

# The Novel Coronavirus Infection (COVID-19) and Nervous System Involvement: Mechanisms of Neurological Disorders, Clinical Manifestations, and the Organization of Neurological Care

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The new coronavirus SARS-CoV-2 and the disease it causes COVID-19 involves not only respiratory system damage, but can also lead to disorders of the central and peripheral nervous system, as well as the muscular system. This article presents published data and our own observations on the course of neurological disorders in COVID-19 patients. There is a relationship between the severity of COVID-19 and the severity and frequency of neurological manifestations. Severe neurological disorders are mostly seen in severe cases of COVID-19 and include acute cerebrovascular accidents (aCVA), acute necrotizing encephalopathy, and Guillain–Barré syndrome. Factors potentially complicating the course of COVID-19 and increasing the development of neurological complications include arterial hypertension, diabetes mellitus, and chronic cardiac and respiratory system diseases. Questions of the possible effects of human coronaviruses on the course of chronic progressive neurological diseases are addressed using multiple sclerosis (MS) as an example. We discuss the management of patients with aCVA and MS depending on the risk of developing coronavirus infection.

**Keywords:** COVID-19 SARS-CoV-2, coronaviruses, nervous system, muscular system, stroke, multiple sclerosis, acute necrotizing encephalopathy, Guillain–Barré syndrome.

Cases of a pneumonia of unknown etiology were first detected in Wuhan in December 2019 and spread rapidly, first in China and then throughout the world. The WHO announced that this disease was pandemic on March 11, 2020 [1]. The disease was found to be caused by a new single-stranded RNA virus (ss-RNA, 29,903 bases), a member of the coronaviruses (CoV). The novel coronavirus was designated SARS-CoV-2 (severe acute respiratory syn-

drome coronavirus 2) and the disease caused was termed COVID-19 (coronavirus disease 2019) [1].

Coronaviruses are a large group of viruses infecting various animal species, especially bats and birds. Some of them produce disease in humans – human coronaviruses (HCoV). A total of seven human coronaviruses are currently known (see Table 1). A feature of the coronaviruses circulating in nature is their ability to cross species boundaries and become entirely pathogenic for humans, producing severe infections of the respiratory and other systems, as in the cases of SARS-CoV (SARS-CoV-1) and MERS-CoV [2]. Thus, the studies reported by Guan et al. [3] are of interest; these were published in 2003 just before the first outbreak of atypical pneumonia caused by SARS-CoV-1. The authors investigated wild animals sold at produce markets in China and workers contacting them and found a corona-

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TABLE 1. Human Coronaviruses

Strain	Cell penetration receptor	Risk group	Route of transmission	Clinical features	Mortality, %
HCoV-229E	AAP (ANP)	Children up to 5–7 years, people over than 65–70 years, people with immunodeficiency (including therapeutic)	Airborne droplets, mucosal contact	Damage to the upper respiratory tract, more rarely the lower respiratory tract (bronchiolitis) and lungs (pneumonia). CNS?	
HCoV-OC43*	5-N-acetyl-9-O-acetylneuraminic acid				
HCoV-NL63	ACE2	Children up to 5–7 years, people over 65–70 years, people with immunodeficiency	Airborne droplets, mucosal contact, fecal-oral	Damage to the upper respiratory tract, croup, more rarely the lower respiratory tract (bronchiolitis), and lungs (pneumonia). Damage to the gastrointestinal tract (enteritis)?	–
HCoV-HUK1	N-acetyl-9-O-acetylneuraminic acid				
SARS-CoV-1	ACE2	People over 65–70 years, people with immunodeficiency, people with chronic lung diseases	Airborne droplets. Possibly mucosal contact	Damage to the upper and lower respiratory tract, lungs (pneumonia), severe acute respiratory syndrome	~10
SARS-CoV-2		People over 65–70 years, people with immunodeficiency, people with chronic diseases	Airborne droplets, mucosal contact, fecal-oral	Damage to the upper and lower respiratory tract, lungs (pneumonia), severe acute respiratory syndrome. Damage to the gastrointestinal tract (enteritis)	3–6**
MERS-HCoV		DDP4 (CD26)	Airborne droplets. Possibly mucosal contact	Damage to the upper and lower respiratory tract, lungs (pneumonia), severe acute respiratory syndrome	~40

\*Cross-immunity with HCoV-HUK1 70%; \*\*mortality at the time of publication. AAP (ANP) – alanineaminopeptidase (aminopeptidase N); 5-N-acetyl-9-O-acetylneuraminic acid; ACE2 – angiotensin-converting enzyme 2; DDP4 (CD26) – dipeptidyl peptidase 4.

virus whose RNA differed only very slightly from that of SARS-CoV-1, along with neutralizing antibodies in animals and humans. Results reported by Guan et al., suggest the possibility of rapid crossing of the species barrier and development of an epidemic of a novel coronavirus infection similar to SARS-CoV-1 in humans.

