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Neurological symptoms as a clinical manifestation of COVID-19: implications for internists

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ABSTRACT

Many experimental and clinical studies have proven that the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has tropism to 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 (ACE2) receptors or by endocytosis. The infection of the central nervous system (CNS) with the systemic inflammation associated with Coronavirus Disease 2019 (COVID-19) 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 damaged, which results in respiratory distress. Apart from typical symptoms of COVID-19 related to the involvement of the respiratory system, neurological manifestations such as headache, dizziness, myalgia, anosmia, ageusia, encephalopathy, encephalitis, stroke, epileptic seizures, rhabdomyolysis and the Guillain-Barre syndrome (GBS) are associated with SARS-CoV-2 infection. In the study, attention was paid to the currently known neurological manifestations of COVID-19 so that they could be considered mainly in COVID-19 asymptomatic patients, which may limit the transmission of coronavirus infection.

Keywords: neurotropism, COVID-19, SARS-CoV-2, meningoencephalitis, GBS, stroke

Introduction
Coronaviruses (CoVs) are a large group of positive RNA viruses genetically classified into four major genera, i.e., alpha, beta, gamma and delta CoVs. They mainly cause respiratory and enteric diseases in animals and humans (1). So far, six subtypes of human CoVs have been recognized, namely human coronavirus NL63 (HCoV-NL63), human coronavirus 229E (HCoV-229E), human coronavirus OC43 (HCoV-OC43), human coronavirus VHKU1 (HCoVHKU1), SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) (2). Although, human CoVs were identified for the first time in the 1960s (3), only the SARS-CoV pandemic in 2003 followed by MERS-CoV in 2013 drew the worldwide attention of researchers (4). While the clinical implications of MERS-CoV are still noticeable, another lethal and highly pathogenic CoV known as SARS-CoV-2 has been reported in China (5).

The first reports of the new CoV infection was observed in Wuhan City, Hubei Province, China in December 2019. Furthermore, a cluster of cases with clinical presentation of viral pneumonia was also noted (6). The assessment of the lower respiratory tract samples confirmed novel CoV, which was contagious among humans. The terms such as “Wuhan CoV” or “the new CoV” (2019-nCoV) were commonly used until January 2020. The official name, i.e., SARS-CoV-2, which was related to the taxonomic designation, appeared on 11th February 2020. At the same time, World Health Organization (WHO) termed the disease “COVID-19” (7). The recent pneumonia outbreak was associated with a large animal and seafood market. However, the investigations are ongoing to establish the origin of the infection (8). To date, over six million infections of human SARS-CoV-2 have been reported and COVID-19 is said to be rapidly spreading worldwide.

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

**Neurological symptoms in patients with COVID-19 - experience from Wuhan**

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 of patients with COVID-19 was conducted in Wuhan (9). This is the only report summarizing all previous neurological symptoms of SARS-CoV-2 invasion on the Chinese population. The clinical data were extracted from 214 patients hospitalized in 3 designated COVID-19 care units from 16th January to 19th February 2020. Overall, neurological symptoms occurred in 36.4% of subjects and they were divided into groups depending on their location, i.e., peripheral nervous system (PNS 8.9%), 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 the complaints related to the CNS included dizziness (16.8%) and headache (13.1%). Based on the diagnostic criteria, 41.1% of patients were classified as severe (SP) and 58.9% as non-severe (NSP). The former group was comprised of older patients who had more often concomitant diseases compared to the latter group (58.2 vs. 48.9 years and 47.7 vs. 32.5%, respectively). Interestingly, disturbances of the nervous system were more prevalent in SP compared to NSP (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%) - 1 patient with cerebral hemorrhage, 4 patients with ischemic stroke in SP and 1 subject with ischemic stroke in NSP. Additionally, patients from the SP group presented with impaired coagulation system with higher D-Dimer levels, more increased inflammatory response and multiple organ insufficiency, including the liver, kidneys and muscles compared to the NSP group (9).

