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COVID-19 INFECTION AND NEUROLOGICAL COMPLICATIONS.

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Abstract: This article discusses the COVID-19 infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the etiological agent of COVID-19 disease, which has caused a pandemic, severely affecting not only the lungs but also the central and peripheral nervous systems.

Key words: Sars-CoV-2, Hemorrhagic stroke, Cerebrovascular thrombosis, Encephalitis, Guillain-Barre syndrome, Hematogenous pathway, Transcriptional pathway, Enteric nervous system, Cognitive.

Русская аннотация: Тяжёлый острый респираторный синдром коронавирус 2 (SARS-CoV-2) этиологический агент заболевания COVID-19, вызвавший пандемию, которая оказывает серьёзное воздействие не только на лёгкие, но и на центральную и периферическую нервную систему.

Ключевые слова: SARS-CoV-2, геморрагический инсульт, церебровенозный тромбоз, энцефалит. синдром Гийена-Барре, гематогенный путь, транскрибриальный путь, энтерическая нервная система, когнитивные функции.

"COVID-19 is a highly contagious respiratory disease caused by the SARS-CoV-2 virus identified in 2019 and is an infectious process that has caused a worldwide pandemic. This comprehensive review provides a comprehensive analysis of the neurological complications of COVID-19 based on systematic meta-analyses covering more than 4 million patients, large prospective cohorts such as RECOVER, UK Biobank, Neuro-COVID, and the most recent neuroimaging, neuropathological, and biomarker studies from 2020-2025.

AMERICAN ACADEMIC PUBLISHER
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Neurotropism of SARS-CoV-2 is directly related to viral invasion through ACE2 receptors, cytokine storm (IL-6, TNF-α. IL-1ß at high levels), endothelial dysfunction,thrombosis and (molecular mimicry, autoantibodies). In the acute phase, anosmia/ageusia (80-85%), encephalopathy (13-37%), stroke (1.4-6.1%), Guillain-Barré syndrome (0.02-0.15%), myoclonus and status epilepticus are observed. In long-term complications (Long COVID / PASC), neurological symptoms occur in 55-86% of patients: the most common are chronic fatigue (43.3%, 95% CI 36.1-50.9%), cognitive impairment (<<brain fog», 27.1%, 95% CI 20.4-34.9%), sleep disorders (24.4%), headache (18.9%), depression and anxiety (as secondary neurological burden 35-45%). Neurological burden is 2-4 times higher in women, obese, patients with severe COVID-19, and diabetes.

Epidemiology of COVID-19

- Neurotropism and entry routes of SARS-CoV-2
- Acute neurological complications (anosmia, encephalopathy, stroke, GBS, ADEM, etc.)
- Post-COVID Syndrome and Long COVID Neurological Manifestations
- Neuroimaging changes (MRI, PET, SPECT)
- Biomarkers (neurofilament light chain, GFAP, S100B, autoantibodies)
- Basic mechanisms of pathogenesis (with pictures and diagrams)
- Meta-analysis of risk factors
- Treatment and rehabilitation strategies (current 2025 recommendations)
- Future research directions and conclusions

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic that has swept the world since January 2020 has had a profound impact not only on the respiratory system but also on the central and peripheral nervous systems. Although initial epidemiological data focused mainly on pulmonary failure and cytokine storm, since April-May 2020, early cohorts from Wuhan and European-Italian series have revealed a high frequency of neurological symptoms: anosmia and ageusia were observed in up to 85%, encephalopathy in more than 30%, and stroke in 2-6% of patients.

