Cognitive dysfunctions in the course of SARS-CoV-2 virus infection, including NeuroCOVID, frontal syndrome and cytokine storm (Review)

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Abstract. During the coronavirus disease 2019 (COVID-19) pandemic, cognitive impairment of varying degrees of severity began to be observed in a significant percentage of patients. The present study discussed the impact of immunological processes on structural and functional changes in the central nervous system and the related cognitive disorders. The purpose of the present review was to analyse and discuss available information from the scientific literature considering the possible relationship between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection and cognitive impairment, including NeuroCOVID, frontal syndrome and cytokine storm. A systematic literature review was conducted using: Google Scholar, Elsevier and the PubMed database. When searching for materials, the following keywords were used: 'cognitive dysfunctions', 'SARS-CoV-2', 'COVID-19', 'Neuro-SARS2', 'NeuroCOVID', 'frontal syndrome', 'cytokine storm', 'Long COVID-19'. A total of 96 articles were included in the study. The analysis focused on the characteristics of each study's materials, methods, results and conclusions. SARS-CoV-2 infection may induce or influence existing cognitive disorders of various nature and severity. The influence of immunological factors related to the response against SARS-CoV-2 on the disturbance of cerebral perfusion, the functioning of nerve cells and the neuroprotective effect has been demonstrated. Particular importance is attached to the cytokine storm and the related difference between pro- and anti-inflammatory effects, oxidative stress, disturbances in the regulation of the hypothalamic-pituitary-adrenal axis and the stress response of the body.

Contents

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1. Introduction

In the course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection, clinical manifestations mainly occur in the respiratory system. As of September 29, 2023, according to World Health Organization estimates, there are 770,875,433 confirmed cases of coronavirus disease 2019 (COVID-19) infection. In this regard, 6,959,316 deaths were recorded, which corresponds to 0,9% of mortality (1). In the initial period of the pandemic, the activities undertaken focused mainly on the treatment of acute respiratory failure, which is the leading cause of death in infected patients (2). This was the third outbreak this century caused by coronaviruses. The two previous outbreaks were caused by SARS-CoV/SARS-CoV-1, which caused Severe Acute Respiratory Syndrome beginning in 2002, and MERS-CoV causing Middle East Respiratory

Syndrome, which was recognised in 2012. The aforementioned three viruses were detected in some patients with neurological symptoms in the cerebrospinal fluid and within the brain in post-mortem examinations (2,3). A previously published systematic review and meta-analysis showed the occurrence of nervous system symptoms in a number of patients. A decrease in neurocognitive functions was found during SARS-CoV-2 viral infection. In the acute phase of the disease, memory disorders, confusion, insomnia, depressed mood and anxiety were observed. The aforementioned symptoms affected between 27.9 and 41.9% of respondents (3). In the post-morbid phase, 32.2% of respondents experienced symptoms of post-traumatic stress. A total of ~15% of the respondents were diagnosed with depression and anxiety disorders with the simultaneous occurrence of chronic fatigue syndrome and fibromyalgia (3,4).

2. Etiology of cognitive dysfunction in patients with COVID-19 infection

SARS-CoV-2 activation occurs with the participation of proteases, such as transmembrane serine protease 2 (TMPRSS2). In order to enter host cells, the expression of the angiotensin-converting enzyme 2 (ACE-2) receptor is required (5). According to a previous study, the binding of ACE-2 to the spike (S) protein of SARS-CoV-2 is at least 10-fold more potent than in the case of other SARS viruses, which may significantly increase the incidence of infection (6). However, Rombel-Bryzek *et al* (7) analysed the differences in ACE-2 binding by SARS-CoV-1 and SARS-CoV-2 S proteins using isothermal titration calorimetry and showed that both receptor-binding domains (SARS-CoV-1 and SARS-CoV-2) bind to the hACE-2 with similar and high affinity but different thermodynamics.

Potential coreceptors or other receptors for infection have also been identified. These include the following: Integrins, glucose-regulating protein 78 (GRP78), vimentin, sialic acid, heparan sulphate, receptor tyrosine kinase (AXL), asialoglycoprotein receptor-1 (ASGR1), kringle containing transmembrane protein 1 (KREMEN1), furin, neuropilin-1, cadherin-17, CD133, CD147, CD209 and CD26 (8-12).