The novel virus SARS-CoV-2 primarily infects the respiratory tract and lungs, inducing an acute respiratory syndrome, leading to adoption of the term “severe acute respiratory syndrome (SARS)” on February 11, 2020. The clinical signs of infection with SARS-CoV-2 are similar to those of SARS caused by SARS-CoV-1 in 2003.

The virus SARS-CoV-2, like SARS-CoV-1, enters human cells by means of the angiotensin-converting enzyme 2 receptor (ACE2) [4]. In humans, ACE2 is expressed by most organs and tissues and, according to data reported by Zou et al. [5], the lungs, lower parts of the respiratory tract, heart, kidneys, intestine, and smooth muscle cells in vessel walls (particularly in the microcirculatory bed) are most susceptible to SARS-CoV-2. In assessing the damaging actions of the virus on the brain and other parts of the central and peripheral nervous system, it is important to note that ACE2 is expressed by neurons, glial cells, and endothelial cells [6, 7].

Considering previous publications on neurological impairments in infections with SARS-CoV-1 and MERS-CoV, neurological impairments due to SARS-CoV-2 can be divided into two groups. The first group of impairments con-

sist of damage to the central and peripheral nervous system due directly to the SARS-CoV-2 virus. The second group consists of changes in the course of neurological diseases on the background of infection with SARS-CoV-2, especially on development of pneumonia and SARS.

Neurological impairments due to human coronaviruses, including SARS-CoV-2, are of interest to investigators [8, 9]. Studies using experimental models showed that the SARS-CoV-2-related virus SARS-CoV-1 can enter the brain and cause serious neurological disorders [10]. During the SARS-CoV-1 epidemic in 2002–2003, viral protein structures and RNA were detected in the brains and cerebrospinal fluid (CSF) of patients with SARS, along with symptoms of nervous system damage [11, 12].

The pathophysiology of neurological impairments in SARS-CoV-2 infection are probably similar to those in SARS-CoV-1 and penetration into the brain may occur via the hematogenous and/or perineural pathways.

Studies have now been published [13, 14] addressing the questions of nervous system damage by SARS-CoV-2 (henceforth COVID-19). The first review of neurological manifestations was presented by Mao et al. [9] in patients with confirmed diagnoses of COVID-19 in hospital in Wuhan. The data reported by Mao et al. showed that of 214 patients, 88 (41.1%) had severe illness, while 126 (58.9%) had mild or moderate severity. The group with a severe course were older ( $58.7 \pm 15.0$  vs.  $48.9 \pm 14.7$  years) and more often had concomitant pathology (47.7% and 32.5%).

