Acute and long-term neurological disorders in patients with coronavirus infection

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Currently, patients who attribute their complaints and disorders to the past COVID-19 are turning to a neurologist for a consultation. One should consider dangerous complications of COVID-19 such as stroke, including cerebral venous thrombosis, autoimmune encephalitis and myelitis, posterior reversible encephalopathy syndrome, Guillain–Barré syndrome. Disorders of consciousness, disorders of smell and taste, headache and dizziness are significantly more often present in the acute period of COVID-19. Long-term persistence of complaints and disorders after COVID-19 is regarded as post-COVID syndrome (PCS). Neurological complaints and disorders in a patient who has had COVID-19 are often caused by the development or exacerbation of a comorbid disease, including primary headache, musculoskeletal pain in the neck and back, various vestibular disorders, Alzheimer's disease, anxiety and depressive disorders. Unfortunately, in real clinical practice, these diseases are often not diagnosed, patients are observed with a diagnosis of PCS, and it is not taken into account that the basis for diagnosing PCS is the exclusion of other diseases that can explain complaints and disorders in a patient who has suffered from COVID-19.

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After the pandemic caused by the SARS-CoV-2 virus, more and more patients who attribute their complaints and disorders to the past COVID-19, turn to a neurologist for a consultation. Long-term persistence of these complaints and disorders is regarded as post-covid syndrome (PCS), or "Long-COVID" [1, 2]. However, there is still a lot of uncertainty in this issue, which makes it necessary to carefully explore a new nosology. Uncertainty concerns the mechanisms of the effect of SARS-CoV-2 on the central and peripheral nervous system, the ability of the virus to persist, the presence of unique clinical features in the neurological manifestations of PCD, as well as the treatment and course of the disease. It is important not to miss the dangerous complications of COVID-19, such as cerebral venous thrombosis, Guillain–Barré syndrome, acute disseminated encephalomyelitis, posterior reversible encephalopathy syndrome, and others, the description of which is quite fully presented in the literature [3–6]. In this article, we tried to reflect the current understanding of COVID-associated symptoms, building a presentation from the most dangerous and specific complications to relatively benign and non-specific neurological manifestations of PCD, as well as comorbidities.

Mechanisms of the central nervous system damage

Mechanisms of central nervous system injury in SARS-CoV-2 infection include: direct infection, via transneuronal and angiotensin-converting enzyme 2 (ACE-2) mediated pathways, hypoxic and immune-mediated injury. At present, the hypothesis that the neurotropic properties of the virus allow it to evade the immune response and achieve latency, which can determine the ability to cause both acute and delayed neurological disorders, has not been proven, but not refuted either. The transneuronal mechanism of brain damage consists in the primary penetration of the virus from the nasal cavity through the olfactory nerve system (olfactory epithelium – olfactory bulb) into the primary olfactory cortex with further hypothetical spread through neuronal circles: amygdala nuclei (emotional disorders), hypothalamic nuclei (neuroendocrine control), hippocampus (memory impairments), thalamic nuclei (sensory and motor impairments), frontal and insular cortex (cognitive impairments – CI) and brainstem (autonomic dysfunction) [3, 7]. The interaction of the virus with ACE-2 receptors can lead to an increase in the permeability of the blood-brain barrier (BBB) and, due to the high density of receptors in neurons, to its persistence with a potential delayed development of demyelination and neurodegeneration [8, 9]. It should be noted that these hypothetical effects do not yet have experimental and clinical confirmation. The main evidence of the possibility of virus invasion into the central nervous system is the development of a disorder of smell and/or taste with verification using magnetic resonance imaging (MRI) of such phenomena as reversible hyperintensity of the rectus gyrus and olfactory bulbs [10], accumulation of contrast and microbleeding in the olfactory bulbs [11], as well as atrophy of the olfactory bulb after 3 months of anosmia [12]. On the other hand, the absence of the virus and intrathecal synthesis of antibodies to it in the cerebrospinal fluid (CSF) has now been proven [13].

Acute specific neurological complications

The most severe neurological manifestations of SARS-CoV-2 infection, described at the beginning of the pandemic, include: encephalitis, myelitis, acute disseminated encephalomyelitis, Guillain–Barré syndrome and stroke. Their development occurs, as a rule, in the first 2 weeks after the onset of systemic or respiratory symptoms of the disease [3–6, 14].

