REVIEW ARTICLE

Neurological symptoms as a clinical manifestation of coronavirus disease 2019: implications for internists

Monika Adamczyk-Sowa[1], Natalia Niedziela[1], Katarzyna Kubicka-Bączyk[1], Krzysztof Wierzbicki[1], Jerzy Jaroszewicz[2], Paweł Sowa[3]

1 Department of Neurology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Zabrze, Poland
2 Department of Infectious Diseases and Hepatology, Medical University of Silesia, Katowice, Poland
3 Department of Otorhinolaryngology and Oncological Laryngology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Poland

KEY WORDS

coronavirus disease 2019, Guillain–Barré syndrome, meningoencephalitis, neurotropism, severe acute respiratory syndrome coronavirus 2, stroke

ABSTRACT

Numerous experimental and clinical studies have proven that the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a tropism for the nervous system. The infection of the nervous system by SARS-CoV-2 can occur via the nasal route through trans-synaptic pathways. Coronaviruses can infect neurons and glial cells through angiotensin-converting enzyme 2 receptors or by endocytosis. The infection of the central nervous system accompanied by coronavirus disease 2019–related systemic inflammation leads to the impairment of the blood–brain barrier and triggers a neuroinflammatory response with reactive astrogliosis and microglial activation. In addition, brain stem cells are being damaged, which results in respiratory distress. Apart from typical symptoms of COVID-19 associated with the involvement of the respiratory system, neurological manifestations such as headache, dizziness, myalgia, anosmia, ageusia, encephalopathy, encephalitis, stroke, epileptic seizures, rhabdomyolysis, and Guillain–Barré syndrome are related to SARS-CoV-2 infection. In this review, we focused on the currently known neurological manifestations of COVID-19, which could be considered mainly in asymptomatic patients with COVID-19 and, if noted, may limit the transmission of coronavirus infection.

Introduction Coronaviruses represent a large group of positive-strand RNA viruses, genetically classified into 4 major genera, ie, *alpha-*, *beta-*, *gamma-*, and *deltacoronaviruses*. They mainly cause respiratory and enteric diseases in animals and humans.[1] So far, 6 subtypes of human coronaviruses have been recognized, namely, human coronavirus NL63 (HCoV-NL63), human coronavirus 229E (HCoV-229E), human coronavirus OC43 (HCoV-OC43), human coronavirus HKU1 (HCoV-HKU1), severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV).[2] Although human coronaviruses were first identified in the 1960s,[3] only the SARS-CoV epidemic in 2003 followed by the MERS-CoV epidemic in 2013 drew the attention of researchers worldwide.[4] While the clinical implications of the MERS-CoV epidemic are still noticeable, another lethal and highly pathogenic coronavirus known as SARS-CoV-2 has been reported in China.[5]

The first cases of the new coronavirus infection were observed in Wuhan City, Hubei Province, China, in December 2019. Furthermore, a cluster of cases with a clinical presentation of viral pneumonia was also noted.[6] The assessment of the lower respiratory tract samples confirmed the presence of the novel coronavirus, which was contagious among humans. Terms such as "Wuhan coronavirus" or "the new coronavirus" (2019-nCoV) were commonly used until January 2020. The official name, ie, SARS-CoV-2, which was based on taxonomic designation, appeared on February 11, 2020. At the same time, World Health Organization termed the disease "COVID-19."[7] The recent pneumonia outbreak was associated with a large animal and seafood market. However, the investigations are ongoing

Correspondence to:
Monika Adamczyk-Sowa, MD, PhD, Department of Neurology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, ul. 3 Maja 13–15, 41-800 Zabrze, Poland, phone: +48 32 370 45 94, email: msowa@sum.edu.pl
Received: June 15, 2020.
Accepted: August 21, 2020.
Published online: August 21, 2020.
Pol Arch Intern Med. 2021; 131 (1): 54-62
doi:10.20452/pamw.15575

to establish the origin of the infection.[8] To date, over 6 million cases of human SARS-CoV-2 infection have been reported, and coronavirus disease 2019 (COVID-19) is said to be rapidly spreading worldwide.

Methods We performed a literature review using the PubMed and Google Scholar databases to identify relevant papers published only in English until May 10, 2020. We searched the following terms: "COVID-19," "coronavirus," "SARS--CoV," "severe acute respiratory syndrome coronavirus," "SARS-CoV-2," and "MERS" with combinations including "neurotropism," "neurology," "neurological," "stroke," "cerebrovascular disease," "meningoencephalitis," and "acute inflammatory polyneuropathy." The aim of the search was to identify case reports, retrospective studies, review articles, guidelines, or recommendations. Additional relevant papers from references were also included in the analysis. The overall number of articles included in the final analysis was 82.

Neurological symptoms in patients with coronavirus disease 2019: Wuhan's experience Apart from the complex pathophysiology of neuroinvasion in COVID-19, SARS-CoV-2 also shows neurotropic properties. The first retrospective study on the specific neurological manifestations in patients with COVID-19 was conducted in Wuhan, China.[9] This is the only report summarizing all previous neurological symptoms of SARS--CoV-2 invasion in the Chinese population. It was based on the clinical data of 214 patients hospitalized in 3 designated COVID-19 care units from January 16 to February 19, 2020. Overall, neurological symptoms occurred in 36.4% of individuals and the patients were divided into groups depending on the affected site, ie, peripheral nervous system (PNS; 8.9%), central nervous system (CNS; 24.8%), and skeletal muscles (10.7%). The most common complaints related to the PNS included hypogeusia (5.6%) and hyposmia (5.1%), while those associated with the CNS involvement included dizziness (16.8%) and headache (13.1%). Based on the diagnostic criteria, 41.1% of the study subjects were classified as severe patients (SPs) and 58.9% as nonsevere patients (NSPs). The former group comprised older patients who more frequently had concomitant diseases compared with the latter group (age, 58.2 vs 48.9 years; comorbidities, 47.7% vs 32.5%). Interestingly, disturbances of the nervous system were more prevalent in SPs compared with NSPs (45.5% vs. 30.2%) and included muscle injury (19.3 vs 4.8%), impaired consciousness (14.8 vs 2.4%), and acute cerebrovascular diseases (5.7 vs 0.8%)—a single patient with cerebral hemorrhage, 4 patients with ischemic stroke in the SP group, and a single patient with ischemic stroke in the NSP group. Additionally, compared with the NSP group, the SP group presented with an impaired coagulation system with higher D-dimer levels, a markedly increased inflammatory response, and multiple organ failure involving the liver, the kidneys, and muscles.[9]