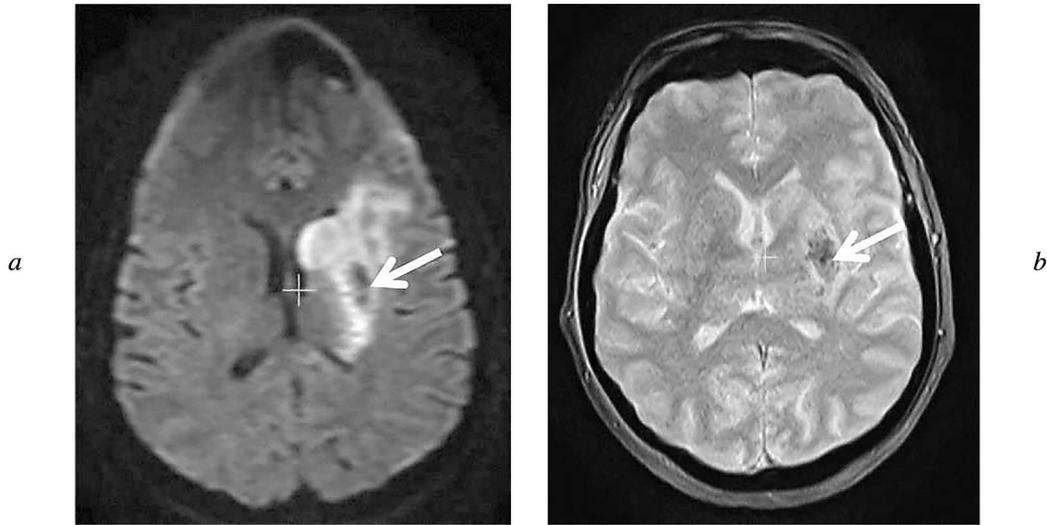


Fig. 1. MRI brain scan, DWI (a) and T2\* (b) modes. Ischemic focus with hemorrhagic transformation (arrow) in the left hemisphere.

Neurological symptomatology was found in 78 patients (36.4%) of the 214 patients and was more common in those with severe disease (45.5% and 30.2%). This same group also more commonly developed cerebral stroke (5.7% and 0.8%), alterations of consciousness (14.8% and 2.4%), and muscle damage (19.3% and 4.8%).

Overall, if we sum all currently available reports, three variants of nervous system damage can be identified in COVID-19: CNS damage, peripheral nervous system damage, and damage to the muscular system.

**CNS Damage. Cerebrovascular complications.** The combination of COVID-19 and acute cerebrovascular accidents (aCVA) is of particular note. It should be noted that in acute severe viral diseases, including during influenza epidemics, cardiovascular deaths are the commonest, outstripping pneumonia [15]. In patients with COVID-19, the most important factor in the development of aCVA is evidently decompensation of the concomitant risk factors, especially diabetes mellitus, ischemic heart disease, and arterial hypertension [9]. It should be noted that ACE2 receptors are present in the microcirculatory bed of the brain, which may be the cause of its vulnerability in COVID-19. It is also important to consider the role of acute diffuse myocardial damage in the development of cerebrovascular disorders [16, 17]. In addition, a severe course of infection is independently promoted by proinflammatory changes, shifts in hemostasis towards procoagulation, and microcirculatory disorders. Another aspect of the problem of the combination of cerebrovascular pathology and COVID-19 is that of the influence of stroke on the course of the infection. Stroke is accompanied by activation of the sympathetic nervous system and acute immunosuppression, which may increase the severity of COVID-19 with subsequent aggravation of stroke.

Thus, it is interesting to present the case of a patient with ischemic stroke and clinically asymptomatic COVID-19 pneumonia.

**Case history.** Patient K, female, age 51 years, a Muscovite, was at home in self-isolation with no contact with anyone for eight days before onset of stroke. There was no epidemiological history. The patient had not been abroad in the last six months. Her husband reported that she became acutely ill at about 12:00, when she ceased to be in contact. For three days prior to admission to the clinic she noted general weakness and a dry cough. There was no increase in body temperature. There was a history of myocardial infarction in 2018. Review on admission: condition severe, conscious, verbal contact limited due to aphasia, body temperature 36.7°C, respiratory rate 21 per min, SpO<sub>2</sub> 95% breathing atmospheric air. Auscultation: respiration vesicular, softened at the posteroinferior surface, dry crepitations both sides. Arterial blood pressure (BP) 130/80 mmHg, heart rate 60 bpm, normal rhythm. No changes on ECG. Neurological status: right-sided hemiparesis ~1 point with impaired sensation, speech disorders, total NIHSS score 18. During examination there was a single convulsive seizure with no increase in focal neurological symptomatology. MRI: focus in the deep segments of the left hemisphere with hemorrhagic transformation (Fig. 1). CT lungs: signs of bilateral polysegmental viral pneumonia highly likely to be COVID in origin (Fig. 2). Blood: RBC 4.4·10<sup>12</sup>/liter, hemoglobin 85 g/liter, WBC 10·10<sup>9</sup>/liter, neutrophils 80%, lymphocytes 12%, monocytes 7%, plasma cells 1%, ESR 41 mm/h, D-dimer 759 ng/ml ( $n = 0-243$ ), iron 4.7 mM ( $n = 6.6-26.0$ ), ferritin 398 µg/liter ( $n = 20.0-300.0$ ), C-reactive protein 163.1 mg/liter ( $n \leq 10.0$ ). The first throat swabs for COVID-19 were taken in the admission room. Given the hemorrhagic transformation, use of thrombolytic therapy and/or endovascular interventions was not considered. For subsequent treatment the patient was transferred to the specialist unit for COVID-19 patients.