Previous studies have demonstrated the widespread expression of ACE-2 mRNA. Nevertheless, its level varies depending on the location. Kidney and heart cells, lung epithelial cells and vascular endothelium are characterised by high expression (13). Within the nervous system, these include neurons, oligodendrocytes, macrophages/microglia, astrocytes, ependymal cells, neural stem cells (NSCs)/non-parenchymal cells (NPCs) (Fig. 1). The aforementioned cells vary depending on their function, shape, size, subtype and location (11). Neuronal ACE-2 receptors are located mainly in the structures of the brain stem, which are responsible for the regulation of cardiac and respiratory functions (14-17).

The infection routes of the SARS-CoV-2 virus within the nervous system remain a topic of research. Potential ones include retrograde axonal transport and transneuronal invasion, with transmission through the intranasal and olfactory epithelium, as well as through the oral cavity, gustatory nerves and trigeminal nerve and lymphatic drainage. Additionally, the subject of research is infection through the skin, peripheral nervous system and intestinal vasculature. Hematogenous pathways include the route through the ventricular system and choroid plexus, damaged blood-brain barrier and infected immune cells (2,13). For a holistic approach to the impact of SARS-CoV-2 on the nervous system, both the mechanisms of infection, as well as the neurological-psychiatric effects and direct and indirect cellular consequences are important (13,18-23).

As a result of SARS-CoV-2 infection, anatomical and functional changes in the nervous system may occur. As a result of infection of the olfactory nerve, the virus can directly penetrate the brain. A weakened sense of smell or its loss is observed in patients with confirmed cognitive disorders and depressive disorders (3,24,25). There is also a known route through peripheral nerves using intersynaptic transmission (26,27). The results of studies on the presence of SARS-CoV-2 in the cerebrospinal fluid of the examined patients are ambiguous (28). The presence of the virus was confirmed in NSCs, neurons and microglia. Infections also involve ependymal cells, endothelial cells and astrocytes (27,29). In numerous patients with symptoms of the nervous system, the presence of SARS-CoV-2 was detected by reverse transcription-quantitative PCR (RT-qPCR). However, there are anecdotal studies of negative test results in this group of patients (28,30-34). The aforementioned differences may be related to the discrepancy in the time of collection of test samples as well as the stage of the patient's disease. An additional factor is the varying sensitivity of RT-qPCR tests. The presence of neurological symptoms and the presence of SARS-CoV-2 in the cerebrospinal fluid in some patients is evidence of the possibility of the virus affecting the nervous system. Nevertheless, this issue is a starting point for further research (28,30-34).

3. Cytokine storm and neuroinflammation

The main role in the pathogenesis of cognitive impairment in the course of COVID-19 is played by the cytokine storm, which activates numerous leukocytes, mast cells, macrophages and endothelial cells. As a consequence, significant amounts of chemokines and pro-inflammatory cytokines are released (27,35,36). The key released mediators that have a significant impact on the course of the cytokine storm include interleukins: Tumour necrosis factor-α (TNF-α), interferon-γ (IFN-γ), IL-6, IL-1, IL-1β, IL-2, IL-3, IL-8, IL-12, IL-17, IL-18, IL-33 and chemokines [C-C motif chemokine ligand 2 (CCL2), CCL5, CCL8, CCL11, C-X-C motif chemokine ligand 1 (CXCL1), CXCL10 and CXCL12] as well as granulocyte-macrophage colony-stimulating factor (GM-CSF) (35,37). In particular, the pathogenesis of the aforementioned phenomenon is related to the action of mast cells involved in the inflammatory and neuroinflammatory response (38-43).

The peripheral immune reaction may intensify or induce an acute or chronic neuroinflammatory response (44). SARS-CoV-2 viral infection may result in the activation of mast cells residing in the respiratory tract at the initial stage of the disease. At this level, they play the role of the body's first line of defence against infection. Thus, taking part in the direct elimination of the threat or in supporting the immune system response. Mast cells, having a role in inflammatory diseases, may also be associated with the genesis of neuroinflammatory