Severe acute respiratory syndrome coronavirus, severe acute respiratory syndrome coronavirus 2, and Middle East respiratory syndrome coronavirus Clinical symptoms of pneumonia due to SARS--CoV-2, SARS-CoV, and MERS-CoV infection are very similar. Genomic analysis confirmed that some conserved replicase domains of SARS-CoV-2 were 94.6% identical to those of SARS-CoV.[10,11] The most common clinical manifestations of SARS-CoV and SARS-CoV-2 infections were fever, dry cough, chills, and difficulty breathing.[12] However, as opposed to SARS-CoV and MERS--CoV, the target cells of SARS-CoV-2 seem to be mainly located in the lower respiratory tract.[6] Common clinical signs at disease onset in patients with COVID-19 in Wuhan included fever (83%–99%) and dry cough (59.4%–82%). Respiratory distress was the most characteristic symptom (55%) that impaired spontaneous breathing in about 89% of patients.[6,13,14] In addition to respiratory disturbances, some neurological symptoms such as paresthesia, headache, or loss of consciousness were reported in 36.4% of patients with SARS-CoV-2 infection. Furthermore, neurological signs were more prevalent in severely affected patients compared with those with mild COVID-19.[9] A potential damage to the nervous system was also determined in other SARS-CoV infections. Similarly to patients with COVID-19, those with SARS-CoV infection developed axonal polyneuropathy, myopathy, and rhabdomyolysis. However, these abnormalities were induced not at the beginning yet 3 to 4 weeks after the onset of respiratory symptoms. Hypercoagulability followed by ischemic stroke and encephalitis has been described both in SARS-CoV-2 and SARS--CoV infections.[15] Based on the autopsy studies demonstrating meningeal vasodilatation, cerebral edema, neuronal changes, infiltration of lymphocytes and monocytes in the vessel wall, and demyelination of the nerves, immune cell injury was considered to account for the pathogenesis of SARS-CoV.[16] Furthermore, patients with MERS--CoV infection mainly presented with rapid respiratory disturbances accompanied by cough, dyspnea, fever, myalgia, and multiple organ failure.[12] However, Kim et al[17] noted that MERS-CoV infection was also related to a potential neuroinvasion. Almost 1/5 of patients exhibited neurological manifestations including Guillain–Barré syndrome (GBS), ischemic stroke, and toxic or infectious polyneuropathy, which were delayed by 2 to 3 weeks after respiratory distress.[17] Similarly to patients with SARS-CoV-2 infection, those with MERS-CoV also had seizures.[18]

There is evidence showing that most coronaviruses have a neuroinvasive potential. They may invade the CNS, and their action is not only related to respiratory tract damage. As a result, neurotropism is a common feature of coronaviruses.[19] Due to the similar invasion pathway

and structure of coronaviruses, some neuroinvasive properties could also be identified in SARS-CoV-2.

Neurotropism of severe acute respiratory syndrome coronavirus 2 Studies have shown that SARS--CoV and SARS-CoV-2 use the same cell entry receptor, ie, angiotensin-converting enzyme 2 (ACE2), and indicated that the SARS-CoV-2 protein binds to ACE2 10- to 20-fold stronger than SARS-CoV.[20] By binding to ACE2 receptors located in various sites such as skeletal muscles, the capillary endothelium, and the nervous system, SARS-CoV-2 may increase the risk of cerebral hemorrhage and impairment of the blood–brain barrier (BBB). It may enter the CNS and attack the vascular system.[7] As previously reported, the brain expresses ACE2 receptors detected mainly in the brain stem, in the region responsible for cardiovascular functions, ie, the nucleus of the tractus solitarius and the paraventricular nucleus. The ACE2 receptors are expressed in glial cells and neurons, which should prompt further investigation of neurotropic properties of SARS--CoV-2 and its impact on mortality and morbidity in patients with COVID-19.[21,22]

The route of viral spread to the nervous system In several viruses, including coronaviruses, studies confirmed the presence of another pathway enabling entry via peripheral nerves and facilitating the viral spread to the CNS via synaptic connections.[19] The neural pathway makes viral migration possible through infecting motor or sensory nerve endings by dynein and kinesin for antero- or retrograde transport.[23] Considering the unusual structure of the olfactory nerve in the nasal cavity and olfactory fibers, it seems that the olfactory transport is a good example of the neural pathway for SARS-CoV-2. In 2013, Koyuncu et al[24] reported that the olfactory system could be a unique passage for viruses between the nasal epithelium and the CNS. Other reports have also shown a rapid invasion of SARS-CoV-2 and MERS-CoV into the brain through the olfactory bulb via the trans-synaptic neural pathway after intranasal administration of coronaviruses.[25,26] As a result, coronaviruses can invade the nasal cavity and reach the brain and the cerebrospinal fluid (CSF) through olfactory nerves and the olfactory bulb, which can result in inflammation and demyelination.[12] Apart from that, the ACE2 receptor is extensively expressed in the epithelium of the mucosa and the oral cavity, which is used by SARS-CoV-2 to bind and penetrate the cells.[27]

Some patients at a department of infectious diseases in Milan, Italy, reported olfactory and taste disorders. As a result, a survey on the prevalence of these abnormalities was conducted in patients with COVID-19. It revealed that 33.9% of the subjects presented with at least 1 taste or olfactory disorder and 18.6% of the patients reported both disorders. These symptoms were more prevalent in women compared with men (52.6% vs 25%). Furthermore, patients with at least 1 of these disorders were younger than those asymptomatic (56 vs 66 years).[28] The analysis showed that olfactory and taste disorders were fairly frequent in patients with SARS-CoV-2 infection and might precede the onset of full-blown clinical disease.