**Acute necrotizing (hemorrhagic) encephalopathy (ANE).** ANE may be another cause of brain damage in COVID-19. Overall, ANE is a rare variant of brain damage occurring



Fig. 2. CT scan of lungs. Multiple focal changes (arrows) in both lungs of the ground glass type and consolidation.

on the background of viral infections [18, 19]. The mechanisms of development of ANE remain incompletely understood. The role of excessive activation of proinflammatory cytokines, i.e., a cytokine storm, is under discussion [20, 21]. The possibility of a pathological autoimmune response due to polyclonal stimulation of the immune system by the virus, with an overlap with brain damage, has also been considered. Experimental studies with influenza H7N1 [22] demonstrated the potential for indirect entry of virus into endothelial cells in the microcirculatory bed of the brain, with subsequent damage to gap junctions between them and increased penetrability of the blood-brain barrier. The most typical radiological sign of ANE is the presence of symmetrical foci of thalamic involvement. The white matter of the cerebral hemispheres is also not infrequently involved, along with the brainstem and cerebellum [23]. Morphologically, a combined disseminated necrotic process is generally noted, with microcirculatory damage, minor inflammatory changes, and secondary demyelination [24].

Poyiadji et al. [25] published the first description of COVID-19-associated hemorrhagic ANE. Disease in the 60-year-old woman debuted with cough, elevated temperature, and subsequent impairment to consciousness. The diagnosis of COVID-19 was confirmed by a nasopharyngeal swab. CSF analysis for bacterial flora, herpes simplex virus types 1 and 2, herpes type 3 (varicella zoster), and West Nile fever was negative. CSF tests for COVID-19 were not run for technical reasons. MRI scan (T2 FLAIR, SWI, contrast-ing): depending on mode, hyper- and hypointense foci and foci with peripheral contrast uptake in the medial thalamic nucleus, the central part and mediobasal parts of the temporal lobe. Clinical and radiological data were used to diagnose hemorrhagic ANE. The patient was started on i.v. immunoglobulin. Steroids were not given because of the risk of developing severe respiratory impairments. The leading pathogenetic factor in this complication in this patient may be a “cytokine storm” as described in other patients with severe COVID-19 [17].

**Multiple Sclerosis (MS).** The role of viruses in the development of MS has been discussed for several de-

caes. It has been suggested that certain neurotropic viruses, Epstein–Barr virus, endogenous retroviruses, and others may be directly or indirectly involved in the progression of MS. We have not found any reports on the combination of COVID-19 and MS. At the same time, various studies performed in recent years have noted a possible link between human coronaviruses and MS. Thus, data reported by Arbour et al. [26] and Desforgues et al. [8] indicate that HCoV-OC43 RNA was found in the brain significantly more frequently in MS patients than in a control group. The brains of MS patients also showed single-nucleotide changes in HCoV-OC43 RNA more frequently than those of the control group, suggesting the possibility that HCoV-OC43 “adapted” to the “host” with subsequent direct or indirect actions on the brain. In addition, coronaviruses, particularly HCoV-229E and HCoV-OC43, can induce immune responses with overlapping reactivity with myelin basic protein [27]. Analogous data for HCoV-229E had previously been obtained by Talbot et al. [28]. Their results indicated that almost 30% of T-cell lines in MS proteins cross-react with myelin basic protein antigen and HCoV-229E antigens, while cross-reaction in the control group were seen in only 1.3% of cases. Thus, the question of the mutual influence of COVID-19 and MS remains open.

**Peripheral Nervous System Damage.** One variant of peripheral nervous system damage with the subsequent possibility that infection enters the brain consists of damage to the olfactory nerves. Previous experiments showed that SARS-CoV-1, which is related to SARS-CoV-2, penetrates from the nasal cavity into the cranial cavity and thence into the brain via the olfactory nerves, producing severe brain damage [10]. Mao et al. [9] diagnosed impaired olfaction in 5.1% of COVID-19 patients, somewhat more often in patients with the mild form of the disease. This latter may be associated with difficulties detecting olfactory changes in patients with the severe form. Gane et al. [29] took the view that the loss of olfaction not only preceded symptoms of infection, but could also be the only clinical manifestations of COVID-19. This was supported by Eliezer et al. [30], who found that a significant reduction or complete loss of olfaction without other clinical or CT/MRI changes in the nasal cavity and nasal passages could be the sole early sign of COVID-19. Data from the British Rhinological Society [31] indicated that acute decline/loss of olfaction should be regarded as a marker of COVID-19. It is important to note that olfactory impairments in COVID-19 are to some extent different from changes to olfaction in other viral infections, which produce nasal congestion. In cases of hyposmia or anosmia in COVID-19, the question of the possibility of further penetration of the virus into the brain via the olfactory pathway remains open and important.