**SARS-CoV, SARS-CoV-2 and MERS-CoV**

Clinical symptoms of pneumonia due to SARS-CoV-2, SARS-CoV and MERS-CoV are very similar. Simultaneously, the genomic analysis confirmed that in SARS-CoV-2 some conserved replicase domains were 94.6% identical to SARS-CoV (10, 11). The most common clinical manifestation in SARS-CoV as well as in SARS-CoV-2 infection 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). The common clinical signs at the onset of the disease in COVID-19 patients in Wuhan included fever (83%-99%) and dry cough (59.4%-82%). Respiratory distress was the most characteristic symptom (55%) that caused the impairment of 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 SARS-CoV-2 patients. Furthermore, neurological signs were more prevalent in severely affected patients compared to those with mild COVID-19 disease (9). The potential nervous system damage was also determined in others SARS-CoV infection. Similarly to the COVID-19, SARS-CoV infected patients developed axonopathic polynuropathy, myopathy and rhabdomyolysis. However, these pathologies were induced not at the beginning but 3-4 weeks after the onset of the respiratory symptoms. Comparable to the SARS-CoV-2, in SARS-CoV infection hypercoagulable status with
following ischemic stroke and encephalitis were described (15). Based on the autopsy studies demonstrating meningeal vasodilatation, cerebral edema as well as changes of the neurons, infiltration of lymphocytes and monocytes in the vessel wall and demyelination of the nerves, immune cell injury for the pathogenesis of SARS-CoV was taken into account (16). Furthermore, patients with MERS-CoV infection presented mainly rapid respiratory disturbances with cough, dyspnea, fever, myalgia and multi organ failure (12). However, Kim et al. observed that MERS-CoV infection was also related to the potentially neuroinvasion. Almost 1/5 of patients exhibited neurological manifestations including GBS, ischemic stroke and toxic or infectious polyneuropathy which were delayed by 2-3 weeks after respiratory distress (17). Similarly to the SARS-CoV-2, there were found seizures in MERS-CoV infected patients (18).

There is evidence that most CoVs have a neuroinvasive propensity. They may invade the CNS and their action is not only related to the damage to the respiratory tract. As a result, neurotropism is a common feature of CoVs (19). Based on the similar invasion pathway and structure of CoVs, some neuroinvasive properties could be also applicable to SARS-CoV-2.

**Neurotropism of SARS-CoV-2**

Studies showed the same cell entry receptor, i.e., ACE2 for SARS-CoV and SARS-CoV-2 and indicated simultaneously that SARS-CoV-2 protein binds to ACE2 10- to 20-fold higher than SARS-CoV (20). By binding to the ACE2 receptors located in a variety of organs such as skeletal muscles, capillary endothelium and nervous system, SARS-CoV-2 may increase the risk of cerebral hemorrhage and the impairment of the blood-brain barrier (BBB). It may enter the CNS and attack the vascular system (7). Previously, it was also reported that the brain expressed ACE2 receptors that were detected mainly in the brain stem, in the region responsible for cardiovascular functions, i.e., nucleus of the tractus solitarius and the paraventricular nucleus. ACE2 receptors were 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 the case of several viruses, including CoVs, studies confirmed another pathway which allows entry via peripheral nerves and facilitates spread to the CNS via synaptic connections (19). The neural pathway allows viral migration by infecting motor or sensory nerve endings via dynein and kinesin for antero- or retrograde transport (23). Due to the unusual structure of the olfactory nerve in the nasal cavity and olfactory fibers, it seems that the olfactory transport is a great example of the neural pathway for SARS-CoV-2. In 2013, Koyuncu et al. reported that the olfactory system could be a unique passage for viruses between the nasal epithelium and the CNS (24). Other reports also showed rapid invasion of SARS-CoV-1 and MERS-CoV into the brain through the olfactory bulb via the trans-synaptic neural pathway after intranasal administration of the CoVs (25, 26). As a result, CoVs 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 demyelinating reaction (12). Apart from the above, it is well known 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 the Infectious Disease Department in Milan, Italy reported the olfactory and taste disorders. As a result, the survey on the prevalence of these abnormalities was conducted in patients with COVID-19. It revealed that 33.9% of subjects presented with at least one taste or olfactory disorder and 18.6% of patients reported both disorders. Such disorders were more prevalent among females compared to males (52.6% v. 25%). Furthermore, patients with at least one of these disorders were younger than those without the symptoms (56 years v. 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 lymphatic pathway which consisted of cervical and olfactory vessels could provide other significant entry route for SARS-CoV-2 to the brain (29). The postmortem histological examination indicated that SARS-CoV-2 can cause endothelial dysfunctions with lymphocytic endothelitis in multiple internal organs such as heart, kidney, lung, liver, the small intestine and in the lymphatic drainage existing in the brain (30, 31). Moreover, Paniz-Monodolfi et al. described SARS-CoV-2 in frontal lobe tissue at transmission microscopy which showed growing evidence the hematogenous route as a pathway for SARS-CoV-2 entry to the brain (32). To sum up, SARS-CoV-2 can infect the brain and CNS causing many different neurological symptoms while the entry side include several mechanisms.

