Direct and Indirect Neurological Signs of COVID-19

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Objective. To systematize the neurological manifestations of COVID-19. **Materials and methods.** A systematic computerized analysis of all currently available publications on the neurological manifestations of COVID-19 was undertaken (2374 reports in PubMed) by topological data analysis. **Results.** A set of interactions between infection with SARS-CoV-2, metabolic impairments affecting neurotransmitters (acetylcholine, dopamine, serotonin, and GABA), enkephalins, and neurotrophins, micronutrients, chronic and acute inflammation, encephalopathy, cerebral ischemia, and neurodegeneration (including demyelination) was described. The most typical neurological manifestations of COVID-19 were anosmia/ageusia due to ischemia, neurodegeneration, and/or systematic increases in proinflammatory cytokine levels. COVID-19 provoked ischemic stroke, Guillain–Barré syndrome, polyneuropathy, encephalitis, meningitis, and parkinsonism. Coronavirus infection increased the severity of multiple sclerosis and myopathies. The possible roles of the human virome in the pathophysiology of COVID-19 are considered. A clinical case of a patient with neurological complications of COVID-19 is described. **Conclusions.** In the long-term perspective, COVID-19 promotes increases in neurodegenerative changes, which requires special neurological rehabilitation programs. Use of cholinergic drugs and antihypoxic agents compatible with COVID-19 therapy is advised.

Keywords: COVID-19, neurological symptoms, complications, cholinergic drugs.

Introduction. Coronavirus COVID-19 infection (ICD-10 U07.1), due to SARS-CoV-2 virus (NCBI genome NC_045512.2), is highly contagious and produces complications including acute respiratory failure and lesions to many organs (particularly the liver, kidneys, and heart). The lack of specific therapy, especially in severe forms of the disease (up to 15% of cases), is involved in the high risk of lethal outcomes.

It was initially felt that this coronavirus infection was limited to damaging the respiratory system. it has now become clear that COVID-19 affects not only the liver and kidneys, but also the nervous system [1]. Neuroinvasiveness is known for many human coronaviruses (OC-43, 229E, MERS, and SARS-CoV-1) [2], and SARS-CoV-2 also shows tropism for CNS and peripheral nervous system (PNS) cells [3]. About 36% of patients with the severe form of COVID-19 experience one or another neurological complication [4] (including cerebrovascular diseases, encephalopathies, and Guillain–Barré syndrome [5]).

Neurological manifestations induced by SARS-CoV-2 virus are due to hyperinflammatory and hypercoagulatory states, direct viral invasion of the CNS and PNS, and postinfectious immune reactions. The neurological manifestations of COVID-19 (particularly hyposmia and anosmia) often precede the typical signs of infectious diseases (hyperthermia, cough, throat pain, etc.) [6].

Acute inflammation induced by COVID-19 can develop into a chronic phase and enhance neurodegenerative processes, which can have long-lasting consequences for the CNS and PNS. Formation of neurological complications is more likely in severe forms of COVID-19 accompanied by a so-called cytokine storm (especially on the background of comorbid pathologies – obesity, type 2 diabetes mellitus,

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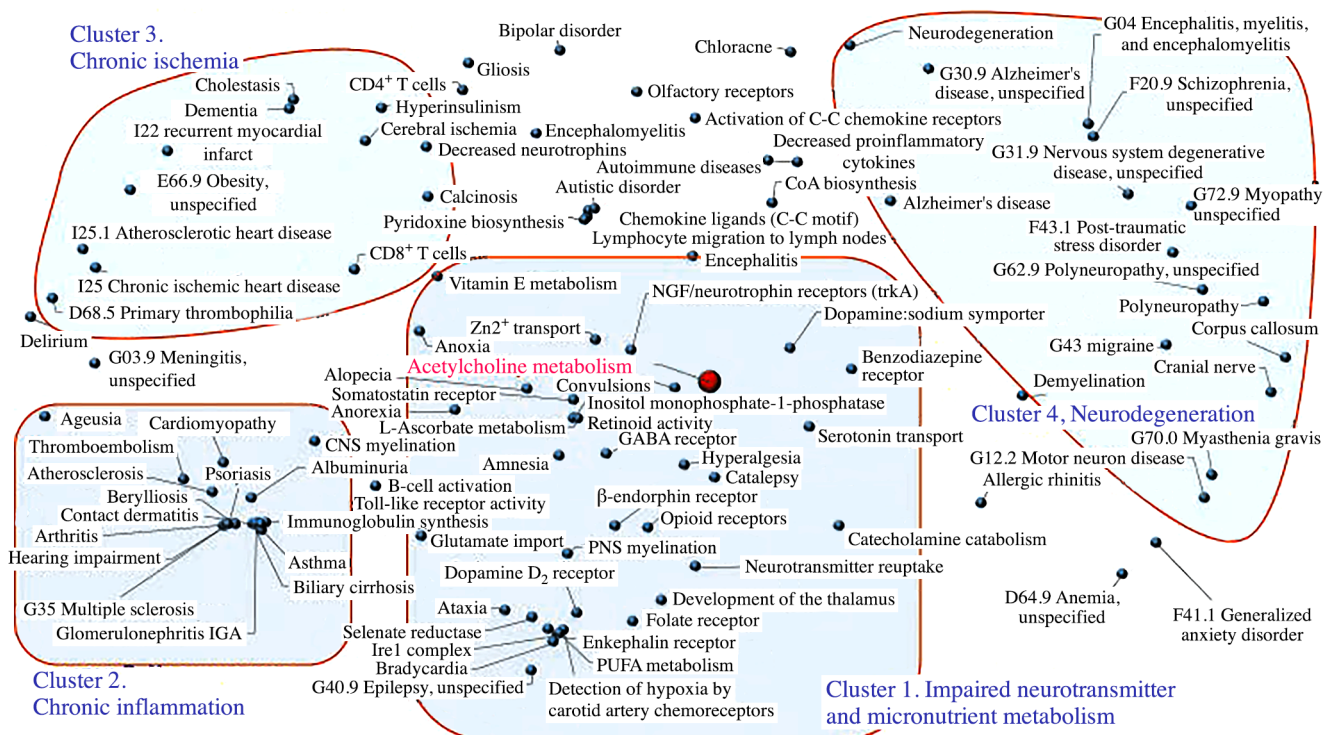
Fig. 1. Metric diagram showing a map of the molecular neuropathophysiology of COVID-19. Distances between points corresponding to terms are inversely proportional to the occurrence of combinations of terms in the study set of publications (the closer two points, the more frequently the combination of the two corresponding terms was used). ICD-10 diagnoses are given, along with individual symptoms, syndromes, and the corresponding biological processes. Biological activities are shown using the international GO (Gene Ontology) nomenclature without codes.