Data on changes in the sense of taste are also interesting. Mao et al. [9] found changes in taste in 5.6% of observations, somewhat more frequently in mild than severe disease (7.1% and 3.4%). Differences in frequency, as in

the case of changes in olfaction, probably need to be interpreted with consideration of the difficulty in identifying them in patients with the severe form. Changes in taste in 1.5% of cases occurred before symptoms of infection and their frequencies were different between patients with the mild and severe forms of disease. Questions of the location of the process and pathogenetic mechanisms of impaired gustation in COVID-19 remain open. Given that ACE2 receptors are abundant on the gustatory surface of the tongue [32], it is impossible to exclude direct effect of the virus on taste receptors and/or nerve fibers.

Wei et al. [33] published a possible onset of COVID-19 with impairments to the oculomotor nerve in a 62-year-old man who experienced double vision and a change in the position of the left eye for five days before the onset of symptoms of infection. Neurological examination revealed ptosis and external ophthalmoplegia on the left. No changes were seen on MRI brain scan or MR angiography. On day 2 of the admission, body temperature rose to 38.9°C, respiratory failure started, and a CT scan of the lungs demonstrated pneumonia. A SARS-CoV-2 test was positive and the patient was diagnosed with COVID-19 with SARS and possible onset as neuropathy of the third cranial nerves.

There is also a description of a combination of Guillain-Barré syndrome with COVID-19 [34]. The 61-year-old female patient attended hospital with weakness in the arms and legs. Other clinical symptoms, including signs of infections, were not present at admission. Admission blood tests demonstrated lymphopenia ( $0.52 \cdot 10^9/\text{liter}$ ,  $n = 1.1\text{--}3.2 \cdot 10^9/\text{liter}$ ). The history indicated that the patient had returned from Wuhan four days before onset of neurological symptomatology. The patient was diagnosed in hospital with Guillain-Barré syndrome on the basis of clinical data, CSF changes, and electroneuromyographic studies and treatment with immunoglobulins was initiated. During the admission, the patient had no contact with COVID-19 carriers/patients. Dry cough and elevated temperature appeared on hospital day 8. A lung CT showed “ground glass” changes and SARS-CoV-2 virus was detected in oropharyngeal swabs. A diagnosis of COVID-19 was made and combined antiviral therapy was started. On day 30 after admission the patient was discharged without somatic or neurological symptoms. Considering the history and severity of lymphopenia on admission, Zhou et al. [34] did not exclude the possibility that the patient acquired SARS-CoV-2 virus infection in Wuhan and that this infection was the cause of the Guillain-Barré syndrome.

**Damage to the Muscular System.** Various viral infections can be accompanied by direct damage to the skeletal musculature [35, 36]. On the other hand, damage to the skeletal musculature may be secondary to severe viral infection, especially when complicated by sepsis, multiorgan failure, or acute respiratory distress syndrome [37]. On the basis of elevated creatine phosphokinase (CPK) and lactate dehydrogenase (LDH), Mao et al. [9] diagnosed the involvement of the muscular system in 10.7% of patients, predominantly among

those with severe disease (19.3% and 4.8%). In groups with mild and severe COVID-19, CPK and LDH levels were significantly greater in patients with muscle weakness than in those without it. CPK and LDH levels in patients with muscle symptoms were significantly greater in the severe form of the disease than in the group with mild disease. This distribution suggests that the cause of muscle system damage may be not only direct viral action but also the generally severe state, with metabolic impairments. Increases in laboratory markers reflecting skeletal muscle and myocardial damage in COVID-19 were noted by Ruan et al. [17]. This group, like Mao et al. [9], drew attention to the link between disease severity and increase myoglobin levels. The mechanisms of skeletal muscle damage in COVID-19 are not entirely clear. They may presumptively be linked with ACE2 receptors, which are widely distributed in skeletal muscles and the myocardium [17, 38] and whose expression is increased in viral infections and severe conditions with elevated breakdown of muscle tissue [37]. Furthermore, Baird et al. [39] regarded excessive cytokine release in inflammation as a direct damaging factor for muscle tissue. A role for a pathological autoimmune reaction in polyclonal stimulation of the immune system with viruses with cross-reactivity to skeletal muscle antigens is not excluded.