COVID-associated stroke. A meta-analysis of data from 31,634 patients with COVID-19 showed that the risk of ischemic stroke is increased by 2.4 times with infection [15]. Another meta-analysis (n=26,691) shows an ischemic stroke rate of 2%, with a 35% rate of cryptogenic stroke [16]. The average interval between the onset of the disease and the development of a stroke is 10 days. Stroke associated with COVID-19 is characterized by a severe course and high mortality [17, 18]. There are three main mechanisms for the development of COVID-associated stroke: COVID-associated coagulopathy (may cause paradoxical embolism), vasculitis, and cardiomyopathy [19–21]. Intracerebral hemorrhage with COVID-19 develops much less frequently, and it is extremely difficult to prove its association with the infection.

Cerebral venous thrombosis. Represents a rare complication of COVID-19, with only 57 cases (0.08%) included in the largest systematic review. It occupies 4.2% in the structure of acute cerebrovascular events in COVID-19. In 9 out of 10 patients, cerebral venous thrombosis develops after respiratory symptoms, on average after 13 days. 67% of patients have multiple localization of thrombosis, in 37% of cases the deep venous system is affected. Parenchymal hemorrhage is detected in 42% of patients, hospital mortality reaches 40% [22].

Autoimmune damage of brain and spinal cord. Autoimmune encephalitis, which develops by the mechanism of molecular mimicry, is a rare parainfectious complication of COVID-19. An analysis of 24 adult cases published in 2022. The development of encephalitis does not depend on the severity of the infectious process and may even be the first clinical manifestation. Antibodies detected in autoimmune encephalitis include: anti-NMDA (most common), anti-CASPR2, anti-MOG, anti-GAD, etc. Limbic encephalitis develops most often, less often – cerebellitis and brainstem encephalitis. Against the background of immunotherapy (glucocorticoids, intravenous immunoglobulin – IVIG), 67% of patients experience a complete or almost complete recovery [23].

There are also descriptions of cases of development of acute disseminated encephalomyelitis against the background of SARS-CoV-2 infection, which occurs more often in children, usually has a monophasic course, causes multifocal damage of the hemispheres, brainstem and spinal cord (involving gray and white matter) and manifests itself as polymorphic focal neurological symptoms in combination with encephalopathy. The most severe variant of encephalomyelitis is acute necrotizing hemorrhagic leukoencephalitis. Compared to the disease before the SARS-CoV-2 pandemic, the cases reported so far are characterized by older age (mean 53–55 years), a short interval between infection and the onset of neurological symptoms (1–2 weeks), greater disability and mortality reaching 36% [24–26].

Acute transverse myelitis, manifested by ascending sensory and motor disorders in combination with dysfunction of the pelvic organs, is a rare postinfectious complication of COVID-19 [27–29]. In 58% of cases, tetraparesis develops. 70% of patients have longitudinally extended acute transverse myelitis involving four or more segments of the spinal cord. The interval between the onset of an infectious disease and the appearance of myelitis symptoms varies from 10 days to 6 weeks [30].

Posterior reversible encephalopathy syndrome (PRES). It usually develops in patients with renal insufficiency, autoimmune diseases and acute hypertension (particularly in eclampsia) and is associated with endothelial dysfunction and BBB disruption, which leads to reversible vasogenic edema of the occipital and parietal lobes with the development of seizures, headache, cortical blindness and sensory symptoms [7]. The largest systematic analysis includes 56 cases of SARS-CoV-2-associated PRES: the average age of patients was 56 years, and in half of the cases there was a severe course of the infectious disease. The average interval between hospitalization and the development of PRES was 20 days. Three out of four patients experienced complete or partial recovery [31].

Guillain–Barré syndrome. It is a parainfectious complication of COVID-19. Analysis of data from 136,746 patients showed that the prevalence of the syndrome in COVID-19 is 0.15% (15 per 100,000 people), which is 3.3 times higher than in uninfected individuals. 41% of patients with Guillain–Barré syndrome and SARS-CoV-2 have an olfactory disorder, and 43% have cranial nerve damage. The clinical outcome of the disease is comparable in patients with and without COVID-19. The prevalence of Miller–Fisher syndrome and acute motor axonal neuropathy does not differ from the population [32, 33].

Damage of the cranial nerves. As part of the clinical picture of COVID-19, damage of cranial nerves II, III, V, VI, VII, VIII, and X has been described [34]. Idiopathic neuropathy of the facial nerve is observed in 0.08% of patients with COVID-19 [35]. The largest systematic analysis included 20 cases of Bell's palsy as the only neurological manifestation of severe infection (mean age of patients was 40 years, half had a history of palsy) [36]. Data on the relationship between the incidence of Bell's palsy and COVID-19 remain controversial [37]. There are also reports of cases of vestibular neuritis associated with COVID-19 [38, 39]. Most of the described clinical cases are characterized by spontaneous recovery.