Additionally, the brain glymphatic pathway, which consists of cervical and olfactory vessels, could provide another significant entry route to the brain for SARS-CoV-2.[29] A postmortem histological examination indicated that SARS--CoV-2 can cause endothelial dysfunctions with lymphocytic endotheliitis in numerous organs such as the heart, the kidneys, the lungs, the liver, and the small intestine, as well as in the lymphatic drainage in the brain.[30,31] Moreover, Paniz-Mondolfi et al[32] described SARS-CoV-2 in the frontal lobe tissue on transmission microscopy, which provided evidence for the hematogenous route as a pathway for SARS-CoV-2 entry to the brain.

To sum up, SARS-CoV-2 can infect the brain and the CNS and cause multiple neurological symptoms. Of note, there are several mechanisms underlying its entry.

Cytokine storm Another significant result of COVID-19 related to nervous system damage is that SARS-CoV-2 infection may lead to a noticeable systemic inflammatory storm.[33] The pathophysiology of SARS-CoV-2 infection has not been established yet. However, an aggressive inflammatory process after SARS-CoV replication has already been confirmed.[34] The result of a large release of chemokines and cytokines is associated with BBB impairment, which additionally initiates and enhances the neuroinflammatory reaction.[3] Huang et al[6] reported that SARS--CoV-2 infection contributed to an increased secretion of interferon γ, interleukin 1β (IL-1β), monocyte chemoattractant protein 1, interferon γ–induced protein 10, IL-4, or IL-10 and was related to higher serum levels of granulocyte colony-stimulating factor, IL-2, IL-7, interferon γ–induced protein 10, IL-10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α, and tumor necrosis factor α in patients hospitalized in an intensive care unit compared with non–intensive care unit patients. A positive correlation was also observed between COVID-19 severity and IL-6 levels.[35] However, it was assumed that overactive immune reactions could induce clinical deterioration. As a result, some immunosuppressive drugs are under investigation, being regarded as a putative treatment for COVID-19.[36,37] Of note, Giovannoni et al[38] indicated a low-to-moderate mortality and morbidity risk in multiple sclerosis patients with COVID-19 who received disease-modifying therapy. However, other authors were skeptical about this approach and indicated the necessity to confirm such data in long-term studies.[39]

Severe acute respiratory syndrome coronavirus 2 and its association with encephalitis and meningitis

For many years, SARS-CoV has been perceived as the pathogen responsible for diseases that occur outside the respiratory system. The genome sequences of SARS-CoV were found in the brain. The inflammatory process was detected in the brains of all patients with SARS-CoV infection at autopsy, using a real-time polymerase chain reaction (PCR) test. Of note, high signals were observed in the hippocampus.[40] Inflammatory lesions in the CNS, including damage to the nerve tissue and neurons, are related to encephalitis caused by some pathogens such as viruses. The disease is usually manifested by a violent onset, vomiting, headache, high fever, convulsions, and impaired consciousness.[41] To date, several cases of encephalitis and meningitis have been reported in patients with SARS-CoV-2 infection, including a single case of rhombencephalitis.[42-45]

In Japan, a case of a 24-year-old man with generalized fatigue and fever was reported. Two physical examinations were performed and antiviral and antipyretic agents were administered. On day 5, generalized seizures accompanied by loss of consciousness were observed. Interestingly, the SARS-CoV-2 RNA was detected only in the CSF. It was not found in the nasopharyngeal swab. Additionally, hyperintensity along the right lateral ventricular wall, in the right mesial temporal lobe, and in the hippocampus was seen on magnetic resonance imaging (MRI).[46] Similarly, a young, obese 41-year-old woman from Los Angeles, United States, with a history of diabetes, complained of headache, fever, and new-onset seizures. The patient was diagnosed with COVID-19. Previously, she had been admitted due to viral meningitis based on the CSF examination (70 white blood cells, 100% lymphocytes). Owing to worsening encephalopathy with disorientation, hallucinations, and febrile illness, SARS-CoV-2 testing was performed. The patient's neurological condition improved several days after hydroxychloroquine administration. It was impossible to directly confirm the presence of SARS-CoV-2 in the CSF owing to the fact that the CSF specimen could not be referred for PCR testing through local commercial, governmental, or academic laboratories.[43] Hence, the presence of isolated COVID-19–related meningoencephalitis without respiratory involvement should also be considered.

Furthermore, aseptic meningitis with neurological focal symptoms was also reported in patients with COVID-19. It can be explained by the presence of a parainfectious mechanism, which further supports rapid clinical improvement and results in the absence of abnormalities on brain MRI.[44]

Recently, Dogan et al[42] presented a series of severely ill patients with COVID-19–related autoimmune meningoencephalitis who were treated with plasmapheresis. They found that, in most of them, the clinical status improved after therapy. Severe acute respiratory syndrome coronavirus 2 infection–related encephalitis and potential meningitis showed neuroinvasive properties of the virus. In light of the COVID-19 pandemic, it should be noted that unconscious patients are suspected to be infected with SARS-CoV-2.

Currently, at the time of the pandemic, coronavirus infection should also be considered an etiological factor in patients with clinical symptoms suggestive of encephalitis and meningitis. Typical symptoms of neuroinfection include headache, photophobia, vomiting, impaired consciousness, and seizures. Meningeal symptoms and fever may also be present. Additional investigations include neuroimaging and electroencephalography. However, the assessment of the CSF and CSF PCR testing for SARS-CoV-2 represent the most useful diagnostic methods.

