Neurological manifestations of SARS-CoV-2 - a controversy “gone viral”

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first appeared in December 2019 in Wuhan, China and developed into a worldwide pandemic within the following three months causing severe bilateral pneumonia (Coronavirus disease 2019; COVID-19) with in part fatal outcomes. After first experiences and tentative strategies to face this new disease, several cases were published describing SARS-CoV-2 infection related to the onset of neurological complaints and diseases such as, for instance, anosmia, stroke or meningoencephalitis. Of note, there is still a controversy about whether or not there is a causative relation between SARS-CoV-2 and these neurological conditions. Other concerns, however, seem to be relevant as well. This includes not only the reluctance of patients with acute neurological complaints to report to the emergency department for fear of contracting SARS-CoV-2 but also the ethical and practical implications for neurology patients in everyday clinical routine. This paper aims to provide an overview of the currently available evidence for the occurrence of SARS-CoV-2 in the central and peripheral nervous system and the neurological diseases potentially involving this virus.

Key words: COVID-19, SARS-CoV-2, neurological manifestations

Glossary: ACE2 = angiotensin converting enzyme 2, ADEM = Acute disseminated encephalomyelitis, ARDS = acute respiratory distress syndrome, ATM = acute transverse myelitis, BBB = blood-brain-barrier, CCL-2 = chemokine ligand 2, CIP = critical illness polyneuropathy, COVID-19 = coronavirus disease 2019, CRS = cytokine release syndrome, CVT = cerebral venous thrombosis, CXCL-10 = C-X-C motif chemokine 10, DIC = disseminated intravascular coagulation, DWI = diffusion-weighted magnetic resonance imaging, FDPs = fibrin degradation products, FLAIR = fluid-attenuated inversion recovery sequence, GBS = Guillain-Barré-Syndrome, GD1b = ganglioside D1b, GQ1b = ganglioside Q1b, HCoV-OC43 = human β-coronavirus OC43, ICP = intracranial pressure, Ig = immunoglobulin, IL = interleukin, MERS-CoV = middle east respiratory syndrome coronavirus, PNS = peripheral nervous system, RT-PCR = reverse transcriptase polymerase chain reaction, SARS-CoV = severe acute respiratory syndrome coronavirus, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, TMPRSS2 = transmembrane protease, serine 2, TNFα = tumour necrosis factor alpha.
Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel β-corona single stranded RNA virus, first appeared in Wuhan, China in December 2019 and developed into a worldwide pandemic within the following three months. This makes it the third coronavirus epidemic after the outbreak of SARS-CoV in 2003 and MERS-CoV in 2012. Beyond its enormous multi-faceted medical aspects the pandemic also challenges us to re-think daily hospital routines ranging from the implementation of telephone and video consultations for patients to the organization of interdisciplinary e-conferences (Grossman et al., 2020; McArthur, 2020). Similar to other human coronaviruses, SARS-CoV-2 primarily targets the upper and lower respiratory system and was first isolated from cases of bilateral pneumonia termed COVID-19 (Lau and Peiris, 2005; Hirano and Murakami, 2020; Rockx et al., 2020; Wang et al., 2020a; Zhou et al., 2020). Apart from this, numerous studies have been published that describe nervous system involvement in SARS-CoV-2 positive patients (Table 1). Of the four SARS-CoV-2 structural proteins spike, membrane, envelope and RNA-containing nucleocapsid, the spike protein is responsible for viral pathogenicity by binding to the human angiotensin converting enzyme 2 (ACE2) receptor. Of note, SARS-CoV-2 binds to ACE2 receptor with a 10-20-fold higher affinity than SARS-CoV. ACE2 receptor is, *inter alia*, expressed on the lung epithelium (Hirano and Murakami, 2020) where its activation ultimately results in an infiltration of lung alveoli by activated T lymphocytes, natural killer cells and activated monocytes/macrophages. Moreover, it causes a deleterious cytokine release syndrome (CRS; i.e. cytokine storm). In the brain, ACE2 receptor can be found in the piriform cortex (Doobay et al., 2007), the brain stem (Lenkei et al., 1996; Lin et al., 2008) and cardiovascular regulatory areas (Doobay et al., 2007; Yamazato et al., 2007; Feng et al., 2008) such as the subfornical organ, the paraventricular nucleus, the nucleus of the tractus solitarius and the rostral ventrolateral medulla. On the cellular level, it was found on neurons (Doobay et al., 2007; Xiao et al., 2013; Mukerjee et al., 2019; Chen et al., 2020b; Zhu et al., 2020), glial cells (Gallagher et al., 2006; Gowrisankar and Clark, 2016; Chen et al., 2020b; Zhu et al., 2020) and non-neural olfactory epithelial cells (i.e. horizontal basal cells and Bowman’s gland cells (Brann et al., 2020)). Interestingly, among CNS cells, oligodendrocytes seem to be of particular interest as they not only express ACE2, but also the transmembrane protease, serine 2 (TMPRSS2), an important SARS-CoV-2 co-receptor (Needham et al., 2020). Epidemiologically, it remains currently unclear how many COVID-19 patients exhibit neurological complications with numbers ranging from a few per cent to up to 80% (Helms et al., 2020a; Mao et al., 2020). However, whether or not these complications are based on direct
effects of the virus on the central nervous system (CNS) or the peripheral nervous system (PNS) still needs to be clarified.