Data on the clinical picture, examination and treatment of patients with the main acute neurological complications of COVID-19 are shown in the table.

Non-Specific Neurological Symptoms

In addition to the clinical syndromes outlined above, COVID-19 can present with a wide range of non-specific neurological symptoms. Thus, in the acute period of the disease, 20–40% of patients experience headache, dizziness, impaired taste and smell, emotional disorders, and sleep disturbance [40]. A meta-analysis of data from early studies (first half of 2020), which included 13,480 patients, showed that the most common neurological symptoms in the acute period of the disease are: myalgia (28.1%), taste disturbance (19.6%), smell disturbance (18.3%), headache (12.1%), dizziness (11.3%) and encephalopathy (9.4%) [41].

Neuropsychiatric manifestations. The frequency of neuropsychiatric manifestations of COVID-19 depends on the severity of the disease, reaching 70% in patients with severe forms (confusion, agitation) [40]. The most striking acute neurological manifestation of the disease is encephalopathy, which is usually understood as impaired consciousness, mental disorders, confusion, agitation, delirium, or dysregulatory syndrome. Are these symptoms specific to COVID-19? It is likely that the mechanisms of development of cognitive and neuropsychiatric symptoms in SARS-CoV-2 infection are of a secondary nature – as a manifestation of hypoxia, inflammation, fever, and side effects of drugs. The most universal manifestation of a severe infection that develops in every tenth patient during hospitalization (more often in the elderly and people with CI) is delirium [42].

Clinical presentation, examination and treatment of major acute neurological complications of COVID-19

Complication	Clinical features	Examination	Primary treatment
Stroke	Acute development of focal cerebral neurological deficit	Emergency neuro- and angioimaging, blood tests	Reperfusion therapy (intravenous thrombolysis, mechanical thrombectomy) if indicated, secondary prevention
Cerebral venous thrombosis	Headache, seizures, focal neurological deficit	Emergency neuro- and angioimaging	Anticoagulant therapy
Autoimmune encephalitis	Mental status alterations, psychomotor agitation, memory impairment, delirium, ataxia, seizures	CSF analysis, MRI	Pulse steroid therapy, IVIG
Acute disseminated encephalomyelitis Acute necrotizing hemorrhagic leukoencephalitis	Multifocal neurological deficit, encephalopathy	MRI of the brain	Pulse steroid therapy, IVIG
Acute transverse myelitis	Sudden development of para- or tetraparesis with dysfunction of the pelvic organs	MRI of the spinal cord	Pulse steroid therapy
Posterior reversible encephalopathy	Headache, seizures, blurred vision	MRI of the brain	Symptomatic therapy
Guillain–Barré syndrome	Ascending weakness and/or numbness in limbs, weakness of mimic muscles (especially bilateral), dysarthria	Analysis of CSF (protein-cell dissociation); electroneuromyography	Plasmapheresis or IVIG

Cognitive impairment. Short-term CI in COVID-19 affects the attention and cognitive processing speed (45% of patients), executive functions (33% of patients) as well as memory (28% of patients) [40] and are commonly described as "brain fog". Assessment of the neuropsychological profile of CI in hospitalized patients (n=57) at the stage of rehabilitation (1.5 months after the onset of the disease; 77% of patients required mechanical ventilation, 66% of patients developed delirium in the acute period) showed that mild CI was observed in 47% examined, moderate – in 25% and severe – in 9%. The most frequently noted deficits were working memory (55%), attention shift (47%), divided attention (46%), and information processing speed (40%). It is noteworthy that cognitive dysfunction was not associated with the duration of mechanical ventilation [43].