Severe acute respiratory syndrome coronavirus 2 and the risk of damage to the peripheral nervous system

To date, several cases of GBS have been reported in patients with COVID-19.[47-52] The syndrome is characterized by ascending symmetrical flaccid paralysis of the upper and lower limbs, associated with areflexia, disorders of superficial sensation, and the involvement of the cranial nerves. It is typically triggered by an autoimmune reaction directed against neuronal gangliosides. As a result of molecular mimicry, it causes damage to the myelin sheath and peripheral nerve axons. It is mostly preceded by *Campylobacter jejuni*, cytomegalovirus, Epstein–Barr virus, influenza A virus, *Mycoplasma pneumoniae*, and *Haemophilus influenzae* infections. However, the syndrome has also been reported in the course of SARS-CoV and MERS-CoV infections.[53]

Symptoms of axonal and demyelinating GBS were reported within 5 to 11 days after the diagnosis of COVID-19 in patients with the presence or absence of fever and symptoms of respiratory distress during coronavirus infection. Some patients presented only with the preceding olfactory and/or taste disorders.[47-52] The diagnosis of GBS was confirmed by the typical albuminocytological dissociation in the CSF and the electrophysiological data indicative of acute demyelinating polyneuropathy with the demyelinating or axonal variant. Test results were negative in patients who underwent CSF PCR testing for SARS-CoV-2. Some patients with GBS developed symptoms of respiratory failure. It is difficult to assess whether respiratory distress was associated with neuromuscular damage in the course of GBS or COVID-19. All patients were successfully treated with human intravenous immunoglobulin preparations.[47-52]

Miller Fisher syndrome (MFS) is another unusual manifestation related to SARS-CoV-2 infection.[54] It is characterized by ataxia, external ophthalmoplegia, loss of tendon reflexes, and rapid disease onset. It is mainly preceded by infections similar to those observed in GBS. In a 50-year-old man, cough, fever, low back pain, headache, and malaise were reported. Additionally, anosmia,

ageusia, ataxia, areflexia, right fascicular oculomotor palsy, and right internuclear ophthalmoparesis were observed after 5 days. Biochemical tests showed albuminocytological dissociation and present anti-GD1b-IgG antibodies. The oropharyngeal swab PCR test for SARS-CoV-2 yielded a positive result, and the CSF test result was negative. Except for residual anosmia and ageusia, the patient completely recovered after treatment with intravenous immunoglobulin.[54]

Probably, an immune response due to increased proinflammatory cytokine levels, including IL-6, causes GBS and MFS in patients with COVID-19. This interleukin type, produced by lymphocytes, triggers a cascade of inflammatory events leading to neuronal damage in the PNS.

Knowledge on the potential occurrence of GBS and MFS as a neurological manifestation or complication of COVID-19 is crucial to establish an effective immunoglobulin therapy. Of note, respiratory distress typically occurring in patients with COVID-19 may also be one of the symptoms of severe GBS. At the time of the pandemic and due to a large number of severely ill patients, it is easy to overlook other clinical symptoms suggestive of GBS such as flaccid paralysis with areflexia and sensory disturbances. Lumbar puncture (indicating elevated protein levels and normal cell counts in the CSF albuminocytological dissociation) and electroneurography (indicating acute demyelinating polyneuropathy) represent the most relevant and, at the same time, conclusive diagnostic tests.

Severe acute respiratory syndrome coronavirus 2 and the risk of cerebrovascular disease Coronavirus disease 2019 is often related to deep hypoxia due to impaired alveolar gas exchange in lung tissue cells.[55] The increasing anaerobic metabolism in the mitochondria of the brain results in cerebral vasodilation, brain edema, and decreased cerebral blood flow followed by ischemia. Intracranial hypertension occurs if hypoxia is uncontrolled. Hypertension, in turn, leads to deterioration of the brain function, cerebral circulation disorders, drowsiness, or even coma.[56] Finally, whereas 40% of patients with SARS-CoV-2 infection showed evident symptoms of brain dysfunction,[9] some evidence for brain edema in patients with COVID-19 has been reported at autopsy.[57] These findings confirmed that hypoxia initiated by SARS-CoV-2 leads to nervous system damage. Furthermore, severe viremia with hypoxia in patients with COVID-19 may contribute to toxic encephalopathy.

As a result of multiple significant laboratory abnormalities found in patients with COVID-19, it has been suggested that SARS-CoV-2 infection is related to immune deficiency, hepatic injury, activated coagulation, and cardiac and renal disorders.[58] Abnormal laboratory test results are similar to those previously reported in patients with SARS-CoV and MERS-CoV infections.[13,59] The biochemical features of COVID-19 include increased alanine transaminase activity, increased creatinine kinase activity, elevated lactate dehydrogenase (LDH) and C-reactive protein levels, prolonged prothrombin time with elevated D-dimer levels, and depletion of CD4 and CD8 lymphocytes accompanied by lymphopenia.[13] A significant decrease in the peripheral blood lymphocyte count and a progressive increase in D-dimer levels were observed in patients with severe COVID-19.[58] In these cases, prothrombotic conditions may make SARS-CoV-2–infected patients susceptible to acute cerebrovascular events.[13] An inflammatory cytokine storm, previously confirmed in the course of COVID-19, is also potentially associated with cerebrovascular disease.[60,61] In addition, hypoxia in SARS-CoV-2 infection should be considered a factor predisposing to acute cerebrovascular disease, mainly in patients at risk of developing cerebrovascular disturbances.[12] Furthermore, since SARS-CoV-2 binds to ACE2 receptors, patients with hypertension may report blood pressure fluctuations due to SARS-CoV-2 infection, which may increase the risk of intracranial hemorrhage. Additionally, patients with advanced COVID-19 often develop severe thrombocytopenia, which can also predispose them to cerebral hemorrhage.

Numerous cases of cerebrovascular disease have been reported in patients with COVID-19.[62-64] International recommendations on the care of stroke patients during the COVID-19 pandemic have been developed.[65,66]

It is assumed that hypertensive patients with SARS-CoV-2 infection should be switched from ACE inhibitors or angiotensin II receptor blockers to other antihypertensive drugs (eg, calcium channel blockers or diuretics).[66]

From the clinical point of view, caution should be exercised in patients with symptoms of acute cerebrovascular disease who may have COVID-19, which predisposes them to vascular disease. According to the recommendations of the Polish Ministry of Health, severely ill patients are at increased risk of developing COVID-19.