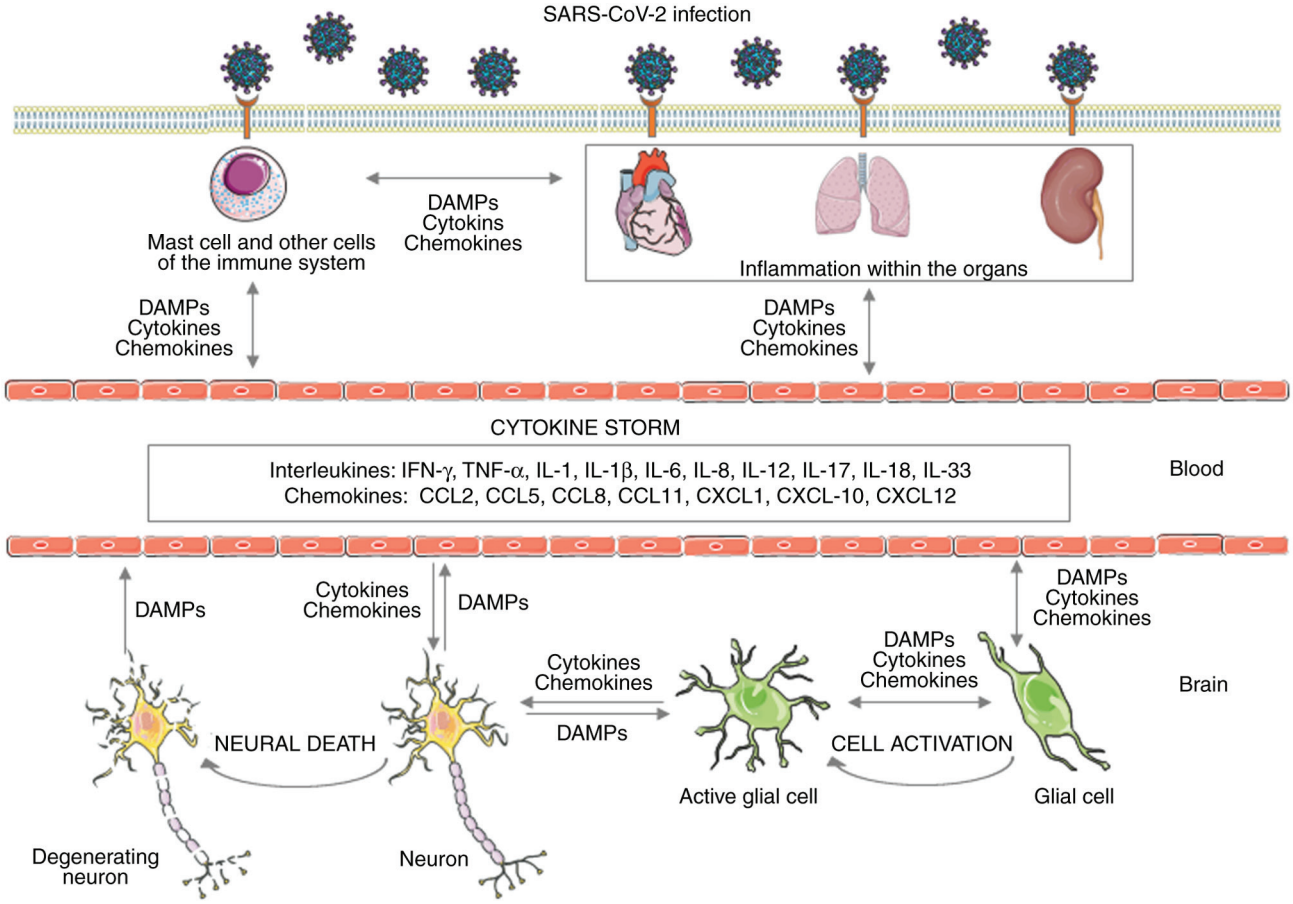

Figure 1. Systemic immune response to SARS-CoV-2 infection with particular emphasis on neuroinflammation. Figure was created using the Servier Medical Art Commons Attribution 3.0 Unported Licence [http://smart.servier.com (accessed 07.12.2023)]. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; DAMPs, damage-associated molecular patterns; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α; IL, interleukin; CCL, C-C motif chemokine ligand; CXCL, C-X-C motif chemokine ligand.

diseases, the occurrence of stress-related disorders, and may also participate in post-traumatic brain damage and the development of stroke. Mast cells occur in large numbers in the nasal passage and the meninges. They are characterised by high heterogeneity of morphology, varying degrees of response to specific stimuli and performing different protective functions. In the case of long-term protective effects, the nature of their response may change to a harmful response (41).