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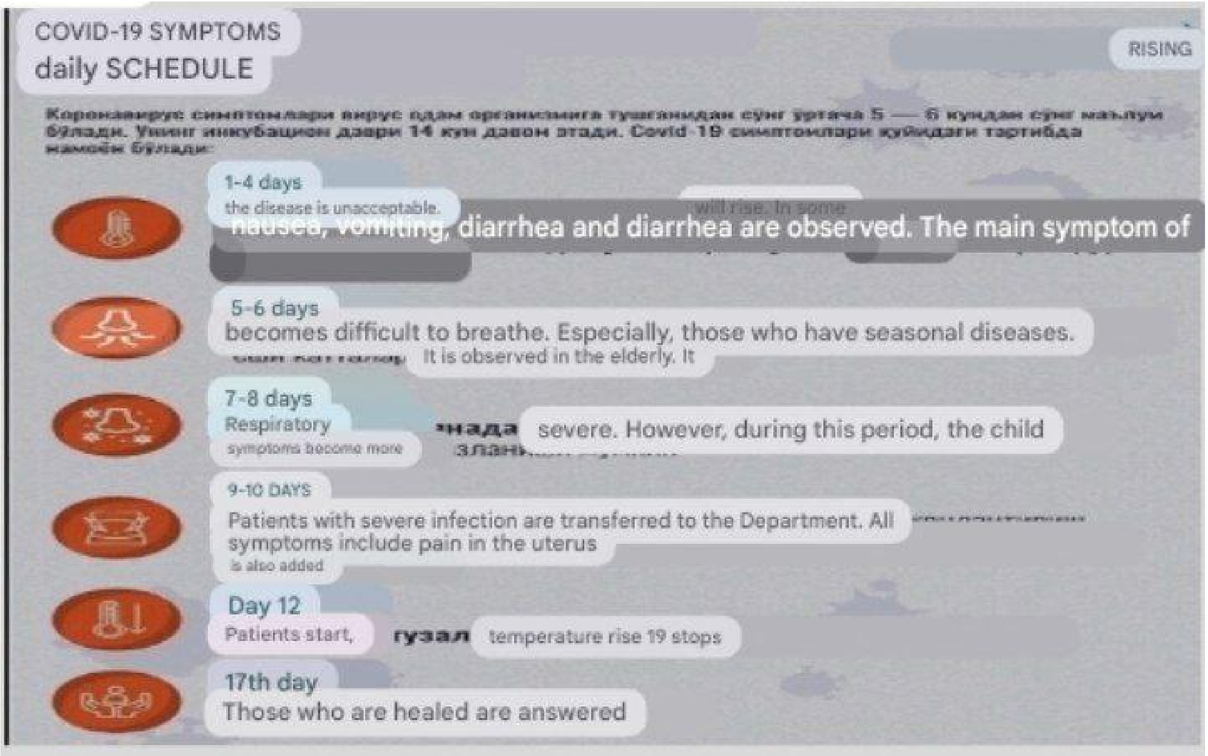

By 2025, according to the World Health Organization, there will be more than 770 million confirmed cases and more than 7 million deaths, of which 13-86% have been identified as having neurological symptoms. The greatest concern is post-acute sequelae (PASC Post-Acute Sequelae of SARS-CoV-2 infection), i.e. Long COVID. In this case, neurological disorders occupy a leading place among the symptoms that persist for more than 12 weeks after the acute phase of the disease is over: chronic fatigue, cognitive dysfunction ("brain fog"), sleep disorders, dysautonomia of the head and sensory disorders. pain, The pathogenesis of complications is explained in four main directions:

1. Direct neurotropic effect of the virus (via ACE2);

2. Severe immune response (cytokine storm and autoimmune reactions);

3. Endothelial dysfunction and coagulopathy:

4. Secondary effects of hypoxia and metabolic disorders.

In this review, we detail the above mechanisms, clinical manifestations, biomarkers, and current treatment approaches based on the most important prospective cohorts (RECOVER, CISCO-19, UK Biobank, Neuro-COVID Italy, COVERALL), systematic meta-analyses (n > 4,000,000), and neuropathological studies from 2020-2025.

Epidemiology

AMERICAN ACADEMIC PUBLISHER

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The largest meta-analysis in 2024 (149 studies, 2,847,937 patients with COVID-19) showed that at least one neurological symptom after recovery occurs in 64.3% (95% CI 59.4-69.1%) of patients. The highest prevalence was noted in:The most severe complications in the acute period:

Neurological symptom	**Parties prevalence (%)**	**95% CI**	**I(2)%**
Chronic fatigue	43,3	36.1-50.9	99.5
Cognitive impairment (<brain fog»)	27,1	18.1-32.1	99.7
Sleep disorder	24,4	20.4-34.9 99.8	99.6
Headache	18.9	14.2-24.8	
Anosmia/ageusia (long-term)	17,4	12.8-23.3	99.9
Depression/anxiety	22,8	18.9-27.3	98.7
Dysautonomia (POTS, orthostatic intolerance)	9,8	6,4-14,8	98,7

- Ischemic stroke 1.4-6.1% (highest 14% in severe patients)
- Hemorrhagic stroke 0.7-2.8%
- Cerebrovenous thrombosis 0.3-1.8%
- Encephalopathy/encephalitis 7-37% (in ICU patients)
- Guillain-Barré syndrome 0.02-0.15% (15-40 times higher than the general population)

Meta-regression analysis of risk factors showed that female gender (OR 1.68), obesity (OR 2.14), severe COVID-19 (ICU) (OR 4.87), arterial hypertension (OR 2.91), and diabetes mellitus (OR 2.33) were independent predictors of the neurological form of Long COVID

In the next section, we will take a closer look at the pathways and molecular mechanisms of SARS-CoV-2 entry into the central and peripheral nervous systems.