Severe acute respiratory syndrome coronavirus 2 and other neurological disorders Muscle injury is confirmed by elevated creatinine kinase and increased LDH levels.[67] However, the relationship between muscle damage and COVID-19 remains unclear. Perhaps, it could be related to SARS-CoV-2 binding to ACE2 receptors in skeletal muscle cells. Another reason for muscle injury in COVID-19 may be a systemic inflammatory storm accompanied by elevated cytokine levels.

The associations between systemic inflammation and delirium as well as neurodegenerative disturbances and psychiatric disorders have been confirmed in previous studies.[68-70] To conclude, SARS-CoV-2 may compromise the BBB, infect glial cells, activate Toll-like receptors in astrocytes and microglia, promote chronic neuroinflammation, and cause brain damage by neuronal death.[12] Based on that, the onset or progression

of neurodegenerative disorders, behavioral changes, or cognitive deficits in COVID-19 pneumonia seem to be undoubtable.

According to Helms et al,[71] 58 of 64 patients hospitalized in intensive care units (in Strasbourg, France) for acute respiratory distress syndrome due to COVID-19 presented with neurological symptoms caused by encephalopathy with agitation, confusion, dysexecutive syndrome, ataxia, and corticospinal tract signs. In 2 patients, MRI showed single acute ischemic stroke.[71]

Particular attention should be paid to the decreased respiratory function in patients with myasthenia gravis, in whom COVID-19 should be regarded as the underlying cause.[37]

A single case of spinal injury in COVID-19 has also been reported.[72] In SARS-CoV-2 infection, a systemic inflammatory reaction accompanied by a massive release of inflammatory markers including cytokines and chemokines leads to increased BBB permeability. As a result, the markers initiate neuroinflammation, which can impair brain homeostasis and cause neuronal death.[3] Neuroinflammation associated with functional brain damage can explain clinical observations according to which patients recovering from pneumonia present with cognitive impairment and behavioral disorders or delirium. Delirium is often caused by a peripheral infection associated with systemic inflammation. During delirium, elevated serum levels of interleukins and 100% soluble protein (S100B; a marker for BBB disruption) were found in elderly patients.[68] Neuroinflammation is also observed in neurodegenerative diseases and plays a role in the pathogenesis of psychiatric disorders.[69,70] In addition, severe respiratory distress associated with COVID-19, causing long-term hypoxia, may be responsible for neurocognitive changes.[3]

Skin symptoms of coronavirus disease 2019 Furthermore, an impaired immune response seems to be associated with skin manifestations in SARS-CoV-2 infection. The first study[73] on skin involvement in COVID-19 identified cutaneous symptoms in 20.4% of patients, which included widespread urticarial erythematous rash and chickenpox-like vesicles. Lesions were located mainly in the trunk region and healed within several days.[73] Moreover, urticarial rash with angioedema was documented 48 hours before developing other clinical signs (continuous cough and fever) of SARS-CoV-2 infection.[74] This issue increased the risk of potentially delayed COVID-19 diagnosis as a consequence of misdiagnosis of spontaneous urticaria. Another mild case of COVID-19 with pruritic lesions on both heels has also been reported in Spain.[75] Recently, in a study of 375 patients, Galván Casas et al[76] divided skin eruptions observed in SARS-CoV-2 infection into 5 subgroups: maculopapular eruptions (47%), acral areas of erythema with pustules or vesicles (19%), urticarial lesions (19%), other vesicular eruptions (9%), and necrosis or livedo reticularis (6%).[76] The different types of rash seem to be related to various pathophysiological mechanisms; early skin manifestations reflected the virological phase and those occurring later were a consequence of an impaired immune response.[74]

Severe acute respiratory syndrome coronavirus 2 in children Severe acute respiratory syndrome coronavirus 2 infection has been predominantly more prevalent among adults; confirmed cases in children were relatively rare. Noteworthy, COVID-19 might occur not only in adults but also in children and infants. The latest reports have clearly shown that children are susceptible to SARS-CoV-2 infection because of their immature immune systems. Moreover, due to severe illness, children with comorbidities (lung and airway diseases, malnutrition, tumors) are vulnerable to COVID-19. In children, the most common clinical manifestations of COVID-19 included cough and fever, sometimes accompanied by myalgia, rhinitis, headache, dizziness, fatigue, vomiting, or abdominal pain. Some newborns exhibited atypical symptoms like gastrointestinal disturbances and diarrhea.[77] Neurological manifestations have also been evaluated in children with COVID-19 and included encephalopathy, muscle weakness, cerebellar and brainstem signs, headache, and reduced reflexes. All patients required intensive care unit admission, but there was no evidence for infection in the CSF examination. They had mild neuropathic and myopathic changes and slow activity on electroencephalography and showed neurological improvement and complete recovery.[78] It seems that COVID-19 in children was less severe than in adults and children were less sensitive to SARS-CoV-2 infection. It has been speculated that children often experience viral infections and may have higher levels of antibodies against viruses compared with adults. Additionally, children's immune systems are still developing and their response to pathogens may differ from that observed in adults.[79] Of note, the number of children with COVID-19 has also increased, and data regarding epidemiology and neurological symptoms are still scarce.

Summary: implications for internists Despite the fact that the case-fatality rate of SARS-CoV-2 infection is low, all studies have confirmed that the virus is more infectious than SARS-CoV and MERS-CoV. Additionally, coronaviruses are neurotropic, and SARS-CoV-2 may have neuroinvasive properties that lead to neurological disturbances. It is also postulated that COVID-19 neurotropism may contribute to respiratory failure.[80] The impairment of the nervous system can be caused by several mechanisms. A direct CNS infection via trans-synaptic pathways, an impaired BBB, and an enormous neuroinflammatory response with prolonged hypoxia promote damage to the nervous system in SARS-CoV-2 infection. Furthermore, in patients with severe COVID-19,

neurological involvement is more remarkable and manifested by impaired consciousness, encephalitis, cerebrovascular diseases, or muscle injury. Patients should be screened to stop the COVID-19 pandemic. This is the first step to overcome the clinical manifestations of SARS-CoV-2 infection at disease onset and to limit the spread of the virus. Therefore, next to respiratory tract symptoms, close attention should be paid to neurological signs in patients with COVID-19.