atherosclerosis, liver pathology). A diet with a high content of saturated fats, simple sugars, and animal protein (which overall constitutes the "western" diet) also increases the severity of the disease and its neurological sequelae [7]. Such a diet, especially on the background of a deficiency of adaptogenic micronutrients (zinc, magnesium, manganese, selenium, and vitamins A, C, D, and B$_{12}$, polyphenol compounds, etc.), not only stimulates the development of chronic inflammation, but also impairs innate immunity against DNA- and RNA-containing viruses [8].

We present here a systematic computerized analysis of the scientific literature on the neurological manifestations of COVID-19. The search "COVID-19 AND (encephalopathy OR neurolog* OR brain OR neuron OR neuronal)" was applied to the PubMed biomedical database and yielded 2374 references. We carried out a systematic computerized analysis of this set of publications using contemporary big data analysis methods developed in the framework of topological [9, 10] and metric [11, 12] approaches to recognition/classification tasks.

Results of Systematic Computerized Analysis. Systematic analysis of the literature yielded 127 informative biomedical terms distinguishing publications on the neurology of COVID-19/SARS-CoV-2 from publications in a control set. The control set of publications consisted of 2400 articles selected randomly from 48281 articles found with the query "COVID-19 NOT encephalopathy NOT neurolog* NOT brain NOT neuron NOT neuronal." Among the terms identified were neurological symptoms characteristic of COVID-19 and about 30 ICD-10 pathologies whose courses could be adversely impacted by coronavirus infection.

Annotation of the terms identified in terms of the molecular-biological processes indicated (in accordance with the international GO (Gene Ontology) nomenclature) [13] extracted the 42 most informative terms which were found significantly more frequently in the set of publications on COVID-19/SARS-CoV-2 than in the control set (4–140 times more frequently, $p < 0.05$ for each of the 42 terms). This yielded a map of the molecular pathophysiology of the neurological manifestations of COVID-19 (Fig. 1).

Analysis of the diagram by metric grouping [9–11] showed that the most informative biomedical terms distinguishing publications on COVID-19/SARS-CoV-2 were grouped into four main clusters: cluster 1, "Impaired metabolism of neurotransmitters and micronutrients;" cluster 2, "Chronic and acute inflammation;" cluster 3, "Chronic ischemia;" and cluster 4, "Neurodegeneration."

COVID-19 infection is indirectly associated with a set of impairments to neurotransmitter metabolism. For example, the term "GO:0008291 Acetylcholine metabolism" was located at the center of the overall metric diagram, pointing to an interaction between many of the neurological manifes-
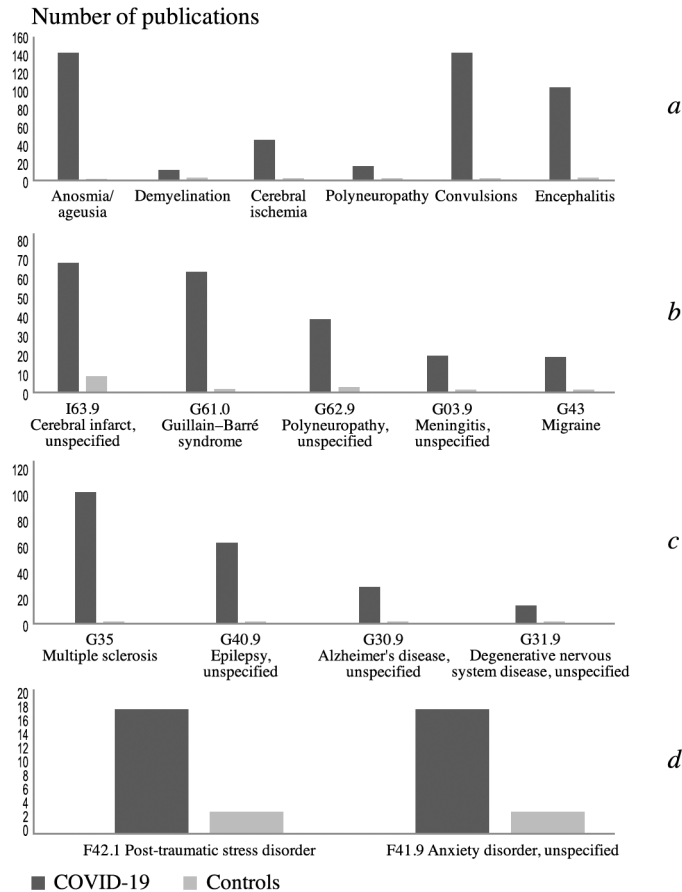
Number of publications

Fig. 2. Classification of the most informative keywords for symptoms and ICD-10 diagnoses. *a*) Neurological symptoms and sequelae of coronavirus infection; *b*) pathologies provoked by COVID-19; *c*) pathologies exacerbated in COVID-19; *d*) neuropsychiatric sequelae of quarantine measures.

tations of COVID-19 and impairments to choline-dependent anti-inflammatory signal pathways. In addition, coronavirus infection can impair the activity of β-endorphin, enkephalin, and neurotrophin receptors and intervenes in the homeostasis of dopamine, serotonin, and GABA.