The medium-term effects of COVID-19 on cognition are well understood. In the study of Mazza et al. [44] (patients with a history of pneumonia; n=226) showed that 3 months after COVID-19, 78% of patients had a decrease in at least one cognitive domain. In half of the patients there was a violation of control functions and psychomotor coordination. At the same time, CI were associated with the level of systemic inflammation and persistence of depression. In a study by Mattioli et al. [45] (n=120), 4 months after a mild illness, the results of cognitive testing did not differ from those of the comparison group, but the levels of anxiety, depression, and stress were higher. At the same time, in patients treated in the intensive care unit (n=52), there was a decrease in executive functions while maintaining the global cognitive status. CI were not associated with hypoxia, diabetes mellitus, arterial hypertension, and the duration of treatment in the intensive care unit, but were associated with age [46]. 6 months after COVID-19 (n=380), CI was detected in half of the patients; anxiety, depression, fatigue, sleep disturbance – in 62%. Notably, 47% of patients were unable to return to work. Patients with neurological symptoms during initial hospitalization had a worse functional outcome after 6 months [47].

Hypometabolism in the frontal and parietal lobes, according to positron emission tomography with fluorodeoxyglucose, observed on average after 1 month, can be considered as a cause of short- and medium-term CI after COVID-19 [48].

A study conducted in Wuhan (China; n=3233) showed that 12.5% of elderly patients had CI one year after COVID-19. A more severe course of an infectious disease is associated with a higher risk of early – the first half of the year (odds ratio – OR – 4.87) and late – the second half of the year (OR 7.58) of cognitive decline, as well as its progression (OR 19) [49]. In a study performed in the USA (n=242), CI occurred 1 year after COVID-19 in 50% of patients who did not have cognitive status abnormalities before the disease. Between the 6th and 12th months of observation, improvement in cognitive functions occurred in 56% of the examined [50].

A study of brain changes in 785 patients from the UK Biobank cohort (age 51 to 81 years) showed that after an average of 141 days, patients who underwent COVID-19, compared with the control group, showed a decrease in gray matter volume in the parahippocampal gyrus, lateral orbitofrontal cortex and insula, especially in the left hemisphere [51].

It has been shown that, on average, 8 months after COVID-19, 16% of patients with a mild form of the disease, 33% with a moderate form, and 35% with a severe form ignore memory problems and other CI [52].

Emotional disorders. According to a systematic analysis of 8 publications, the incidence of depressive symptoms 12 weeks or more after COVID-19 ranges from 11 to 28%, while the incidence of clinically significant depression and/or severe depressive symptoms ranges from 3 to 12% [53].

Cochleovestibular disorders. As shown in a meta-analysis of 12 publications, the prevalence of hearing loss, tinnitus and dizziness is 3.1; 4.5 and 12.2%, respectively [54]. In the study by Gallus et al. [55] (Italy; n=48) demonstrated that within 2 weeks after the second negative swab, 8.3% of patients with COVID-19

have complaints of hearing loss, 4.2% – tinnitus, 10 .3% – dizziness, 8.3% – imbalance. At the same time, pure-tone audiometry and a video impulse head impulse test were normal. In another study (Saudi Arabia; n=301), 4% of patients with COVID-19 have late and persistent audiovestibular symptoms [56]. A multicenter study conducted in Italy found that within 30–60 days after the diagnosis of COVID-19, 18.4% of patients had complaints of balance disorders, and 23.2% of patients had tinnitus [57]. A clinical case of bilateral tinnitus without hearing loss after COVID-19 has been described [58].

Headache. In a multicenter study conducted in Spain (n=905), the average duration of headache with COVID-19 was 14 days, but cephalgia persisted for more than 3 months in 19% of patients, and more than 9 months in 16% of patients. The intensity of headache in the acute period of the disease was associated with its longer duration [59]. A meta-analysis of 235 publications (n=28,438) showed that the prevalence of post-COVID headache averaged 47.1% at the time of admission, 10.2% after 30 days, 16.5% after 60 days, 10.6% after 90 days and 8.4% after 180 days or more [60].

Musculoskeletal pain. Musculoskeletal pain is one of the leading symptoms of COVID-19 [61]. Myalgia, arthralgia, or fatigue occurs in 90% of patients. At the same time, the severity of myalgia correlates with the severity of the disease, while arthralgia is inversely related to it [62–64]. Musculoskeletal pain, in particular back pain, is a typical manifestation of PCS [65] and persists for 1 year after acute illness in 10% of patients [66]. The frequency of musculoskeletal pain reaches 45% 8 months after hospitalization. Chronicity risk factors include: female gender, history of musculoskeletal pain, the presence of myalgia and cephalgia in the acute phase, as well as the duration of hospital treatment [67].