On the one hand, COVID-19-associated neurological disturbance could be simply based on sepsis or multiorgan failure (e.g. lung dysfunction with subsequent hypoxia), or the above-mentioned cytokine storm featuring production of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-2, IL-6, IL-7, IL-8, tumour necrosis factor alpha (TNFα), C-X-C motif chemokine 10 (CXCL-10) and chemokine ligand 2 (CCL2) (Helms et al., 2020a; Huang et al., 2020a; Mehta et al., 2020; Wan et al., 2020). Particularly, TNFα might destabilize the blood-brain-barrier (BBB) rendering the CNS vulnerable (Kim et al., 1992). As a consequence, CNS-resident cells such as microglia or astrocytes could be driven to attack other cells in the brain and spinal cord leading to parenchymal injury. Another conceivable mechanism of direct SARS-CoV-2-mediated CNS damage could consist in an invasion of the virus into the CNS (Table 2). In rodent animal models, mice were exposed to intranasal injections with the SARS-CoV-2-related human β-coronavirus OC43 (HCoV-OC43). Via the nasal mucosa and olfactory bulb, the virus was found to use retrograde axonal transport in order to travel to the brain and brainstem where it might contribute to dysregulated breathing or to compromised pulmonary and cardiac functions (Butler et al., 2006). This portal of entry could also explain the loss of smell and taste in the early stages of the disease or edematous changes in the olfactory bulb (Laurendon et al., 2020; Mao et al., 2020; Meng et al., 2020; Vaira et al., 2020). Of note and interestingly, it has been known for a long time that infection of mice with neurotropic strains of the coronavirus mouse hepatitis virus leads to CNS demyelination mimicking multiple sclerosis (MS) (Haring and Perlman, 2001). Moreover, SARS-CoV-2 might retrogradely travel from the lung or the intestines to the CNS via the vagus nerve (Li et al., 2020b; Machado and Gutierrez, 2020). In addition, it could be shown that human coronaviruses and especially SARS-CoV are able to infect and activate myeloid cells such as monocytes, which may then invade the CNS hematogenously via Trojan horse transit (Law et al., 2005; Yilla et al., 2005; Chen et al., 2020c; Moore and June, 2020). Finally, it is conceivable that in the context of viremia blood-borne SARS-CoV-2 travels to the CNS where it infects the endothelium and might then reach the brain via viral budding (Varga et al., 2020). In summary, each of the above-described mechanisms could help to explain the occurrence of neurological symptoms and diseases in SARS-CoV-2 positive patients.
Methods

For this review a web-based literature search for all English-language studies or preprints was conducted on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), medRxiv and bioRxiv using search terms such as “SARS-CoV-2”, “2019-nCoV”, “novel coronavirus”, “COVID-19”, “neurology”, “neurological disorder”, “neurological disease”, “neurological complication”, “neurological deterioration”, “neurological involvement”, “central nervous system”, “peripheral nervous system”, “cerebrospinal fluid”, “brain”, in combination with each other reporting neurological presentations of patients with clinically- or laboratory-confirmed SARS-CoV-2 infection. Where available, reviews or brief statements from the national or international neurological societies were taken into account. We have incorporated studies made available online between May 1st and August 8th 2020.