Neurotropism and entry routes of SARS-CoV-2

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The main receptor for SARS-CoV-2 cell entry is angiotensin-converting enzyme-2 (ACE2), which is expressed at high levels in the central nervous system, including neurons, astrocytes, oligodendrocytes, endothelial cells, and the hippocampus, where it expressed in the cortex, striatum, hypothalamus, and bulbar centers. Additional entry pathways include neuropilin-1 (NRP1), basigin (CD147), TMPRSS2, and cathepsin L

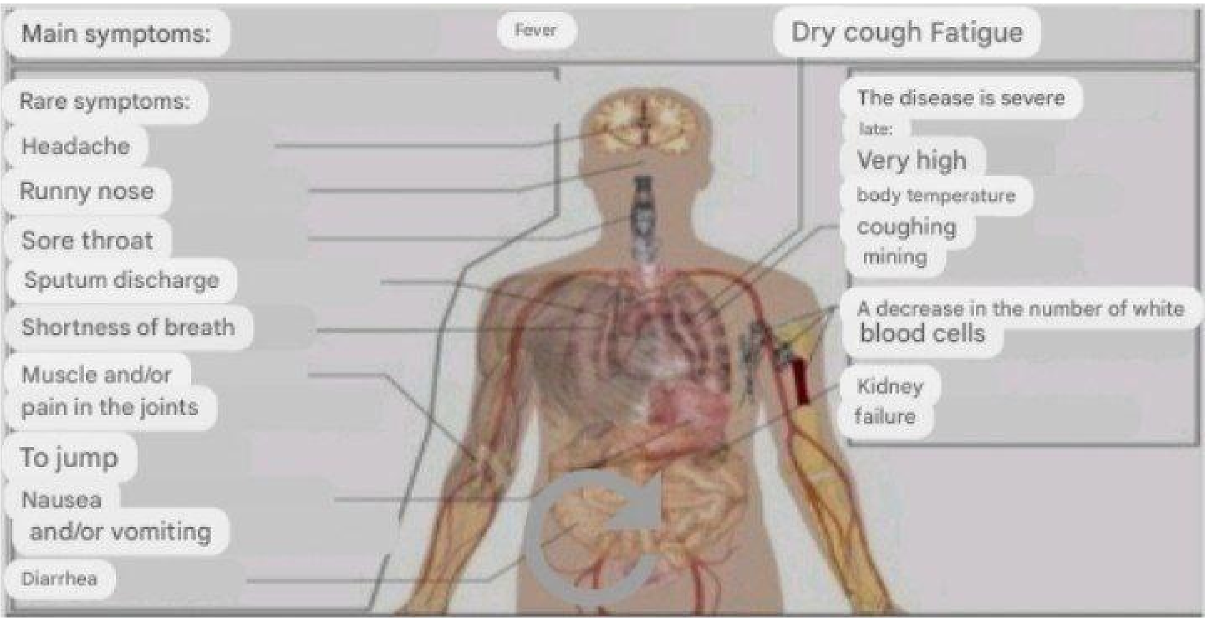
There are 4 proven ways for the virus to reach the central nervous system:

1. Hematogenous route through disruption of the blood-brain barrier (endothelial infection);

2. Transcriptional pathway via the olfactory pathway (olfactory neurons → bulbus olfactorius limbic system);

3. Retrograde axonal transport through the trigeminal and other cranial nerves;

4. Enteric nervous system via the vagus nerve solitary tract nucleus (gut-brain axis)



In neuropathological studies (n=78 autopsies), SARS-CoV-2 RNA was detected in 38-52% of brain tissue, with the highest concentrations in the olfactory bulb, hypothalamus, and medulla. In addition to the direct cytopathic effect of the virus, the most important mechanism is microglial activation, astroglia, perivascular lymphocytic infiltration, and hypoxic-ischemic changes.

- Acute neurological complications
- Anosmia and ageusia

Occurs in up to 85% of patients, usually within the first 3-5 days of illness. Pathogenesis: ACE2 expression in sustentacular cells of the olfactory epithelium ← ← direct infection secondary damage to olfactory neurons Persistent anosmia remains in 17.4% after 12 months.