The cytokine storm results in an increased level of chemokines and pro-inflammatory cytokines secreted by mast cells, mainly including TNF-α, IL-1, in particular IL1B, and IL-6 (35,45,46). In addition, these cells secrete significant amounts of histamine, tryptase, granulocyte growth factor, proteases, as well as CC chemokine and ligand 2-CCL2 from the granules (35-37,45-47). Additionally, they can release leukotriene C4 (LTC4) and prostaglandin D2 (PGD2) at a significantly faster rate. Mast cells are also capable of synthesising further inflammatory mediators in the later stages of infection (48-50). The protease tryptase that is released from mast cell granules may also promote SARS-CoV-2 infection (49). An important aspect is that after entry, viruses can activate mast cells by influencing toll-like receptors and, as a result, increase the expression of inflammatory mediators. Additionally, these cells have the ability to detect damage-associated molecular patterns (DAMPs), which helps them detect and respond to infection with the SARS-CoV-2 virus. The infection is associated with increased levels of procoagulant factors, D-dimers and prolongation of prothrombin time (27,36,51,52). The occurrence of coagulation disorders, which may be associated with the formation of clots and an increased risk of cerebral bleeding, may be positively correlated with the occurrence of ischemic and haemorrhagic stroke and cognitive impairment. This may result in a deterioration of patients' condition, worse prognosis and increased mortality (53-57) (Fig. 1).

According to a previous study, the occurrence of neuroinflammation in severe cases in some patients could correlate with the occurrence of disorders such as cerebrovascular diseases, as well as being a risk factor for stroke, encephalopathy or epilepsy. The most common neurological symptoms include dizziness and headaches, fever, disturbances of consciousness, neuralgia, hyposmia and hypogeusia (58). A number of studies confirm the relationship between the aforementioned process and the occurrence of neuropsychiatric diseases. They indicate the relationship between the severity of central nervous system (CNS) dysfunction and the negative prognosis of patients (58-60).

4. Nerve vs. glial cell

ACE-2 expression in neurons and glial cells makes the CNS more susceptible to COVID-19 infection (61). Inflammatory

molecules secreted as a consequence by infected nerve cells can activate nearby immune cells, mainly remaining mast cells and glial cells. Additionally, other neurons and endothelial cells, pericytes and astrocytes are susceptible to this process. Infection of endothelial cells by SARS-CoV-2, which may be caused by the presence of the virus in the microcirculation, may result in bleeding and blood-brain barrier (BBB) dysfunction (62,63). This may result in the death of nerve cells, deterioration of cognitive functions, and even in very advanced cases, brain swelling, which poses a direct threat to life. Inflammatory factors of the cytokine storm can activate neurons, glial cells and subsequent mast cells, thereby exacerbating or causing acute and chronic neuroinflammatory reactions. Activated glial and immune cells as well as increased activity of cytokines and chemokines positively associate with the pathogenesis of neuroinflammatory and neurodegenerative diseases. These include Alzheimer's disease and Parkinson's disease (64,65). Infection of neurons by the SARS-CoV-2 virus may also directly result in their death (66,67). Thereby causing a greater release of PAMPs and DAMPs and contributing to the increased progression of neuroinflammation.

The susceptibility of white matter to be damaged as a result of ischemia is an element that reduces the mental performance of patients. Some cases of COVID-19 showed decreased cerebral perfusion, which correlated with decreased functioning of the white matter (68). An increasing number of studies suggested that the aforementioned may be related to the pathology of TDP-43 and tau proteins. Accumulation of amyloid beta has also been demonstrated. These changes also concerned the area of the hippocampus responsible for spatial and event memory. The observed memory deficits may be a precursor to dementia disorders and, consequently, contribute to the development of Alzheimer's disease (69-71).

The hippocampal system is a structure particularly susceptible to stress. It has been revealed that as a result of direct and indirect stress, the hypothalamic-pituitary-adrenal (HPA) axis is disturbed among the studied patients. Increased release of steroid hormones and the stress response of the body disturb the functioning of the hippocampal system. Excessive secretion of corticosteroids in stressful situations also negatively affects the amygdala area. Due to the decreased function of the prefrontal cortex, neurocognitive functions are limited (71,72). Patients who succumbed due to SARS-CoV-2 infection were characterised by increased concentrations of pro-inflammatory cytokines. The aforementioned relationship could be another stressor affecting cognitive functions.

Studies using TUNNEL staining and caspase 3 immunostaining reported increased neuronal cell death in the course of COVID-19 (73-76). Significant NSC/NPC cell mortality was also demonstrated. For other supporting cells within the nervous system, less data and researches are available. However, infection of these cells is associated with an immune response, inflammatory reaction and weakening of the neuroprotective function. This may promote the death of neighbouring uninfected cells (73,74).