**Cytokine storm**

Another significant result of COVID-19 related to the damage to the nervous system is that SARS-CoV-2 infection may lead to noticeable systemic inflammatory storm (33). The pathophysiology of SARS-CoV-2 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 related to the impairment of the BBB, which additionally initiates and enhances the neuroinflammatory reaction (3). Huang et al. reported that SARS-CoV-2 infection contributed to an increased secretion of interferon gamma (IFN-γ), interleukin 1 beta (IL-1β), monocyte chemoattractant protein 1 (MCP-1), interferon gamma induced protein 10 (IP-10), interleukin 4 (IL-4) or interleukin 10 (IL-10) and showed higher serum levels of granulocyte colony- stimulating factor (GCSF), interleukin 2 (IL-2), interleukin 7 (IL-7), IP-10, IL-10, MCP-1, macrophage inflammatory protein 1 alfa (MIP-1A) and tumor necrosis factor alfa (TNF-α) in intensive care unit patients compared to
non-intensive care unit patients (6). A positive correlation was also observed between the severity of COVID-19 and the concentration of interleukin 6 (IL-6) (35). However, it was assumed that overactive immune reactions could induce clinical deterioration. As a result, some immunosuppressive drugs are under study as a putative treatment for COVID-19 (36, 37). Of note, Giovannoni et al. indicated moderate to low mortality and morbidity risk in multiple sclerosis patients infected with COVID-19 and treated with disease-modifying therapy (38). However, other authors were more skeptical to this approach and indicated the necessity for confirming such data over time (39).

**SARS-CoV-2 and encephalitis and meningitis**

For many years, SARS-CoV was perceived as the pathogen responsible for the pathologies outside the respiratory system. SARS-CoV genome sequences were found in the brain. The inflammatory process was detected in the brain of all patients with SARS-CoV at autopsy using real-time polymerase chain reaction (PCR). Of note, high signals in the hippocampus were observed (40). Inflammatory lesions in the CNS, including nerve tissue and neuronal damage, are related to encephalitis caused by some pathogens such as viruses. The clinical picture is usually characterized by 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 one 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 given. On day 5 generalized seizures accompanied by unconsciousness 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 wall of the right lateral ventricle, in the right mesial temporal lobe and in the hippocampus was found on magnetic resonance imaging
Similarly, a young obese 41-year-old female from Los Angeles with a history of diabetes complained of headache, fever and new-onset seizures. The patient was diagnosed with COVID-19. Previously, the subject had been admitted for management of viral meningitis due to the results of the CSF analysis (70 white cells with 100% lymphocyte). Due to worsening encephalopathy with disorientation, hallucinations and the febrile illness, COVID-19 testing was performed. The neurological condition improved several days following the administration of hydroxychloroquine. It was impossible to directly confirm the existence of COVID-19 virus in the CSF due to the fact that the CSF specimen could not be referred for PCR testing through local commercial, government or academic laboratories (43). Hence, the presence of isolated COVID-19-related meningoencephalitis without respiratory involvement should be also borne in mind.