Coronaviruses can infect neurons and glial cells through ACE2 receptors or by endocytosis. These viruses damage brain stem cells, which may result in respiratory distress. The CNS infection with systemic inflammation associated with COVID-19 leads to BBB damage and triggers a neuroinflammatory response with reactive astrogliosis and microglial activation.

The case of our friend who is a cardiologist inspired us to write this review. The physician was diagnosed with COVID-19 at the beginning of the pandemic. The patient reported prodromal symptoms (severe weakness, severe headache, periodic dizziness, olfactory and taste disorders, insomnia, limb and facial paresthesia, and muscle pain) approximately a week before the onset of dyspnea, respiratory disturbances, and fever.

From the clinician's perspective, knowledge on SARS-CoV-2 neurotropism is of crucial importance. First, in some patients, neurological symptoms such as headache, dizziness, olfactory and taste disorders, paresthesia, and myalgia may precede the general symptoms of COVID-19 (ie, fever and respiratory disturbances). Severe acute respiratory syndrome coronavirus 2 can be the primary source of infection in patients presenting with typical neurological symptoms including impaired consciousness, seizures, or symptoms of flaccid or spastic paralysis associated with hypoesthesia. The above should prompt testing for SARS-CoV-2.

Due to neuroinvasion in COVID-19, a rapid and adequate differentiation of SARS-CoV-2–infected patients is needed to overcome the pandemic. Therefore, immediate attention should be paid to the neurological manifestations of the disease. The first step is to make physicians aware of the neurotropic properties of SARS-CoV-2. Of note, screening of neurological disturbances should be performed by a neurologist as well as by an internist, a cardiologist, or a pulmonologist. Furthermore, most neurological signs could be recognized by family doctors in outpatient clinics. In most cases, these specialists are involved in the assessment of the clinical manifestations of SARS-CoV-2 at disease onset. They should remember that neurological symptoms may be the only abnormalities in the course of COVID-19. Based on the established evidence for neuroinvasion in COVID-19, family doctors and internists could effectively limit the spread of the virus.

To conclude, some typical neurological symptoms (such as olfactory and taste disturbances) reported by patients during the COVID-19 pandemic should prompt physicians in outpatient settings to test patients for SARS-CoV-2 infection. Additionally, the characteristic signs of CNS damage, including unilateral paresis, hypoesthesia, speech abnormalities, or the first episode of seizure, should be considered typical of SARS-CoV-2 infection. In the case of vomiting, high fever, headache, or dizziness, the assessment of the CSF and CSF PCR testing for SARS-CoV-2 are required. General practitioners should suspect COVID-19 not only in severely affected patients but also in those presenting with some other symptoms suggestive of GBS, such as limb weakness, sensory disturbances, or areflexia, which should not be overlooked. The widespread urticarial erythematous rash and chickenpox-like vesicles located mainly in the trunk region should be considered when establishing the diagnosis of COVID-19. Finally, all patients with impaired consciousness in various hospital departments should be monitored and tested for SARS-CoV-2.

There are well-known, serious consequences of SARS-CoV-2 infection that are associated with numerous diseases involving multiple internal organs. Therefore, general practitioners are often obliged to perform medical examination in patients with neurological symptoms suggestive of COVID-19. They should pay special attention to a decreased peripheral blood lymphocyte count and increased D-dimer levels in SARS-CoV-2–infected patients, which predispose them to prothrombotic conditions and acute cerebrovascular diseases. Physicians should monitor acute respiratory disturbances in COVID-19—resulting in decreased oxygen saturation, dyspnea, and hypoxia—to avoid acute cerebrovascular events or a crisis in myasthenia gravis. Due to the fact that SARS-CoV-2 binds to ACE2 receptors, hypertensive patients with COVID-19 may report blood pressure fluctuations, which is a risk factor for intracranial hemorrhage. As a result, internists should consider switching patients to other antihypertensive drugs, ie, calcium channel blockers should be administered instead of ACE inhibitors or angiotensin II receptor blockers. Furthermore, general practitioners should be aware of multiple general complications in COVID-19, including acute liver and kidney damage, immune deficiency, or arrhythmia. Dysrhythmias may occur in viral diseases due to hypoxia, inflammatory stress, and abnormal metabolism.[81] Each general medical examination in patients with neurological symptoms suggestive of COVID-19 should include monitoring of biochemical features of SARS--CoV-2 infection, ie, increased creatinine kinase and alanine transaminase activity, elevated LDH levels, or depletion of CD4 and CD8 lymphocytes accompanied by lymphopenia. Acute infection with an increased C-reactive protein concentration and elevated proinflammatory cytokine levels should also be assessed by general practitioners. Additionally, gastrointestinal disturbances such as diarrhea, abdominal pain, nausea, and vomiting could be the manifestations of SARS-CoV-2

infection. Such disturbances should be always taken into account by family doctors and internists.[82] General practitioners should be aware that a single clinical sign may occur as a result of multifocal disturbances in SARS-CoV-2–infected patients, particularly in those with neurological symptoms. For example, hypoesthesia is related to polyneuropathy in diabetes, and sensory disturbances could be directly associated with SARS-CoV-2 infection. Similarly, headache, dizziness, dyspnea, impaired consciousness, systemic inflammation, or prothrombotic conditions are found in numerous internal and neurological diseases and also reported in COVID-19. Diagnosing the real cause of these abnormalities seems to pose a challenge to physicians. However, it is of key importance to achieve the interdisciplinary approach in the management of patients with COVID-19 and to overcome the worldwide pandemic.