Transcriptomic analysis revealed transcription defects, particularly in genes related to the response to hypoxia and cytokine storm (73-76). Increased expression of hypoxia inducible factor 1 subunit alpha (HIF1a) was observed in cells in a local hypoxia environment. The studies also showed impaired expression of genes related to intercellular connections, cell secretory function, and, as a result, potential impairment of the BBB and blood cerebrospinal fluid barrier (BCSFB). Furthermore, these studies indicated that the expression of vGLUT1 protein, a marker of presynaptic stimulation, was also reduced. In some cases, abnormal localization of the tau protein in the neuron body was identified (72). This localization was specific to pT231, correlating with cells producing caspase 3. Abnormal phosphorylation within the tau protein was associated with more frequent cell apoptosis. According to observations, this was more related to the response via type II interferon (INF-γ) than type I interferon (IFN-α/β) (73-76).

5. Neuro-SARS, cognitive dysfunction, and COVID-19 infection

In order to define neurological deficits associated with SARS-CoV-2 infection, the following terms were introduced: Neuro-SARS and neuroCOVID (77). It is estimated that in the acute phase of the disease, more than 1/3 of patients exhibit symptoms typical of neuroCOVID (78). These symptoms correlate with a more severe clinical course of the infection and significantly increase the risk of complications. The most common symptoms include loss of taste and smell, recurrent headaches and dizziness, qualitative disturbances of consciousness and depressive symptoms. It has been revealed that the severity of the disease may correlate with the number of lymphocytes in the blood and the current level of antibodies (78,79). Rare occurrences of encephalopathy, strokes and peripheral neuropathies have also been observed. They mainly concern older individuals with predominant immunodeficiencies (78).

The aforementioned group of patients is characterised by a diverse set of cognitive disorders. They include mild deficits, selective, specific and generalised changes with significant symptom severity. The symptoms most frequently mentioned in the literature include: Impaired concentration, attention and executive functions, as well as short-term memory disorders (77-80). According to the authors of most studies, the assessment of cognitive dysfunction in this group cannot be limited only to the use of the so-called screening tests (78-81).

The next group of symptoms includes a syndrome of cognitive dysfunction - frontal syndrome. Its features were observed by Helms *et al* (82) and Zhou *et al* (83) in their research. To assess cognitive functions, Zhou *et al* (83) used the Continuous Performance Test and the Trail Making Test. In both studies, symptoms of cognitive impairment syndrome were observed in a significant group of patients. A correlation of the obtained results with the concentration of pro-inflammatory cytokines and C-reactive protein was also demonstrated (83). These inflammatory processes, which are often chronic, may negatively affect the functioning of the developing brain. Their influence on the development of neurodegenerative diseases and the manifestation of some mental diseases, mainly schizophrenia, is suggested. The symptoms include decreased ability to think abstractly, self-control and assess the own capabilities of the individual. Short-term memory disorders and reduced effectiveness of attention-related processes are also observed (82,83).

Table I. Selected neurological disorders occurring in patients in the course of COVID-19.

Author	Percentage (%)	Neurological symptom	(Refs.)
Mao *et al*, Helms *et al*	36	All patients infected with the SARS CoV-2 virus	(78,82)
Mao *et al*	25	Direct involvement of the CNS	(78)
Lechien *et al*	88	Gustatory dysfunctions	(90)
Lechien *et al*	85.6	Olfactory dysfunctions	(90)
Lechien *et al*	11	Anosmia before other clinical symptoms	(90)
Mao *et al*	5.7	Ischemic stroke in severe cases	(78)

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CNS, central nervous system.

6. Long COVID-19

Prolonged COVID-19 infection may cause psychiatric and neuropsychiatric disorders in patients and their environment (3,60,84). Stressful conditions during the disease worsen the prognosis of patients. As a result, prolonged infection may result in post-stress depression, anxiety and other disorders, including post-traumatic stress disorder (27,36,85,86). Mental stress caused by long COVID-19 results in increased secretion of corticotropin-releasing hormone (CRH) as well as activation of the HPA axis. This process is intensified by the production of additional amounts of CRH and other neuropeptides by mast cells, thereby contributing to the deepening of neuroinflammation (40).