Furthermore, cases of aseptic meningitis with neurological focal symptoms were also reported in patients with COVID-19. It can be explained by a parainfectious mechanism, which further supports rapid clinical improvement and the absence of abnormalities on the brain MRI (44). Recently, Dogan et al. presented a series of severely ill patients with COVID-19–related autoimmune meningoencephalitis who were treated with plasmapheresis. Their study found that most of them improved after therapy (42). SARS-CoV-2 encephalitis and potential meningitis showed neuroinvasive properties of the virus. In light of the pandemic of COVID-19, it should be borne in mind that unconscious patients are suspected as infected by SARS-CoV-2.

Of note, currently, at the time of the pandemic, the etiology of the CoV should be also considered 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
examinations include neuroimaging and electroencephalography (EEG). However, the assessment of the CSF and CSF PCR testing for SARS-CoV-2 are the most crucial.

**SARS-CoV2 and the risk of damage to the PNS**

To date, several cases of the 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 cranial nerves. The syndrome is typically triggered by an autoimmune reaction directed against neuronal gangliosides. As a result of the molecular mimicry, it results in the damage to the myelin sheath and peripheral nerve axons. It is mostly preceded by Campylobacter jejuni infection, cytomegalovirus (CMV), Epstein-Barr virus, influenza-A virus, Mycoplasma pneumoniae, and Haemophilus influenzae. However, the syndrome was also reported in the course of SARS- and MERS-CoV infections (53).

Symptoms of axonal and demyelinating GBS were reported within 5-11 days after the diagnosis of COVID-19 in patients with the presence or absence of fever and the symptoms of respiratory distress during CoV infection. Some patients presented only with the preceding olfactory and/or taste disorders (47-52). The diagnosis of GBS was confirmed by typical albuminocytological dissociation in the CSF and the electrophysiological picture typical of acute demyelinating polyneuropathy with the demyelinating or axonal variant. The test result was negative in patients in whom CSF PCR for SARS-CoV-2 was performed. Some patients developed the symptoms of respiratory failure in GBS. 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).

The Miller Fisher syndrome (MFS) is another unusual manifestation related to the SARS-CoV-2 infection (54). It is characterized by ataxia, external ophthalmoplegia, loss of tendon
reflexes and rapid onset. MFS is mainly preceded by the infections similar to the those in GBS. In the case of 50-year-old man, cough, fever, low back pain, headache and malaise were described. Additionally, after 5 days anosmia, ageusia, ataxia, areflexia, right fascicular oculomotor palsy and right internuclear ophthalmoparesis were observed. The biochemical results included albuminocytologic dissociation, positive testing for GD1b-IgG antibodies, positive oropharyngeal swab test for COVID-19 by PCR and negative in CSF. Except for residual anosmia and ageusia, patient made complete recovery after treatment with intravenous immunoglobulin (54).

Probably, the cause of GBS and MFS in patients with COVID-19 infection is an immune response due to an increase in proinflammatory cytokines, including IL-6. This interleukin, which is produced by lymphocytes, triggers a cascade of inflammatory events leading to neuronal damage in the PNS.

Knowledge on the possibility of the occurrence of GBS and MFS as a neurological manifestation or complication in the course of COVID-19 is of crucial importance when effective therapy with immunoglobulins is considered. It should be borne in mind that respiratory distress typically occurring in patients with COVID-19 may be also one of the symptoms of severe GBS. At the time of the pandemic and due to a large number of patients in severe condition, 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 electroneurographic examination (indicating acute demyelinating polyneuropathy) are the most important and, at the same time, conclusive diagnostic tests.