**Organization of Care for Patients with Neurological Diseases.** The organization of care for patients with neurological diseases is important in conditions of the COVID-19 pandemic. Guidelines for patient care pathways have been developed for a number of neurological conditions involving combined nervous system disease and COVID-19. All patients with neurological pathology are divided into three groups: group 1 consists of patients with no contact with COVID-19 carriers/patients; group 2 consists of patients with contact with COVID-19 carriers/patients; group 3 consists of patients with confirmed decreases of COVID-19. Compliance with all COVID-19 pandemic recommendations of the Russian Federal Healthcare Surveillance Service and the Russian Ministry of Health is of fundamental importance.

*Organization of care for patients with aCVA.* Patients with aCVA are categorized into groups at the urgent care stage and, if necessary, by doctors in the admission room of the receiving hospital. Patients with deranged consciousness or speech disorders, lacking relatives, or in other situations when a history cannot be taken, constitute group 2. Specialized medical care for each group is provided in full compliance with Russian Ministry of Health Order No. 928n of 2012 and the temporary Methodological Guidelines for the Management of Patients with aCVA in the conditions of the COVID-19 pandemic (version 2 of April 16, 2020). Drug therapy of aCVA is, as required, given simultaneously with COVID-19 treatment with adjustment for the severity of the viral infection and the spectrum of antiviral drugs used. The investigation and management of aCVA patients with COVID-19 in secondary medical institutions (infection hospitals, etc.) involves use of telemedicine and other

remote consultation facilities using appropriate specialists at designated regional vascular centers/primary vascular departments (RVC/PVD). Patients with ischemic stroke and COVID-19 admitted within the “therapeutic window” to secondary medical facilities, as long as there are no contraindications, should receive intravenous thrombolytic therapy under remote/telemedicine control by a neurologist from the designated RVC/PVD.

Particular attention in the management of patients with aCVA and COVID-19, including after discharge from hospital, must be paid to correction of risk factors for aCVA, commitment to the use of drugs prescribed for this condition taking account of possible interactions with drugs for the treatment of COVID-19 [<https://www.COVID19-druginteractions.org/>].

*Arterial hypertension (AHT).* On admission of patients with aCVA and COVID-19, the presence of AHT must be regarded as a risk factor potentially complicating the course of COVID-19. In patients with aCVA and COVID-19 and stable BP, the antihypertensive treatment regime should not be altered. There are as yet no reliable data indicating that use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor (AR) blockers increases the severity of COVID-19 or promotes its development [40, 41]. Furthermore, Studies reported by Zhang et al. [42] indicated that use of ACE inhibitors or AR blockers in patients with COVID-19 in hospital conditions, including the emergency room and intensive care unit, is accompanied by lower mortality than seen in patients taking other groups of antihypertensives. Prescription of novel antihypertensives to patients with COVID-19 should be with consideration of their possible interactions with drugs for COVID-19 [<https://www.COVID19-druginteractions.org/>].

*Atrial fibrillation (AF).* There are as yet no data indicating that AF in patients with aCVA and COVID-19 is a risk factor potentially complicating the course of COVID-19. Patients with aCVA with AF should be prescribed anticoagulants by the doctor. The choice of drug is made by the treating doctor. In patients with aCVA and COVID-19 with AF, the selection of anticoagulants must consider possible interactions with drugs used for the treatment of COVID-19 [<https://www.COVID19-druginteractions.org/>].

*Diabetes mellitus (DM).* On admission of patients with aCVA and COVID-19, the presence of DM should be regarded as a risk factor potentially complicating the course of COVID-19 [43]. Patients with aCVA and COVID-19 with DM must undergo regular blood glucose monitoring to keep it within the individual’s optimum range by strict maintenance of the selected DM treatment regime. Severe COVID-19 in patients with aCVA and DM can lead to unstable glucose levels with the need to adjust DM treatment schemes, which should be done only by the endocrinology physician. In cases of combined aCVA and COVID-19 with DM, hypoglycemic therapy must take account of possible drug interactions [<https://www.COVID19-druginteractions.org/>].