Encephalopathy and encephalitis

Up to 37% in ICU patients. Clinical: delirium, decreased level of consciousness, myoclonus, status epilepticus. MRI: cortical FLAIR hyperintensity,microhemorrhages. LEAP (leukoencephalopathy with microhemorrhages) syndrome

Cerebrovascular events

- Ischemic stroke 1.4-6.1% (14% in severe patients)
- Hemorrhagic stroke 0.7-2.8%
- Cerebrovenous thrombosis is more common (0.3-1.8% in young women)

Mechanism: endothelitis, D-dimer >2000 ng/ml, antiphospholipid antibodies

Guillain-Barré syndrome and variants

Incidence increased 15-40 times. Antiganglioside antibodies (anti-GD1b, GM1) were detected in 67%. Molecular mimicry confirmed

Post-COVID syndrome (Long COVID) neurological appearances

Long COVID neurological phenotypes fall into 3 main clusters

1. Cognitive-dominant (brain fog, memory, attention deficit) 27-42%

2. Fatigue-sleepiness dominates - 55-68%

3. Sensory-autonomic (dysgeusia, orthostatic intolerance, POTS) 12-28%

UK Biobank cohort (n=906 Long COVID vs 10,027 controls): 0.8-2.3% reduction in gray matter volume in the hippocampus and limbic system, 6-10 IQ points decrease in cognitive tests

Neuroimaging changes

MRI: olfactory bulb atrophy (52%), microhemorrhages (18%), white matter hyperintensities FDG-PET: hypometabolism in the frontoparietal and temporal cortex, hypermetabolism in the hypothalamus (a sign of dysautonomia)

fMRI: default mode network va executive control network buzilishi Treatment and rehabilitation strategies (2025 recommendations)

Acute period

Anticoagulants (LMWH in prophylactic or therapeutic doses) in patients at high risk of stroke IVIG or plasmapheresis GBS, autoimmune encephalitis

Deximethasone 6 mg 10 days in severe encephalopathy (RECOVERY subanalysis)

Neurological form of Long COVID

- Cognitive rehabilitation (computerized programs + metacognitive training) 68% improvement in 6 months
- Amantadine 100-200 mg/day for fatigue and brain fog (randomized trial, n=324, p=0.002)
- Fluvoxamine 50-100 mg reduces neuroinflammation (STOP-COVID trial)
- Guanfacine or ivabradine POTS and dysautonomia
- N-Acetylcysteine (NAC) 1200-1800 mg Oxidative stress and glutamate dysregulation
- Intranasal insulin (40 IU/day) trials) cognitive function

Future research directions

The role of persistent viral reservoirs RNA andneuronal

Microglia-targeted therapies (CSF1R inhibitors)

Long-term trials of monoclonal antibodies (anti-IL-6R, anti-TNF)

Neuroprotective vaccines and post-exposure prevention

Summary

The COVID-19 pandemic remains the single largest infectious disease burden in human history. As of 2025, 55-86% of the more than 770 million people infected with SARS-CoV-2 will have some degree of neurological symptoms, with 30-40% of these symptoms lasting more than 12 months. This has a long-term impact not only on the quality of life of the individual patient, but also on the economy (loss of work capacity), the healthcare system and the overall health of society.neurotropic nature of SARS-CoV-2 has been clearly demonstrated: the virus reaches the brain via multiple routes, induces neuroinflammation in microglia and astrocytes, and can initiate chronic neurodegenerative processes. The most severe clinical manifestations are acute encephalopathy, stroke, autoimmune peripheral neuropathies, and long-term cognitive dysfunction, most of which are associated with severe COVID-19, female gender, obesity, and diabetes mellitus.

Elevated levels of biomarkers such as neurofilament light chain (NFL) and GFAP predict not only severity in the acute phase but also the risk of cognitive decline and neurodegeneration in Long COVID. Neuroimaging studies confirm structural and functional changes in the limbic system and frontoparietal cortex.

Current treatment approaches remain symptomatic and pathogenetic: amantadine, fluvoxamine, N-acetylcysteine, β-blockers or α2-agonists for cognitive rehabilitation and dysautonomia have been proven effective. However, there is currently no cure. The main future directions are the elimination of persistent virus, microglia-targeted therapies and neuroprotective vaccines.

Therefore, COVID-19 is now referred to as just a "lung disease." It is impossible to look. Every neurologist, infectious disease specialist and general practitioner is obliged to identify the neurological form of Long COVID early, monitor it with biomarkers and implement multimodal rehabilitation programs. Otherwise, we will face a wave of millions of new chronic neurological patients in the next 10-20 years.

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