**SARS-CoV-2 and the risk of cerebrovascular disease**

COVID-19 is often related to deep hypoxia due to alveolar gas exchange impairment in lung tissue cells (55). The increasing anaerobic metabolism in the mitochondria of the brain results
in cerebral vasodilation, brain edema and a decreased cerebral blood flow with following ischemia. Intracranial hypertension occurs if hypoxia is not controlled. Hypertension, in turn, leads to deterioration of the brain function, cerebral circulation disorders and drowsiness or even coma (56). Finally, while 40% of patients with SARS-CoV-2 infection showed evident symptoms of brain dysfunction (9), some evidence of brain edema in COVID-19 patients was reported at autopsy (57). These findings confirmed that hypoxia initiated by SARS-CoV-2 leads to the damage to the nervous system. Furthermore, severe viremia with hypoxia in patients with COVID-19 may contribute to toxic encephalopathy.

As a result of many significant laboratory abnormalities found in COVID-19 patients, it has been suggested that SARS-CoV-2 infection is related to the immune deficiency, hepatic injury, coagulation activation, cardiac and renal disturbances (58). Abnormal laboratory test results are comparable to those previously reported in patients with SARS-CoV and MERS-CoV (13, 59). Biochemical features of COVID-19 include increased alanine transaminase activity and increased creatinine kinase activity, elevated lactate dehydrogenase (LDH) and C-reactive protein, prolonged prothrombin time with elevated D-Dimer levels and depletion of CD4 and CD8 lymphocytes with associated lymphopenia (13). A significant decline of peripheral blood lymphocytes and a progressive increase in D-Dimer levels were observed in severe COVID-19 patients (58). In these cases, prothrombotic conditions may render SARS-CoV-2-infected patients susceptible to acute cerebrovascular events (13). The cytokine inflammatory storm, previously confirmed in the course of COVID-19, is potentially also connected 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 the risk of developing cerebrovascular disturbances (12). Furthermore, since SARS-CoV-2 binds to ACE2 receptors, patients with hypertension may report blood pressure fluctuations following 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 to cerebral hemorrhage.

Many 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-2 receptor blockers (ARBs) to other antihypertensive drugs (e.g. calcium channel blockers or diuretics) (66).

From the clinical point of view, caution should be exercised in patients with the 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 belong to a group at increased risk of developing COVID-19.

**SARS-CoV-2 and other neurological disorders**

Muscle injury is confirmed by elevated creatinine kinase levels and increased LDH (67). However, the explanation of the relationship with muscle damage in COVID-19 remains uncertain. Perhaps, it could be related to the SARS-CoV-2 binding to ACE2 receptors in skeletal muscle cells. Another reason is that the systemic inflammatory storm with elevated cytokines may be responsible for muscle injury in COVID-19.

Previously, the associations between the systemic inflammation and delirium, neurodegenerative disturbances and psychiatric pathologies were confirmed (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 the above, the onset or progression of
neurodegenerative disorders, behavioral changes or cognitive deficits in COVID-19 pneumonia seem to be warranted.

According to Helms et al., 58 of 64 patients from intensive care units (in Strasbourg) with acute respiratory distress syndrome (ARDS) due to COVID-19 presented with neurological symptoms caused by encephalopathy with agitation, confusion, dysexecutive syndrome, ataxia and corticospinal tract signs. MRI of two patients showed single acute ischemic strokes (71).

Particular attention should be paid to the decrease in respiratory function in patients with myasthenia gravis in whom COVID-19 infection should be considered the cause of such a decrease (37).