The corresponding impairments to neurotransmitter metabolism are probably associated with the sharp increase in the background of acute and chronic inflammation (cluster 2) due to the "cytokine storm," which also stimulates the development of neuron demyelination. These processes can be attenuated in conditions of increased supply of a number of micronutrients (folates, pyridoxine (vitamin B_6) retinoids (vitamin A), L-ascorbate, monoinositol, zinc, selenium, and ω-3-polyunsaturated fatty acids) to adequate levels. Restoration of the activity of the corresponding neurotransmitter pathways can also be achieved using neurotransmitter metabolism modulators (for example cytidylphosphocholine to activate cholinergic neurotransmission, etc.).

The effects of coronavirus SARS-CoV-2 will increase significantly when the patient has pathology with a strong chronic inflammatory component (osteoarthritis, asthma, atherosclerosis, biliary cirrhosis, glomerulonephritis, multiple sclerosis, psoriasis, etc.) (see cluster 2 in Fig. 1). Chronic in-

flammation will promote more severe impairments to myelination in the CNS, greater activation of B-lymphocytes, elevated synthesis of immunoglobulins, increased activity of toll-like receptors (which enhance the formation of a "cytokine storm"), thromboembolism, and renal damage (albuminuria).

Acute and chronic inflammation and activation of thrombus formation processes make known contributions to the pathophysiology of chronic cerebral ischemia (see cluster 3 in Fig. 1) associated with atherosclerosis and arterial calcification (especially on the background of obesity), $CD4^+$ and $CD8^+$ T-cell dysfunction, and decreased synthesis of neurotrophins. These processes increase the risk of developing vascular dementia and cardiovascular pathology [14].

In addition, acute and chronic inflammation induced by coronavirus SARS-CoV-2 promotes demyelination, polyneuropathy, and, overall, an acceleration in the rate of neurodegenerative pathologies (see cluster 4 in Fig. 1), which includes diagnoses such as G30.9 Alzheimer's disease, unspecified, G31.9 Degenerative diseases of the nervous system, unspecified, and G62.9 Polyneuropathy, unspecified. Neurodegenerative changes in the PNS promote impairments to muscle function (G70.0 Myasthenia gravis, G72.9 Myopathy, unspecified) and others [15].

TABLE 1. Incidences of Various Neurological Manifestations on the Background of COVID-19 (results of original research and meta-analyses cited here). Manifestations Are in Order of Descending Mean Frequency

Manifestation	Frequency, %	Notes
Anosmia/ageusia	5–88	Both symptoms can arise simultaneously; early symptomatology persisting throughout the duration of illness
Myalgia	11–54	Linked with fatigue, anomalous levels of creatine kinase and inflammatory markers
Headache	8–34	Unspecified
Vertigo	9–25	Unspecified
Hypoxic encephalopathy	5–9	More severe cases are also known – necrotic and hemorrhagic encephalopathy, encephalomyelitis (<1%)
Cerebrovascular diseases	2–6	Mainly ischemia (rarely – hemorrhagic), including cases accompanied by venous thrombosis
Meningitis/encephalitis	4–7	Acute, viral
Epileptic seizures	1–3	–
Neuralgia	<2	Unspecified
Rhabdomyolyis		–
Guillain–Barré syndrome	<1	Including acute motor axon neuropathy, Miller Fisher syndrome
Ataxia, convulsions		Accompany encephalopathy, stroke

Classification of the more informative keywords as ICD-10 diagnoses demonstrates the complexity of associations between COVID-19 infection and neurological manifestations (Fig. 2). Firstly, infection itself is characterized by a particular neurological symptomatology (anosmia, ageusia, headache). Secondly, COVID-19 provokes a number of sequelae such as I63.9 Cerebral infarct, unspecified, demyelination, G62.9 Polyneuropathy, unspecified, G61.0 Guillain–Barré syndrome, and G03.9 Meningitis, unspecified. Thirdly, COVID-19 exacerbates the course of various serious neurological diseases (G35 Multiple sclerosis, G40.9 Epilepsy, unspecified, G30.9 Alzheimer's disease, unspecified, and G31.9 Degenerative disease of the nervous system, unspecified. Fourthly, disproportionately strict quarantine stimulates the development of neuropsychiatric disorders F43.1 Post-traumatic stress disorder, and F41.9 Anxiety disorder, unspecified).

Neurological symptomatology characteristic of COVID-19 and the mechanism of neuropathogenesis in coronavirus infection, including disruption of the integrity of the blood–brain barrier (BBB), were then considered sequentially, and, separately, the most important neurological manifestations of COVID-19 – anosmia/ageusia, cerebral ischemia, encephalitis, meningitis, neurodegeneration, and demyelination – were also considered.

Neurological Symptomatology of COVID-19. CNS manifestations are entirely typical of coronavirus infection. For example, analysis of a dataset from patients from Wuhan hospitals ($n = 214$) showed that 25% of patients experienced impairment to CNS functions, including vertigo (17%), headache (13%), impaired consciousness (7.5%), acute cerebrovascular pathology (3%), ataxia (0.5%), and convulsions (0.5%) [1]. Retrospective studies of neurological manifestations in severely ill patients with COVID-19 ($n = 86$) showed that 65% displayed at least one neurological symptom. Twenty patients (23.3%) showed symptoms affecting the CNS (including delirium, cerebrovascular diseases, and hypoxic-ischemic damage to the brain), while six patients (7%) had neuromuscular lesions [16].