*Organization of care for patients with MS.* A number of guidelines have already been published for the care of patients with MS [44–48]. The question of prescribing MS disease-modifying drugs (MSDMD) in the pandemic must always be addressed individually.

Patients of group 1 must comply with self-isolation and must not alter their treatment plans. More severe COVID-19 occurs in patients aged over 60 years, and these patients must comply with self-isolation with particular stringency. There are as yet no data on the influences of COVID-19 on the course of MS and treatment results. When MS is an initial diagnosis, injected MSDMD can be prescribed from the moment of diagnosis. Initiation of courses of teriflunomide or dimethylfumarate should perhaps be avoided temporarily because of the potential risk of lymphopenia.

If patients with highly active MS and receiving effective treatment with second-line drugs (fingolimod, natalizumab, ocrelizumab, alemtuzumab, cladribine as tablets), they should continue their courses in conditions of complete self-isolation. Withdrawal of courses can lead to exacerbation of MS. Exacerbations can be treated with standard courses of pulse therapy with methylprednisolone or additional guidelines for people at risk of serious complications of COVID-19 must be observed. MS patients for whom changes in MSDMD therapy are planned (due to lack of efficacy), with prescription of drugs with stronger immunosuppressive actions, should take account of the COVID-19 pandemic and should be warned of all risks and possible times for initiation of new second-line MSDMD treatment and the risks of disease activity. Considering the epidemiological situation, six-month prescriptions for MSDMD can be issued. The optimum arrangement is issue of prescription with home delivery.

Patients of group 2 can continue treatment with injected first-line MSDMD (glatiramer acetate or interferon-beta, s.c.). The question of continuing courses of drugs with good immunosuppressive actions or likely to induce lymphopenia (teriflunomide, dimethylfumarate, fingolimod, natalizumab, ocrelizumab, alemtuzumab, cladribine, as tablets) must be answered on an individual basis depending on the level of MS activity. If the condition is stable, patients can temporarily be transferred to  $\beta$ -interferon – which has antiviral activity – or if MS is highly active patients can be transferred to natalizumab, which has the lowest level of systemic immunosuppressive action. At the same time, it remains unknown how blockade of adhesion molecules affects the course of pneumonia and SARS. Patients of this group should not make precipitate decisions regarding changes in treatment; courses of MSDMD can be optimized when the COVID-19 pandemic is over.

Patients of group 3 can continue treatment with injected MSDMD (glatiramer acetate or beta-interferons) but should not start new MSDMD or change their treatment. In this case, the primary need is for adequate COVID-19 treatment. Thus, various guidelines have noted that teriflun-

omide, dimethylfumarate, and fingolimod should be withdrawn and replaced with injectable MSDMD, with transfer to periods of repeat treatment with ocrelizumab, alemtuzumab, or cladribine tablets until SARS settles. If MS is highly active, natalizumab can be prescribed on an individual basis; continuation of courses of this drug can include an increase in the intervals between i.v. doses of drug from four to six weeks.

Approaches to the management of patients aged 50 years and older (especially the over-60s) with primary or secondary progressive MS in exacerbation and receiving ocrelizumab treatment require separate consideration. Initiation of courses of this drug should be postponed for at least a number of months, until the risk of COVID-19 infection decreases. If courses are already under way, tests for blood CD19<sup>+</sup> cells should be run, preferably at home, and repeat administration should be postponed for 1–2 months from the planned time if the dose was scheduled to be given in April–June 2020. At low (less than 3%) levels of CD19<sup>+</sup> cells, the decision regarding repeat drug administration should be temporarily postponed. All questions on the management of patients with MS can be answered individually depending on the COVID-19 risk and MS activity.

**Conclusions.** Thus, the new coronavirus infection – COVID-19 – due to SARS-CoV-2 virus, not only produces damage to the respiratory system, but can also lead to the involvement of the central and peripheral nervous system and the muscular system. There is a link between the severity of COVID-19 and the extent and frequency of neurological impairments. Severe neurological disorders mainly complicate severe COVID-19 and can be apparent as aCVA, ANE, and Guillain–Barré syndrome. Factors potentially complicating the course of COVID-19 and promoting the development of neurological complications are AHT, DM, heart diseases, and chronic lung diseases. The question of the influence of SARS-CoV-2 on the course of chronic progressive neurological diseases, including MS, remains open. Future studies will help answer these questions.

The authors have no conflicts of interests.

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