Peripheral autonomic failure. One of the manifestations of PCS is orthostatic intolerance, including orthostatic hypotension and postural orthostatic tachycardia syndrome. Orthostatic hypotension has been reported in 10–41% of patients with PCS [68, 69]. Persistent tachycardia in PCS is often a manifestation of postural orthostatic tachycardia syndrome, which is a persistent increase in heart rate by 30 beats per minute or more for 10 minutes of standing, manifested by a feeling of palpitations, chest pain, and intolerance to physical or orthostatic activity [70, 71]. In the study by Blitshteyn et al. [71] described a series of 20 patients with autonomic failure after COVID-19. Of these, 15 had postural orthostatic tachycardia syndrome, three had neurocardial syncope, and two – orthostatic hypotension. During 6–8 months of follow-up, 17 patients had residual autonomic symptoms, 12 patients could not return to work. In a study by Shouma et al. [69] (n=27) showed that in the first 4 months after an acute infection, 93% of patients experienced dizziness (lightheadedness), 22% – orthostatic headache, 11% – syncope, 11%m-hyperhidrosis and burning pain. When testing autonomic functions, sudomotor functions were impaired in 36% of patients, cardio-vagal – in 27%, cardiovascular adrenergic – in 7% of patients. The most common type of dysfunction was orthostatic symptoms without tachycardia or hypotension (41%), 22% of patients met the criteria for postural orthostatic tachycardia syndrome, and 11% had borderline criteria for orthostatic intolerance.

Postcovid syndrome. Neurological symptoms of PCS include central (fatigue, brain fog, headache, sleep disturbance, CI, emotional disturbances, dizziness, dysautonomy) and peripheral (muscle weakness, myalgia, hyposmia, hypogeusia, hearing loss/tinnitus, sensorimotor disorders – hypesthesia, dysesthesia, tremor) [1].

As defined by The National Institute for Health and Care Excellence (NICE) 2021, PCS is a collection of signs and symptoms that develop during or after an infection, last more than 12 weeks, and cannot be explained alternative diagnosis. Among the neurological manifestations are cognitive ("brain fog", problems with memory and concentration) and psychiatric (anxiety and depression) [72].

Studies within the framework of the PCS concept show that cognitive dysfunction is one of the most common persistent symptoms, after fatigue, and occurs in 70% of patients [73, 74]. A meta-analysis of data from 10,530 patients showed that 32% of patients had “brain fog” 3 months or more after COVID-19, sleep disturbance in 31%, memory loss in 28%, anxiety in 23%, decreased attention – in 22% and depression – in 17% of patients. Notably, the incidence of sleep disturbance, anxiety, and depression increases over time (3–6 months versus >6 months) [74]. The development and manifestations of PCS do not depend on the initial severity of COVID-19 [75]. One year after COVID-19, there are complaints of fatigue (in 38% of patients), impaired concentration and forgetfulness (25% each), sleep disturbance (22%), myalgia and weakness in the limbs (17% each), headache and sensory impairment (16% each), hyposmia (15%). It is noteworthy that when testing after 3 and 12 months from the onset of the disease, no positive dynamics of neurocognitive symptoms is observed: after a year, 18% of patients have CI, 6% have depression, and 29% of patients have anxiety [76].

Neurological complaints and disorders in a patient who has had COVID-19 are often caused by the development or exacerbation of a comorbid disease that may not have been identified before the development of COVID-19. Such diseases include primary headache, including migraine, tension headache, chronic daily pain, drug-induced headache, musculoskeletal (non-specific) pain in the neck and back, sleep disorders, various vestibular disorders, Alzheimer's disease and vascular CI, anxiety and depressive disorders. The development or exacerbation of these diseases could be caused not by the neurotropic effect of COVID-19, but by a number of circumstances associated with its course, including stress and physical inactivity, and in cases of severe COVID-19, prolonged bed rest, hypoxic disorders. When examining a patient, it is extremely important to identify these diseases and carry out their adequate treatment. Unfortunately, in real clinical practice, these diseases are not diagnosed, patients do not receive effective treatment, they are observed with a diagnosis of PCS, and it is not taken into account that the basis for diagnosing PCS is the exclusion of other diseases that can explain the complaints and disorders of a patient who has undergone COVID-19.

Conclusion

Thus, when examining a patient who has had COVID-19, one should take into account the possibility of specific causes: cerebral venous thrombosis, autoimmune damage of the brain and spinal cord, reversible encephalopathy syndrome, Guillain–Barré syndrome, cranial nerve damage, etc. In many cases, long-term complaints and disorders can be caused not only by PCD, but also by the exacerbation or development of neurological diseases not associated with COVID-19, the treatment of which can have a positive effect.

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