Overall, the neurological symptomatology of COVID-19 in relation to the CNS includes manifestations such as headache, vertigo, encephalopathy (including the necrotizing hemorrhagic form [17]), encephalitis, acute disseminated encephalomyelitis, meningitis, ischemic hemorrhagic stroke, convulsions, Guillain–Barré syndrome, impaired consciousness [18], and neuropsychiatric disorders (depression, delirium, etc.). Refractory respiratory failure seen in patients severely ill with COVID-19 may be linked with penetration of SARS-CoV-2 virus into the respiratory center of the medulla oblongata [19]. In the CNS, COVID-19 infection is associated with myalgia, rhabdomyolysis, and Guillain–Barré syndrome. In addition, COVID-19 impacts the sensory sphere – anosmia and ageusia are typical.

Meta-analysis of seven investigations of COVID-19 patients ($n = 409$) showed that the main neurological changes were headache (16.8%), vertigo (13.9%), changes in consciousness (11.2%), acute viral meningitis/encephalitis (6.1%), hypoxic encephalopathy (5.6%), epileptic seizures (1.7%), neuralgia (1.2%), and ataxia (0.7%) [20]. The results of this and other studies are summarized in Table 1.

Analysis of EEG recordings from patients with COVID-19 ($n = 40$) showed that EEG traces without any abnormalities were seen in 42% of patients. The main neurological symptom in 58% of patients was clouding of

consciousness, accompanied by pathological epileptiform activity on the EEG. The most typical EEG anomalies in patients with coronavirus infection were peak-slow wave complexes, multifocal periodic discharges, or rhythmic δ activity. EEG changes were not stereotypical or specific to COVID-19 [21].

A retrospective cohort study of patients hospitalized with confirmed COVID-19 ($n = 3218$) showed that 14% of patients underwent brain MRI or CT scans. Acute stroke was the most frequent neuroimaging finding (up to 92.5% of patients).

Mechanisms of Pathogenesis of Coronavirus Infection. After SARS-CoV-2 virus particles contact the mucous membranes of the nose, eyes, throat, trachea, lower respiratory tract, or gastrointestinal tract, the virus stimulates increases in cytokine release, leading to tissue damage. In patients with weakened immunity, the virus can penetrate into the brain through the hemovascular network or peripheral nerves [23].

Neurological symptoms in COVID-19 patients are often transient in nature and disappear as patients recover. However, virtually no clinical observations assessing the long-term sequelae of coronavirus infection have been reported. Severe cases of COVID-19 show high levels of proinflammatory cytokines (interleukin (IL)-1β and IL-2, IL-2, -4, -10, and -18 receptors, interferon-γ, C-reactive protein, tumor necrosis factor (TNF)-α granulocyte colony-stimulating factor, chemokine CXCL10, monocyte chemoattractant protein MCP-1, proinflammatory macrophage protein MIF1α, ferritin, etc.). It is widely known that acute respiratory dysfunction and systemic inflammation promote reductions in cognitive functions [24]. Hyperactivation of proinflammatory factors, increases in the tendency to thrombus formation, and dysfunction of the vascular endothelium promote increases in the risk of cerebrovascular pathology and degenerative changes affecting nervous tissue.

The manifestations of COVID-19 may be linked with impaired cholinergic neurotransmission associated with the regulation of neuroinflammation. This hypothesis is based on the fact that some of the symptoms and clinical signs of COVID-19 (primarily the "cytokine storm") can be explained by dysfunction of the cholinergic anti-inflammatory signal pathways. For example, nicotinic acetylcholine α7 receptors are potentially involved in modulating the secretion of proinflammatory cytokines (and, thus, in suppressing the "cytokine storm"). Such clinical manifestations of COVID-19 as anosmia and thromboembolic complications may also be linked with dysfunction of the nicotinic cholinergic system [25]. Furthermore, infection with SARS-CoV-2 is associated with formation of antibodies to acetylcholine receptors [26]. Actions on nicotinic cholinergic receptors should therefore be regarded as a possible variant of the treatment of the neurological sequelae of coronavirus infection [27].

SARS-CoV-2 and Impaired BBB Integrity. An elevated background of inflammation, along with the possibility that SARS-CoV-2 virions penetrate the BBB, promotes damage to the brainstem respiratory center, exacerbating hypoxia in COVID-19 patients. Hypoxia stimulates further damage to nervous tissue and BBB degradation, which leads to the formation of the vicious circle: viral pneumonia – cerebral hypoxia – respiratory center damage – increased hypoxia and explains the frequent occurrence of neurological impairments in patients with severe infection [17].

It is important to note that in conditions of BBB damage in COVID-19 patients confirmed by PCR virus tests, the cerebrospinal fluid (CSF) may be completely free of virus particles [26]. For example, studies of CSF samples from patients with positive tests for SARS-CoV-2 ($n = 31$) evaluated BBB integrity using the so-called albumin coefficient Q (the ratio of albumin concentrations in the CSF and serum) with correction for age. Values of coefficient Q were abnormally elevated in 58% of the patients investigated, indicating impaired BBB integrity. At the same time, one study demonstrated the absence of SARS-CoV-2 RNA and antibodies to the virus in the CSF [27]. No traces of viral RNA were found in patients with polyradiculoneuropathy (Guillain–Barré syndrome) [28]. The state of the virome of the specific patient may play an important role in protection of the BBB from penetration by virus particles.