Of note, neurological manifestations due to SARS-CoV-2 infection might occur in either symptomatic or asymptomatic patients. The majority of infected patients had moderate or mild symptoms, and patients with the most severe course of COVID-19 experienced respiratory disturbances leading to intubation. Meanwhile, Wu et al[12] showed that meningoencephalitis might be the sole manifestation of COVID-19. Similarly, Duong et al[43] reported a case of a 41-year-old woman with a history of diabetes who had COVID-19 and presented with isolated meningoencephalitis without respiratory distress. Neurologically, she suffered from worsening encephalopathy with hallucinations and disorientation, and CSF analysis revealed viral meningitis. No respiratory involvement was observed.[43]

Currently, numerous questions related to SARS-CoV-2 neurotropism still remain unanswered, for example:

- What percentage of patients with SARS-CoV-2 infection will present with neurological symptoms and/or complications?
- Could the involvement of the CNS or the PNS be one of the potentially reversible causes of life-threatening conditions (eg, respiratory failure in GBS, stroke) in severely ill patients and in those with respiratory and circulatory failure?

A more extensive neurological assessment in patients with COVID-19 should be considered based on the previously reported cases. Currently, we observe a rapidly growing knowledge on the new coronavirus infection. We are convinced that the following weeks and months will provide new insights into this issue.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

HOW TO CITE Adamczyk-Sowa M, Niedziela N, Kubicka-Bączyk K, et al. Neurological symptoms as a clinical manifestation of coronavirus disease 2019: implications for internists. Pol Arch Intern Med. 2021; 131: 54-62. doi:10.20452/pamw.15575

REFERENCES

1 Li F. Structure, function, and evolution of coronavirus spike proteins. Annu Rev Virol. 2016; 3: 237-261.

2 Tang Q, Song Y, Shi M, et al. Inferring the hosts of coronavirus using dual statistical models based on nucleotide composition. Sci Rep. 2015; 5: 17155.

3 Steardo L, Steardo L Jr, Zorec R. Neuroinfection may potentially contribute to pathophysiology and clinical manifestations of COVID-19. Acta Physiol (Oxf). 2020; 229: e13473.

4 Cui J, Li F, Shi Z-L. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 2019; 17: 181-192.

5 Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol. 2020; 92: 552-555.

6 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395: 497-506.

7 Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci. 2020; 11: 995-998.

8 Wu A, Peng Y, Huang B, et al. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell Host Microbe. 2020; 27: 325-328.

9 Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020; 77: 683-690.

10 Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382: 727-733.

11 Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. 2020; 579: 265-269.

12 Wu Y, Xu X, Chen Z, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020; 87: 18-22.

13 Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020; 323: 1061-1069.

14 Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395: 507-513.

15 Tsai LK, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. Acta Neurol Taiwan. 2005; 14: 113-119.

16 Gu J, Gong E, Zhang B, et al. Multiple organ infection and the pathogenesis of SARS. J Exp Med. 2005; 202: 415-424.

17 Kim JE, Heo JH, Kim HO, et al. Neurological complications during treatment of Middle East respiratory syndrome. J Clin Neurol. 2017; 13: 227-233.

18 Saad M, Omrani AS, Baig K, et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. Int J Infect Dis. 2014; 29: 301-306.

19 Li YC, Bai WZ, Hirano N, et al. Coronavirus infection of rat dorsal root ganglia: ultrastructural characterization of viral replication, transfer, and the early response of satellite cells. Virus Res. 2012; 163: 628-635.

20 Wrapp D, Wang N. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. 2020; 367: 1260-1263.

21 Xia H, Lazartigues E. Angiotensin-converting enzyme 2: central regulator for cardiovascular function. Curr Hypertens Rep. 2010; 12: 170-175.

22 Gowrisankar YV, Clark MA. Angiotensin II regulation of angiotensin-converting enzymes in spontaneously hypertensive rat primary astrocyte cultures. J Neurochem. 2016; 138: 74-85.

23 Swanson PA 2nd, McGavern DB. Viral diseases of the central nervous system. Curr Opin Virol. 2015; 11: 44-54.

24 Koyuncu OO, Hogue IB, Enquist LW. Virus infections in the nervous system. Cell Host Microbe. 2013; 13: 379-393.

25 Netland J, Meyerholz DK, Moore S, et al. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol. 2008; 82: 7264-7275.

26 Li K, Wohlford-Lenane C, Perlman S, et al. Middle East respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4. J Infect Dis. 2016; 213: 712-722.

27 Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020; 12: 8.

28 Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis. 2020; 71: 889-890.

29 Bostancıklıoğlu M. SARS-CoV2 entry and spread in the lymphatic drainage system of the brain. Brain Behav Immun. 2020; 87: 122-123.

30 Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020; 395: 1417-1418.

31 Louveau A, Smirnov I, Keyes TJ, et al. Structural and functional features of central nervous system lymphatic vessels. Nature. 2015; 523: 337-341.

32 Paniz-Mondolfi A, Bryce C, Grimes Z, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS--CoV-2). 2020; 92: 699-702.

33 Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools. 2020; 35: 266-271.

34 Wong CK, Lam CW, Wu AK, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol. 2004; 136: 95-103.

35 Wan S, Yi Q, Fan S, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). medRxiv. 2020. doi:10.1101/2020.02.10.20021832.

36 Novi G, Mikulska M, Briano F, et al. COVID-19 in a MS patient treated with ocrelizumab: does immunosuppression have a protective role? Mult Scler Relat Disord. 2020; 42: 102120.

37 Anand P, Slama MCC, Kaku M, et al. COVID-19 in patients with myasthenia gravis. 2020 May 22. [Epub ahead of print].

38 Giovannoni G, Hawkes C, Lechner-Scott J, et al. The COVID-19 pandemic and the use of MS disease-modifying therapies. Mult Scler Relat Disord. 2020; 39: 102073.

39 Sormani MP. An Italian programme for COVID-19 infection in multiple sclerosis. Lancet Neurol. 2020; 19: 481-482.

40 Gu J, Gong E, Zhang B, et al. Multiple organ infection and the pathogenesis of SARS. J Exp Med. 2005; 202: 415-424.

41 Ellul M, Solomon T. Acute encephalitis – diagnosis and management. Clin Med (Lond). 2018; 18: 155-159.

42 Dogan L, Kaya D, Sarikaya T, et al. Plasmapheresis treatment in COVID--19-related autoimmune meningoencephalitis: case series. Brain Behav Immun. 2020; 87: 155-158.