One case of spinal injury in a patient with COVID-19 was also reported (72). In SARS-CoV-2 infection, the systemic inflammatory reaction with a massive release of inflammatory markers including cytokines and chemokines leads to the increased BBB permeability. As a result, the markers initiate neuroinflammation that 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 the systemic inflammation. During delirium, elevated serum levels of interleukins and protein soluble in 100% (S100B; marker for BBB disruption) were found in elderly patients (68). Neuroinflammation is also observed in neurodegenerative disorders and plays a role in the pathogenesis of psychiatric diseases (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 COVID-19

Furthermore, an impaired immune response seems to be associated with skin manifestations in SARS-CoV-2 infection. The first study on skin involvement in COVID-19 found cutaneous symptoms in 20.4% of patients that included widespread urticarial erythematous rash and chickenpox-like vesicles. The 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 heightened 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 was also reported in Spain (75). Recently, based on the groups of 375 patients, Galvan et al. divided the eruptions in SARS-CoV-2 infection into five subgroups: maculopapular eruptions (47%), acral areas of erythema with pustules or vesicles (19%), urticarial lesions (19%), other vesicular eruptions (9%) and necrosis or livedo (6%) (76). The different kinds of rashes seems to be related to the various pathophysiologies; early skin manifestations reflected the virological phase and those occurring later as a consequence of impaired immune response (74).

SARS-CoV-2 in children

SARS-CoV-2 infection was predominantly more prevalent among adults; confirmed cases in children were relatively small. Noteworthy, COVID-19 might occur not only in adults but also in children and infants. The latest reports made it clear that children are susceptible to SARS-CoV-2 because of the immaturity of the immune system. 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 were cough and fever with some accompanied by myalgia, runny nose, headache, dizziness, fatigue, vomiting or abdominal pain. Some newborns exhibited atypical symptoms like
gastrointestinal disturbances and diarrhea (77). Neurological manifestations have been also evaluated in children with COVID-19 and it included encephalopathy, muscle weakness, cerebellar and brainstem signs, headaches and reduced reflexes. All patients required intensive care unit admission but they had no evidence of infection in CSF. They had mild neuropathic and myopathic changes, slow activity in EEG with neurological improvement and complete recovery (78). It is seems that children’s COVID-19 cases were less severe that adults and they were less sensitive to SARS-CoV-2 infection. It is speculated, that children often experience viral infections and may have higher levels of antibodies against virus compared to the adults. Additionally, children’s immune systems are still developing and can have other response to pathogens than in adults (79). Noteworthy, the number of children with COVID-19 has also increased and the information regarding the epidemiology and neurological symptoms are still lacking.

Summary - implications for internists

Despite the fact that the case-fatality rate of SARS-CoV-2 is much lower, all studies have confirmed that the virus is more infectious than SARS-CoV and MERS-CoV. Additionally, CoVs 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 the respiratory failure (80). Impairment of the nervous system can be due to several mechanisms. A direct CNS infection via trans-synaptic pathways, impairment of the BBB and massive neuroinflammatory response with prolonged hypoxia promote the damage to the nervous system in the case of SARS-CoV-2. Furthermore, in patients with severe COVID-19, neurological involvement is more distinct and includes impaired consciousness, encephalitis, cerebrovascular diseases or muscle injury. To stop the pandemic of COVID-19, screening of patients should be done, which is the first step to overcome clinical manifestations of SARS-CoV-2 at the onset of the disease 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.

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

The case of our friend who is a cardiologist was the inspiration to write this paper. 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 one 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 (i.e., fever and respiratory disturbances). It should be borne in mind that SARS-CoV-2 can be the primary source of infection in patients presenting with the typical neurological symptoms with the occurrence of impaired consciousness, seizures, or symptoms of flaccid or spastic paralysis associated with hypoesthesia. The above should prompt testing for COVID-19.