Anosmia/Ageusia. Impairments to smell and taste are typical symptoms in patients with mild and moderate forms of COVID-19. One multicenter study ($n = 417$) [29] reported olfactory dysfunction in 85.6% of patients and gustatory in 88.0%. Olfactory dysfunction appeared before other symptoms in 11.8% of cases. Among the 18.2% of patients without nasal respiratory obstruction or rhinorrhea, hyposmia or anosmia were seen in 79.7%. Anosmia linked with SARS-CoV-2 may be a COVID-19-specific symptom [30].

The probable mechanisms of development of anosmia in COVID-19 include: 1) direct damage to olfactory and gustatory sensory neurons by virus particles (especially on the background of zinc deficiency; 2) overactivation of inflammatory processes in nervous tissue; 3) impairments to the functioning of the olfactory and gustatory analyzers [31]. SARS-CoV-2 infects and damages mature and immature olfactory sensory neurons in experimental animals [32]. Intranasal inoculation of SARS-CoV-2 into the turbinates was followed by infiltration of inflammatory cells and increases in proinflammatory cytokines. These changes were maximal at 2–4 days after infection, at the peak of viremia.

It is important to emphasize that the anosmia/ageusia seen in most COVID-19 patients can be explained not only by ischemic damage to the CNS or viral damage to neurons in the olfactory bulbs, but also by sharp increases in IL-6 concentrations in sensory neurons. IL-6 is known to play one of several key roles in forming cytokine storms [8], promoting induction of acute-phase proteins (C-reactive protein, serum amyloid A, α1-antichymotrypsin, haptoglobin, fibrinogen, complement components, ferritin, etc.) and activation of the blood coagulation cascade, with disseminated intravascular coagulation.

The link between loss of olfaction and increased IL-6 concentrations was demonstrated in a clinical study of patients with COVID-19 and taste or smell disorders which do not require intense therapy ($n = 67$). The sinonasal outcome test-22 (SNOT-22) was used to assess olfactory function. The NHANES 2011–2014 [CDC, 2013b] questionnaire was used to evaluate gustatory functions. A venous blood sample was collected from each patient for determination of IL-6 levels. A statistically significant correlation was found between reductions in IL-6 levels and improvements in olfaction ($p < 0.05$) and taste ($p = 0.047$). The results demonstrated the key role of IL-6 in the pathogenesis of anosmia/ageusia in patients with COVID-19 [33] and showed that rapid restoration of olfactory and gustatory functions could be explained by a simple decrease in the IL-6 concentration occurring on recovery.

Chronic and Acute Cerebral Ischemia on the Background of COVID-19. A retrospective study showed that among patients with COVID-19 ($n = 219$), 4.6% developed acute ischemic stroke (AIS). These COVID-19 patients were significantly older (75.7 ± 10.8 years, compared with 52.1 ± 15.3 years among those without AIS, $p < 0.001$) and were more frequently characterized by a severe course of COVID-19 (81.8% vs. 39.9% without AIS, $p < 0.01$), and more often suffered arterial hypertension, type 2 diabetes mellitus, or ischemic heart disease ($p < 0.05$). These patients also showed higher levels of C-reactive protein (51.1 ± 30.0 mg/liter vs. 12.1 ± 11.0 mg/liter in patients without AIS) and D-dimers (6.9 ± 5.0 mg/liter vs. 0.5 ± 0.5 mg/liter in those without AIS, $p < 0.001$) [34].

Analysis of venous and arterial thromboembolic complications in COVID-19 patients hospitalized in Milan ($n = 388$, 66 ± 10 years, 68% men) showed that 16% of patients required intensive care and thrombolysis. Thromboprophylaxis was provided in all these patients. Despite this, thromboembolic complications were recorded in 28 patients within 24–72 h of admission to hospital. These complications included venous thromboembolism ($n = 16$), pulmonary artery thromboembolism ($n = 10$), AIS ($n = 10$), myocardial infarct ($n = 4$), and disseminated intravascular coagulation ($n = 8$) [35].

A meta-analysis of 39 studies of COVID-19 patients showed that the mean incidence of AIS in the combined cohort was 1.2% (54/4466). The age of these patients averaged 63.4 ± 13.1 years and the mean score on the NIHSS was 19 ± 8. Development of AIS was seen 10 ± 8 days after the onset of COVID-19 symptoms. Patients showed elevated D-dimer (9.2 ± 14.8 mg/liter), fibrinogen (5.8 ± 2.0 g/liter), and antiphospholipid antibody levels. Analysis of MRI scans pointed to a predominance of thrombosis and stenosis of the major vessels (62%), which was followed by multiple vascular lesions (26%) [36].

COVID-19 is an independent risk factor for AIS [37]. Studies in 2020 showed that among patients with AIS confirmed by CT cans ($n = 123$), 46.3% had COVID-19 (compared with 18.3% in controls, $p = 0.001$). After correcting for age, sex, and other vascular risk factors, COVID-19 infection was again significantly associated with AIS (OR 3.9, 95% CI 1.7–8.9, $p = 0.001$).

Diseases exacerbating COVID-19 (arterial hypertension, type 2 diabetes mellitus, ischemic heart disease, etc.) also increase the risk of neurological complications [38]. In particular, increased blood cholesterol levels can accelerate vasculopathy induced by SARS-CoV-2. Metabolism-associated comorbid diseases (obesity, diabetes mellitus) are usually accompanied by endothelial cell dysfunction making endotheliocytes more susceptible to viruses. Increasing endothelial inflammation, SARS-CoV-2 stimulates the formation of atherosclerotic plaques, thus provoking and exacerbating vasculopathy [39].

COVID-19-Associated Encephalitis and Meningitis. Coronavirus infection-associated encephalopathy and encephalitis are accompanied by elevated IgM titers to SARS-CoV-2 coronavirus spike protein S1 in the CSF and elevated IL-1β, IL-6, IL-8, and angiotensin-converting enzyme (ACE) levels [40]. At the same time, no coronavirus RNA was found in the CSF [41], as in the cases of BBB damage noted above.

