary pattern combining dyspnea, cough and chest pain (8.5 % of variance). Cardiac pattern combining palpitations or tachycardia with chest pain (7.1 % of variance). Anosmia-dysgeusia pattern — isolated anosmia and dysgeusia (6.8 % of variance). Headache pattern — isolated headache (6.5 % of variance)

It demonstrates that severe COVID-19 which is often complicated by ARDS can have long-term impact on cognitive functions. It is also consistent with the conclusion that high-flow oxygen therapy during acute COVID-19 which can reduce oxygen deficit can protect against post-infection cognitive impairment [34].

Considering that arterial hypertension is the most common pathology in NCVI comorbidities and is related to cognitive status, unstable BP can have an important role to play in cognitive disorders after COVID-19 [29].

One observational study demonstrated that high BP associated among other things with pro-inflammatory status and oxidative stress, functional and structural vascular changes and vascular dysregulation, can cause cerebral disorder in small vessels, stroke, reduced brain volume and, finally, dementia [35].

Taquet M., et al. (2021) demonstrated that COVID-19 was associated with an increased risk of dementia during 6 months after NCVI [36].

UK-Biobank study (Kuo C.-L., et al., 2020) demonstrated that APOE4 homozygotes (adjusted for pre-existing dementia, arterial hypertension, coronary heart disease and type 2 diabetes mellitus) have 2.2-fold risk of COVID-19 infection, cognitive impairments (up to dementia) and particularly negative outcomes (death rate was 4.3 times higher than in APOE3 homozygotes) [37].

Conclusion

Taking into account that in a number of countries the COVID-19 pandemic is still very active and is expected to last for a long period, long-term neuropsychic and cognitive consequences may be a serious healthcare concern. Follow-up of patients who had NCVI are required to better understand long-term cognitive consequences of COVID-19, especially in patients with severe NCVI.

CNS pathologies in NCVI usually include signs of non-specific neural inflammation with microglia activation and lymphoid infiltration, ischemic/hypoxic encephalopathy, astrocytosis, acute cerebrovascular event, secondary myeline damage and microthrombosis.

Neuropathological data for COVID-19 are relatively scarce, since study groups are small and heterogeneous both in regard to the course of NCVI and comorbidity.

Elderly patients are susceptible to a high risk of severe COVID-19 and more severe neuropsychic and cognitive impairments due to, among other things, comorbidities. Associations between cognitive consequences of NCVI and clinical status of the patient have been understudied. The issue of diagnostics of cognitive functions in post-COVID syndrome is yet to be resolved, taking into account NCVI complications, comorbidities and APOE4 carrier status.

It is also reported that, against better judgement, ICU admission is a protective factor for cognitive functions. It can be assumed that patients with ARDS/ respiratory distress who underwent intensive care were suffering less from cerebral hypoxia compared to patients undergoing non-invasive lung ventilation, although this therapy is more aggressive.

Therefore, the known risk factors of cognitive impairment in COVID-19 patients are elderly age, severe COVID-19, ICU admission.

Described study results should be taken into consideration by practitioners, since even mild/subclinical cognitive disorders affect functional outcomes in recovering COVID-19 patients. However, further perspective studies are required to analyse neurocognitive disorders in NCVI, to develop diagnostic and therapeutic algorithms, including management of patients with post-COVID syndrome.

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