Due to neuroinvasion in COVID-19, a rapid and adequate distinction of SARS-CoV-2 infected patients is required to overcome the pandemic. Therefore, immediate attention should be paid to neurological manifestations of the disease. The first step is to make physicians aware of neurotropic properties of SARS-CoV-2. Of note, screening of neurological
disturbances should be done by a neurologist as well as by an internist, a cardiologist or a pulmonologist. Furthermore, most of the neurological signs could be recognized by family doctors in outpatient clinics. In most cases, these specialists are involved in the assessment of clinical manifestations of SARS-CoV-2 at the onset of the disease. They should remember that neurological symptoms may be considered the only abnormalities in COVID-19 infection. Based on the well-known data on the 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 in the COVID-19 pandemic should prompt physicians in outpatient settings to test patients for COVID-19. Additionally, the characteristic signs of CNS damage, including unilateral paresis, hypoesthesia, speech abnormalities or the first 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 examination for SARS-CoV-2 are required. General practitioners should bear in mind that apart from severely affected COVID-19 patients, some other symptoms suggestive of GBS such as limb weakness, sensory disturbances or areflexia cannot be overlooked. The widespread urticarial erythematous rash and chickenpox-like vesicles located mainly in the trunk region should be taken into consideration when diagnosing for COVID-19. Finally, all cases of impaired consciousness in different hospital departments should be monitored and tested for COVID-19.

There are well-known serious internal implications for SARS-CoV-2 infection. Therefore, general practitioners are often obliged to perform medical examination in patients with neurological symptoms in COVID-19. They must pay special attention to the decrease in peripheral blood lymphocytes and an increase in D-Dimer levels in SARS-CoV-2 infected patients which together predispose to prothrombotic conditions and acute cerebrovascular diseases. Physicians should monitor acute respiratory disturbances in COVID-19 infection.
that result in a decrease in oxygen saturation, dyspnea and hypoxia to avoid acute cerebrovascular events or 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, i.e., calcium channel blockers should be administered instead of ACE inhibitors or ARBs. 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 in COVID-19 should be related to the monitoring of biochemical features of SARS-CoV-2 infection, i.e., increased creatinine kinase and alanine transaminase activity, elevated LDH or depletion of CD4 and CD8 lymphocytes with associated lymphopenia. Acute infection with increased C-reactive protein and elevated proinflammatory cytokines should be also 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 one clinical sign may occur as a result of multifocal disturbances in SARS-CoV-2 infected patients, especially in those with neurological symptoms. For example, hypoesthesia is related to polyneuropathy in diabetes mellitus and sensory disturbances could be directly connected to SARS-CoV-2 infection. Similarly, headache, dizziness, dyspnea, impaired consciousness, systemic inflammation or prothrombotic conditions are found in many different internal and neurological diseases and are simultaneously reported in COVID-19. Diagnosing the real cause of these abnormalities seems to be a challenge to physicians. However, it is essential to
achieve the interdisciplinary approach in COVID-19 infected patients to overcome the worldwide pandemic.

It also worthy mentioned that neurological manifestations due to SARS-CoV-2 infection might occur in either symptomatic or asymptomatic patients. Majority of the infected patients had moderate or mild symptoms and in severe cases of COVID-19 most of them experienced respiratory disturbances leading to the intubation. Meanwhile, Wu et al. reported meningoencephalitis might be only the sole presentation of COVID-19 (12). Similarly, Duong et al. showed 41-year-old female with history of diabetes as a case of COVID-19 infection presenting isolated meningoencephalitis without respiratory distress. Neurologically, she suffered from worsening encephalopathy with hallucinations and disorientation and CSF analysis revealed viral meningitis. There was observed no respiratory involvement (43).

Currently, many questions on SARS-CoV-2 neurotropism still remain unanswered. These are as follows:

- What percentage of patients with SARS-CoV-2 infection will present with neurological symptoms and/or complications?

- Could the involvement of the CNS or PNS be one of the potentially reversible causes of life-threatening conditions (e.g. respiratory failure in GBS, stroke) in patients in severe condition 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, the rapidly growing knowledge on the new CoV infection is being observed. We are convinced that the following weeks and months will provide new experience in this respect.
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