The development of meningitis is known to be linked with CNS infection with meningococci, *N. meningitidis*. Damaging the BBB, SARS-CoV-2 virus can stimulate superaddition of meningococcal infection. Cases of bacterial meningitis increased significantly in 2020 over the levels in 2018 ($p = 0.029$) and 2019 ($p = 0.002$) [42]. Our more detailed analysis of the data collected in [43] showed that bacterial meningitis on the background of coronavirus infection COVID-19 could be associated with quite rare *N. meningitidis* strains (Y, C, etc.) rather than more widespread strains of the pathogen (B, W). It is also interesting to note that patients with COVID-19 and meningitis induced by rare *N. meningitidis* strains displayed greater meningococcal sensitivity to penicillin (MIC 0.045 ± 0.021 mg/ml, compared with 0.153 ± 0.128 mg/ml among patients without COVID-19, $p = 0.00146$) and cefotaxime (MIC 0.0043 ± 0.0015 mg/ml, compared with 0.009 ± 0.008 mg/ml in patients without COVID-19, $p = 0.005$).

Neurodegeneration and Demyelination in COVID-19. The COVID-19 pandemic has had significant adverse impact on the state of patients with neuromuscular disorders [43], including multiple sclerosis [44], muscular dystrophies of the Duchenne, Becker, and other types [45], and cerebellar ataxia [46]. COVID-19 infection can elicit loss of dopaminergic neurons in the substantia nigra of the brain and increase the risk of parkinsonism and depression [47].

Various demyelinating lesions of the brain and spinal cord are seen in COVID-19: inflammatory demyelinating polyneuropathy [48], Guillain–Barré syndrome, and inflammatory vasculopathy of the CNS accompanied by elevated blood titers of antibodies to oligodendrocyte glycoproteins and myelin [49].

Guillain–Barré syndrome is an inflammatory polyradiculoneuropathy associated with viral infections. Review of 37 published cases of Guillain–Barré syndrome in COVID-19 showed that the mean time from the onset of COVID-19 symptoms to the development of Guillain–Barré syndrome was 11 days. In half of cases, patients with Guillain–Barré syndrome showed signs of demyelination. The CSF of 76% of patients with Guillain–Barré syndrome was found to show abnormal albumin levels consistent with damage to the BBB (the coefficient Q noted above). Despite this, testing of CSF samples for SARS-CoV-2 RNA was negative in all subjects. Serum antiganglioside antibodies were absent from 15 of the 17 patients studied. Patients received single courses of i.v. immunoglobulin G and in most cases improvements in the state of patients with Guillain–Barré syndrome were noted over the first eight weeks [50].

Analysis of neurochemical markers in patients with the novel coronavirus infection indicated damage to both neurons and astrocytes. Neurofilament light chain (NfL) protein concentrations were measured in the plasma of COVID-19 patients ($n = 47$) [51], this being a marker for intraaxonal neuron damage; glial fibrillary acidic protein (GFAP) levels were also measured, this being a marker for astrocyte damage. As compared with patients with the mild form of COVID-19, those with a severe course of disease were characterized by higher plasma GFAP ($p = 0.001$) and NfL ($p < 0.001$) concentrations. In patients with severe infection, the GFAP concentration peak decreased during follow-up ($p < 0.01$), while the NfL concentration showed a stable increase throughout the whole study period ($p < 0.01$). These results point to a relatively rapid recovery from astrocyte damage and longer-lasting and increasing axon damage.

Postgenomic Studies of SARS-CoV-2 and Its Pathogenic Influence on the Human Body. In the epoch of postgenomic research, systematic biology has reached a new level of data analysis. In the postgenomic paradigm, pathophysiological processes and the effects of various drugs are assessed in relation not to a limited number of parameters, but to a whole mass of biological structural units: the genome (the set of all the genes in the body), the proteome (the set of all the proteins in the body), the microbiome (the set of all the commensal bacteria in a given patient), etc. This approach provides a complex evaluation of the pathophysiology of diseases and the effects of drugs (for example, actions on the microbiome [52]).

In particular, genome-wide and transcriptome studies have provided descriptions of the landscape of the host's genetic factors involved in SARS-CoV-2 infection. Analysis of the associations of the whole transcriptome revealed 114 genes linked with responses to this viral infection. Most of these genes were located on chromosome 6 and the so-called HLA locus, which contains genes encoding class II human leukocyte antigens. In addition, susceptibility to infection by SARS-CoV-2 was associated with the gene encoding epithelium-specific transcription repressor, which is involved in respiratory tract diseases (the *EHF* gene). An association between tissue-specific expression of ACE protein (the *ACE2* gene) with changes in susceptibility to SARS-CoV-2 was confirmed [53].

In relation to COVID-19 coronavirus infection, it is important to understand that postgenomic biology has only just started to recognize the role of endogenous human viruses in the susceptibility of the body to SARS-CoV-2, including in the formation of a severe neurological picture when the BBB is damaged. As compared with the microbiome (the set of symbiotic bacteria), the set of the human viral endogenous flora (the so-called virome) has received insufficient study. This major gap in our knowledge of systematic biology and human virology is particularly dangerous on the background of novel viral pandemics, including COVID-19.

In contrast to many studies of the human microbiome, the first multilateral investigation of the human virome in healthy people a published in June 2020. RNA sequencing data were obtained from samples of 51 somatic tissues collected from 547 healthy volunteers. This identified 39 virus species encountered in different tissues in healthy people [54]. Overall, 1424 human cell membrane proteins make up the receptorome of the human-infecting virome [55].