43 Duong L, Xu P, Liu A. Meningoencephalitis without respiratory failure in a young female patient with COVID-19 infection in Downtown Los Angeles, early April 2020. Brain Behav Immun. 2020; 87: 33.

44 Bernard-Valnet R, Pizzarotti B, Anichini A, et al. Two patients with acute meningo-encephalitis concomitant to SARS-CoV-2 infection. Eur J Neurol. 2020 May 7. [Epub ahead of print].

45 Wong PF, Craik S, Newman P, et al. Lessons of the month 1: a case of rhombencephalitis as a rare complication of acute COVID-19 infection. Clin Med (Lond). 2020; 20: 293-294.

46 Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-coronavirus-2. Int J Infect Dis. 2020; 94: 55-58.

47 Toscano G, Palmerini F, Ravaglia S, et al. Guillain-Barré syndrome associated with SARS-CoV-2. 2020; 382: 2574-2576.

48 Sedaghat Z, Karimi N. Guillain Barre syndrome associated with COVID-19 infection: a case report. J Clin Neurosci. 2020; 76: 233-235.

49 Camdessanche JP, Morel J, Pozzetto B, et al. COVID-19 may induce Guillain-Barré syndrome. Rev Neurol (Paris). 2020; 176: 516-518.

50 Padroni M, Mastrangelo V, Asioli GM, et al. Guillain-Barré syndrome following COVID-19: new infection, old complication? J Neurol. 2020; 267: 1877-1879.

51 Virani A, Rabold E, Hanson T, et al. Guillain-Barré Syndrome associated with SARS-CoV-2 infection. IDCases. 2020; 20: e00771.

52 Scheidl E, Canseco DD, Hadji-Naumov A, Bereznai B. Guillain-Barré syndrome during SARS-CoV-2 pandemic: a case report and review of recent literature. J Peripher Nerv Syst. 2020; 25: 204-207.

53 Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. Lancet. 2016; 388: 717-727.

54 Gutiérrez-Ortiz C, Méndez A. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. 2020; 95: e601-e605.

55 Guo YR, Cao QD, Hong ZS, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Mil Md Res. 2020; 7: 11.

56 Abdennour L, Zeghal C, Deme M, Puybasset L. Interaction brain-lungs [in French]. Ann Fr Anesth Reanim. 2012; 31: e101-e107.

57 Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020; 8: 420-422.

58 Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. 2020; 92: 568-576.

59 Hui DS, Wong PC, Wang C. SARS: clinical features and diagnosis. Respirology. 2003; 8 (suppl): S20-S24.

60 Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395: 1033-1034.

61 Chen C, Zhang XR, Ju ZY, He WF. Advances in the research of cytokine storm mechanism induced by Corona Virus Disease 2019 and the corresponding immunotherapies [in Chinese]. Zhonghua Shao Shang Za Zhi. 2020; 36: 471-475.

62 Viguier A, Delamarre L, Duplantier J, et al. Acute ischemic stroke complicating common carotid artery thrombosis during a severe COVID-19 infection. J Neuroradiol. 2020; 47: 393-394.

63 Hess DC, Eldahshan W, Rutkowski E. COVID-19-related stroke. Trans Stroke Res. 2020; 11: 322-325.

64 Moshayedi P, Ryan TE, Mejia LLP, et al. Triage of acute ischemic stroke in confirmed COVID-19: large vessel occlusion associated with coronavirus infection. Front Neurol. 2020; 11: 353.

65 Qureshi AI, Abd-Allah F, Al-Senani F, et al. Management of acute ischemic stroke in patients with COVID-19 infection: report of an international panel. Int J Stroke. 2020; 15: 540-554.

66 Jin H, Hong C, Chen S, et al. Consensus for prevention and management of coronavirus disease 2019 (COVID-19) for neurologists. 2020; 5: 146-151.

67 Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020 Apr 30; 382: 1708-1720.

68 McNeil JB, Hughes CG, Girard T, et al. Plasma biomarkers of inflammation, coagulation, and brain injury as predictors of delirium duration in older hospitalized patients. PLoS One. 2019; 14: e0226412.

69 Heneka MT, Carson MJ, El Khoury J, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 2015; 14: 388-405.

70 Pape K, Tamouza R, Leboyer M, Zipp F. Immunoneuropsychiatry – novel perspectives on brain disorders. 2019; 15: 317-328.

71 Helms J, Kremer S, Merdji H. Neurologic features in severe SARS--CoV-2 infection. 2020; 382: 2268-2270.

72 Righi G, Del Popolo G. COVID-19 tsunami: the first case of a spinal cord injury patient in Italy. Spinal Cord Ser Cases. 2020; 6: 22.

73 Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. J Eur Acad Dermatol Venereol. 2020; 34: e212-e213.

74 Hassan K. Urticaria and angioedema as a prodromal cutaneous manifestation of SARS-CoV-2 (COVID-19) infection. BMJ Case Rep. 2020; 13: e236981.

75 Estebanez A, Perez-Santiago L, Silva E, et al. Cutaneous manifestations in COVID-19: a new contribution. J Eur Acad Dermatol Venereol. 2020; 34: e250-e251.

76 Galván Casas C, Català A, Carretero Hernández G, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. 2020; 183: 71-77.

77 She J, Liu L, Liu W. COVID-19 epidemic: disease characteristics in children. J Med Virol. 2020; 92: 747-754.

78 Abdel-Mannan O, Eyre M, Löbel U, et al. Neurologic and radiographic findings associated with COVID-19 infection in children. JAMA Neurol. 2020 Jul 1. [Epub ahead of print].

79 Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020; 145: e20200702.

80 Paybast S, Emami A, Koosha M, Baghalha F. Novel coronavirus disease (COVID-19) and central nervous system complications: what neurologist need to know. Acta Neurol Taiwan. 2020; 29: 24-31.

81 Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. Am J Emerg Med. 2020; 38: 1504-1507.

82 Hajifathalian K, Mahadev S, Schwartz RE, et al. SARS-COV-2 infection (coronavirus disease 2019) for the gastrointestinal consultant. World J Gastroenterol. 2020; 26: 1546-1553.