Numerous mediators of the immune response secreted by mast cells play an important role in the pathogenesis of stress-induced diseases, including neuroinflammatory and autoimmune diseases. The presented pathologies related to uncontrolled cytokine storm and neuroinflammation may contribute to neurodegeneration and related disorders (40,41,87). Cytokine storm increases the influx of inflammatory mediators into the brain due to BBB disruption. A defect in this barrier may facilitate the entry of the SARS-CoV-2 virus and, consequently, an uncontrolled influx of immune cells into the brain. In a prolonged immune response in the CNS, activated immune cells, including mast cells and glial cells, release significant amounts of additional inflammatory chemokines and cytokines, increasing inflammation (41,65). A number of studies showed that mast cells may play a significant role in acute and chronic diseases caused by SARS-CoV-2 viral infection. Prolonged infection, in addition to neurological symptoms, may result in other systemic disorders, including the previously mentioned coagulation disorders (88,89). Additionally, it may worsen existing respiratory diseases, including asthma and obstructive pulmonary disease (2,9,49,88). Acute and chronic stress caused by the aforementioned infection may worsen neuroinflammatory disorders, including nerve injuries, traumatic brain injury and stroke (89).

According to studies, a total of 36% of patients infected with COVID-19 experienced neurological symptoms, of which 25% had CNS-related symptoms (64,78,82). In this group, 88% of patients reported taste disturbances and 85.6% of smell disturbances (90). In 11% of patients, anosmia preceded other clinical disorders (90). In total, 5.7% of patients with neurological symptoms experienced ischemic stroke (78) (Table I).

7. Prevention and treatment of cognitive dysfunction in the course of COVID-19

COVID-19 infection may result in both short- and long-term complications and symptoms related to inflammatory processes correlating with the activation of immune cells and the cytokine storm (49,91). Due to the confirmed relationship between neuropsychiatric diseases and infections, especially viral ones, primary and secondary prevention is recommended. The first one involves health education and the use of recommended vaccinations. In the case of secondary prevention, activities aimed at early detection of the disease and implementation of appropriate treatment are involved. In the next stage, activities are based on limiting the medium- and long-term negative effects of the disease process on the patient's health (91). Research on the impact of inflammatory processes in the course of SARS-CoV-2 on the functioning of the CNS suggests enhancing neuroprotective effects. Knowledge about the pathophysiological processes in the course of the aforementioned infection is still developing. The presented research results suggest actions aimed at stabilising proper perfusion and, as a result, adequate oxygenation and nutrition of nerve cells (92,93). A significant part of research deals with the impact of inflammation and immunological factors on the aforementioned processes. Modifying their action is a potential way to reduce the short- and long-term negative consequences of SARS-CoV-2 infection. Conducting neurological and psychiatric diagnostics and psychological tests is necessary in the event of worsening neurological symptoms (94,95).

Research indicates that inhibiting the activation of mast cells and their subsequent degranulation may contribute to reducing the intensity of the inflammatory process. The use of antiviral and anti-inflammatory drugs, or those with a neuroprotective effect, may support the therapeutic process of patients and at the same time positively correlate with an improved prognosis (41,64,96).

8. Conclusions

The presented studies demonstrated the impact of SARS-CoV-2 on cognitive dysfunctions of various nature and severity. A significant impact of immunological factors related to the response against SARS-CoV-2 on impaired perfusion, neuroprotective effect and functioning of nerve cells has been proven. Particular

attention is paid to the cytokine storm and the related disproportion between pro- and anti-inflammatory effects, oxidative stress, disturbances in the regulation of the HPA axis and the body's stress response. An additional element are changes in the expression of genes related to the response to hypoxia and cytokine storm, such as: HIF1a, pT231, vGLUT1, genes related to intercellular connections within the BBB and BCSFB barriers, as well as IFN-γ and IFN-α/β (69-72). These mechanisms directly affect the metabolism of endothelial cells, nerve cells and BBB dysfunction. These processes may be the starting point for cognitive function disorders, including mild, selective, specific and generalised deficits with significant symptom severity. Primary and secondary prevention related to neurological and psychological diagnostics, as well as symptomatic treatment is recommended. The processes occurring as a result of SARS-CoV-2 infection require further research and analysis in order to improve understanding of the pathophysiological mechanisms and expand the possibilities of prevention and treatment.

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Availability of data and materials

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Authors' contributions

JS and TK conceived and designed the study, wrote and prepared the draft of the manuscript, collected the data and created the table. JS and ARB completed the study design and carried out data interpretation. ARB verified the contents, revised the manuscript and prepared the figure. RJB verified the contents and critically revised and edited the manuscript. All authors contributed to manuscript revision, and read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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