Thus, healthy people without any neurological symptoms have a set of not only bacterial symbionts (the microbiome), but also a set of viral symbionts (the virome). In particular, the anellovirus *Torque teno* (TTV) was found in a wide range of human tissues, and its presence was not associated with overactivation of interferon defense [56].

Anelloviruses are transmitted from mothers or the environment at young age, independently of sex, social-economic conditions, and geographical location. The wide distribution of anelloviruses in human populations, along with the absence of significant associations of anelloviruses with any diseases, suggests that TTV constitute a component of the healthy microflora. This suggestion was confirmed by the presence of these viruses in many different tissues, the existence of multiple viral species and variants, the lack of an interferon response to anelloviruses [55], and successful interactions of TTV with the human body due to regulation of N-myc/NMI/STAT signal cascades [56].

Furthermore, TTV and other anelloviruses may play a significant role in maintaining antiviral protection of the body as a whole. It is known that about 100 billion TTV virions are generated in the human body each day and that almost all these virions in the plasma are completely eliminated daily [57], thus maintaining the tissue antiviral protection and viral particle elimination systems in the working state. The latter prevents penetration of virus particles through the BBB even when the barrier is partially damaged, as seen on the background of the neurological complications of COVID-19.

A Clinical Example. The results of systematic computerized analysis of the literature presented above have

been confirmed in real clinical practice. For illustration we present our own observation.

Patient B, male, age 59 years, was admitted to the Department of Infectious Diseases of the Kemerovo Regional Clinical Hospital.

The diagnosis on admission was: COVID-19, virus identified on July 27, 2020.

Disease history: in the patient's own words, over the last 14 days he had not visited any other country or region of the Russian Federation and had had no contact in the last 14 days with people infected with 2019-nCoV or people under observation for infection induced by 2019-nCoV. Two weeks before admission, the patient developed headache, marked general weakness, cough, breathlessness, and myalgia. Temperature as 39.5°C. Out-patient treatment was with antipyretic and antiviral agents (the patient did not remember the names). No improvement was obtained. The patient was admitted to the Department of Infectious Diseases of the Kemerovo Regional Clinical Hospital, where a chest x-ray revealed right-sided lower lobe pneumonia. A COVID-19 swab was positive.

Life history: nonsmoker. No narcotic use. Denied chronic illnesses. No history of allergy.

At admission: general state of intermediate severity. Height 173 cm, weight 72 kg. Skin moist and pale. No marked lower limb edema. Peripheral lymph nodes not palpated. Pulmonary percussion: shortening of lung sounds, SpO_2 93%. Auscultation: vesicular respiration reduced on right, dry creps on right.

Respiratory rate (RR) 20 per min. Heart sounds rhythmic, heart rate (HR) 81 bpm. Arterial blood pressure (BP) 115/83 mmHg. Percussion: nontender in lumbar area.

Micturition normal. History data, the clinical picture, chest x-ray, and a positive COVID-19 test on August 11, 2020 led to a diagnosis of COVID-19 coronavirus infection (confirmed), intermediate severity, U07.1. Complications of main disease: community acquired right-sided lower-lobe pneumonia. Respiratory depression grade 0–1.

Investigation results on admission: hematology: express lymphocytes $6.94 \cdot 10^9$/liter, RBC $4.02 \cdot 10^{12}$/liter, Hb 127.7 g/liter, hematocrit 38.2%, MCV (mean corpuscular volume) 95 fl, MCH (mean corpuscular Hb content) 31.8 pg, MCHC (mean corpuscular Hb concentration) 334 g/liter, platelets $135.7 \cdot 10^9$/liter, segmented neutrophils 80%, lymphocytes 16%, monocytes 4%.

Blood biochemistry: bilirubin 4.9 μM; glucose 6 mM; urea 4.7 mM; creatinine 92 μM; potassium 4.5 mM; sodium 139 mM; aspartate aminotransferase 75 U/liter; alanine aminotransferase 65 U/liter; C-reactive protein 53.2 mg/liter; lactate 3.08 mM; ferritin 1576 μg/liter.

Express clotting tests: activated partial thromboplastin time (APTT) 33 sec; prothrombin index (PTI) 100%; thrombin time 14 sec; fibrinogen 5.11 g/liter; soluble fibrin monomer complexes 21 mg/100 ml; D-dimers 1350 ng/ml.

Chest x-ray on admission: background of enlargement and deformation of the lung pattern on the right and in the root area, infiltration of lower lobes. Roots poorly structured. Sinuses clear. Diaphragm position normal. Heart not enlarged. Conclusions: multisegmental pneumonia on right.

ECG on admission (July 27, 2020) : sinus rhythm, HR 82 bpm. Electrical axis of heart normal. No pathology seen on ECG.

Treatment prescribed:
1. Azithromycin 500 mg once daily p.o. for 5 days;
2. Bronchorus 30 mg 3 times daily p.o.;
3. Levofloxacin 5 mg/ml 100 ml twice daily i.v.;
4. Berodual 2 ml twice daily by inhalation;
5. Enixum 10000 IU/ml 0.4 ml twice daily s.c.;
6. Sodium chloride 0.9% 500 ml once daily i.v. infusion;
7. Potassium chloride 4% 30 ml once daily i.v. infusion;
8. Temperature monitoring;
9. Prone nursing;
10. Oral rehydration;
11. Oxygen therapy;
12. Immard 400 mg twice daily p.o. for 1 day;
13. Perfalgan 10 mg/ml 100 ml once daily i.v. infusion;
14. Ascorbic acid 5% 2 ml once daily i.v. infusion;
15. Immard 200 mg twice daily p.o. for 5 days;
16. Vancomycin 1 g twice daily i.v. infusion daily for 5 days;
17. Sterofundin 1000 ml once daily i.v. infusion;
18. Dexamethasone 4 mg 2 ml once daily i.v. infusion for 2 days

July 29, 2020, two days after admission: the patient's condition deteriorated sharply: severe diffuse headache appeared at night, a sensation of fullness of the eyeballs, and loss of memory for ongoing events (the patient was unable to remember when he had been admitted). Complaints of episodes of vertigo, transient memory loss for ongoing events.

Examination: condition approaching the severe; pulse 90 bpm, HR 90 bpm, RR 18 per min, BP 120/70 mmHg, temperature 38.6°C, SpO_2 95% on O_2.

Additional investigations: 1. CT scan chest with bolus contrast (because of disparity between clinical and x-ray pictures); 2. Neurology consultation.

July 29, 2020, neurology consultation: conscious. Contactable. Disoriented. Cognitive functions reduced. Follows instructions with difficulty, answers questions. No meningeal signs. Orbits – pupils R = L. Light responses and corneal reflexes preserved. Eye movements full range. No nystagmus. Facial musculature symmetrical. Tongue in midline. No paresis. Muscle tone R = L, not altered. Tendon reflexes R = L, low. Babinski reflex negative both sides. Coordination tests satisfactory. No clear sensory impairments. Pelvic organ functions controlled.

Advised: CT brain scan to exclude focal brain lesion.

Investigation results. Chest CT scan with i.v. contrast bolus Omnipak 350, 50 ml. Investigation run in high-resolution multispiral regime followed by 3D, MPR, and MIP reconstruction. Lung volume preserved. Both lungs showed multiple polymorphic areas of consolidation of lung tissue of the "ground glass" type on a background of thick-

ening of intralobular interstitial tissue of different levels of severity, more marked in the lower lobe of the right lung, where signs of consolidation were seen. Volume affected by damage estimated as 25%. Signs of destruction not seen. Bronchovascular picture not altered. Mediastinum structured, not displaced. Pulmonary artery and thoracic aorta not dilated, no contrast defects. Trachea no pathology. Bronchi of 1st to 3rd orders patent. Pleural cavity unremarkable. Lymph nodes not enlarged. Conclusions: bilateral multisegmental pneumonia presumptively of vital etiology (CT1-2).

Brain CT scan. Study run in high-resolution multispiral regime followed by 3D, MPR, and MIP reconstruction. External and internal liquor spaces dilated. Third ventricle width 9 mm. Blood not found in cavity system or supra/intrathecally. Gray/white matter density ratio normal. Midline brain structures not displaced. Basal ganglia symmetrical on both sides with weakly apparent areas of amorphous calcification. Both cerebral hemispheres show weakly apparent small areas of reduced density. CT signs of organic volumic macroscopic changes to brain matter and structures at the moment of this investigation not detected. Severe calcification of anterior third of the falx cerebri. No bony destructive changes seen. Conclusions: signs of atrophic changes to the brain.

Repeat neurology consultation. Diagnosis: encephalopathy, unspecified, probably of viral origin. Chronic cerebral ischemia grade 2. COVID-19 coronavirus infection (confirmed), intermediate severity U07.1.

Advice: neuroprotective therapy to correct neurological impairments: 1) Citicholine (Neupilept) 1000 mg/day i.m. for 10 days; 2) ethylmethylhydroxypyridine succinate (Neurox) 500 mg i.m. for 10 days.

August 10, 2020, 14 days, patient's condition improved, all neurological symptomatology regressed. Neurologist's advice: follow-up by neurologist at place of residence, continue neuroprotective treatment for 1–2 months.

Assessment of treatment proposed by neurologist. There are as yet no guidelines for the management of patients with COVID-19 and cognitive impairments [58], so drug selection is based on the following principles: 1) compatibility with basal therapy; 2) presence of anti-inflammatory and antihypoxic effects and marked neuromediator actions.

Both drugs are compatible with recommended drugs for the treatment of the novel coronavirus infection; Citicoline (Neupilept) decreases arachidonic acid levels and has positive influences on the CD cluster, thus decreasing the harmful actions of "cytokine storms" on neurons [59], and although the drug has a lesser effect on choline secretion than choline alfoscerate, the combination of choline and cytidine is a universal tool for decreasing the signs of cerebral ischemia and stabilizing cognitive status; it surpasses the standard benefits of choline. The various biological mechanisms of Citicoline qualify it as a drug for treatment not only for the acute stage of disease, but also for restoring the brain in the long-term period, conferring on it the status of a universal nootropic compound. At the same time,

Neurox, a powerful energy corrector, antioxidant, and antihypoxic, exerts a therapeutic effect at the cellular level, improving cell metabolism and decreasing neuroinflammation by inhibiting the effects of proinflammatory factors TNF-α, IL-1, IL-6, and leukotriene B4 [59], thus decreasing the signs of hypoxia in both the acute and longer-term periods of virus-induced neuron damage and improving the patient's clinical condition.

Conclusions. Results obtained by systematic computerized analysis of 2374 publications on the neurological manifestations of COVID-19 provided a description of a set of interactions of SARS-CoV-2 infection, impairments of neurotransmitter metabolism, micronutrients, chronic and acute inflammation, encephalopathy, cerebral ischemia, and neurodegeneration (including demyelination). The most typical neurological manifestations of COVID-19 are anosmia/ageusia due to ischemia, neurodegeneration, and/or systemic increases in proinflammatory cytokine levels. COVID-19 provokes ischemic stroke, Guillain–Barré syndrome, meningitis, and migraine, as well as neurodegenerative diseases. Coronavirus infection exacerbates the course of multiple sclerosis and myopathies, and in the longer-term perspective it promotes increases in neurodegenerative changes. In addition, excessively strict quarantine measures stimulate the development of neuropsychiatric disorders (post-traumatic stress disorder, anxiety disorder, depression).

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