SARS-CoV-2 and its involvement in neurological diseases

Meningoencephalitis

At this stage, some case reports have described SARS-CoV-2-associated encephalopathies or meningoencephalitis. It remains, as discussed, unclear whether these diseases result from indirect effects of a systemic pro-inflammatory state, as can be observed in sepsis, or from direct SARS-CoV-2-induced meningeal and neuroglial inflammation. To date, only in a limited number of cases could SARS-CoV-2 be detected in the CNS of patients (Table 3). Moriguchi and colleagues describe a 24-year-old male presenting with headache, fatigue, fever, sore throat, neck stiffness, altered consciousness, pneumonia and new onset generalized seizures. In this case, MRI showed a FLAIR-hyperintensity in the right mesial temporal lobe and hippocampus and a DWI-hyperintensity along the wall of the inferior horn of right lateral ventricle. Furthermore, CSF cell count was mildly elevated to 12/µl and intracranial pressure (ICP) was greater than 320 mmH₂O. Interestingly, SARS-CoV-2 RNA was not detected in the nasopharyngeal swab but in the CSF (Moriguchi et al., 2020). The second case report is still unpublished but officially confirmed by the treating medical institution. It describes the case of a 56-year-old patient with viral encephalitis in whose CSF SARS-CoV-2 was identified by gene sequencing ((Wu et al., 2020; Xiang et al., 2020); http://xinhuanet.com/english/2020-03/05/c_138846529.htm, accessed on May 23rd 2020). The third case was a 41-year-old woman presenting with headache, fever, new onset seizures and signs of meningeal irritation. Cranial CT scan showed no abnormalities but CSF analysis revealed an increased lymphocytic white cell count of 70/µl and a red cell count of 60/µl without evidence for herpes simplex virus infection. The patient underwent SARS-CoV-2 testing although she had no signs of respiratory
discomfort and chest CT did not show any findings suggestive of pneumonia. Both the nasopharyngeal swab test and the CSF sample were positive for SARS-CoV-2 (Duong et al., 2020; Huang et al., 2020b). Moreover, Paniz-Mondolfi and colleagues report a SARS-CoV-2-positive Parkinson’s disease patient with initial reduced vigilance, fever and confusion. Although SARS-CoV-2 was not found in the CSF, the virus was detected postmortem in the frontal lobe by electron microscopy and by RT-PCR (Paniz-Mondolfi et al., 2020). This observation is corroborated by the results of another postmortem case study in which SARS-CoV-2 RNA was detected in brain tissue from four patients who had died from COVID-19 (Wichmann et al., 2020). In contrast to these studies, Schaller and colleagues as well as Barton and colleagues did neither find macroscopic nor histological evidence of SARS-CoV-2-related CNS abnormalities COVID-19 autopsies (Barton et al., 2020; Schaller et al., 2020). On the cellular level, Chu and colleagues detected a modest SARS-CoV-2 replication in the human neuronal U251 cell line (Chu et al., 2020). While this observation suggests that, in principle, CNS cells are susceptible to SARS-CoV-2 infection there are two major caveats. First, the authors did not use primary human CNS cells and secondly they observed no substantial cytopathic effect in the cells investigated.

**Cerebrovascular diseases**

A potential link between acute cerebrovascular diseases such as ischemic and hemorrhagic stroke and SARS-CoV-2 infection is controversially discussed. As of now, evidence suggests that this link is CNS-unspecific and seems to be rather based on an impact of SARS-CoV-2 on the heart and the peripheral vascular system in the general context of a critical disease. Of note, pre-existing conditions such as arterial hypertension, cardiovascular diseases, diabetes mellitus and smoking predispose patients to develop COVID-19 (Emami et al., 2020) while they are, at the same time risk factors for cerebrovascular disease. It is therefore difficult to disentangle these connections regarding causative versus chance relationship. Nonetheless, a recent study demonstrated that SARS-CoV-2 positive patients who were hospitalized due to stroke showed a higher incidence of fever, delirium and ultimately are at greater risk for poor outcomes than SARS-CoV-2 negative patients (Benussi et al., 2020). Observational studies from Europe and China estimate the proportion of COVID-19 patients with concurrent cerebrovascular disease at 1.3-5.0% (Klok et al., 2020; Li et al., 2020a; Lodigiani et al., 2020; Romero-Sánchez et al., 2020). A retrospective observational study by Mao and colleagues reported five cases (2.3%) with ischemic and one case (0.5%) with hemorrhagic stroke in SARS-CoV-2-positive patients (Mao et al., 2020). These results are supported by several case series describing the occlusion
of large arterial vessels in SARS-CoV-2-positive patients (Al Saiegh et al., 2020; Oxley et al., 2020). Pathophysiological, SARS-CoV-2 could have a direct effect on myocardial and endothelial cells via the ACE2 receptor which is expressed not only by type I and type II alveolar epithelial cells but also by myofibroblasts, vascular endothelial and vascular smooth muscle cells (Hamming et al., 2004). This could result in damage of cell-cell-interfaces with subsequent myocardial or vascular cell injury leading to an increased thrombogenicity (Yau et al., 2015). In addition, myofibroblasts activated by SARS-CoV-2 could also interfere with the propagation of electrical signals in the heart resulting in arrhythmia (Quinn et al., 2016). This might, in turn, explain a higher risk for micro- and thrombo-embolic events leading to ischemic strokes in COVID-19 patients. The same circumstance, i.e. an interrupted cell-cell interface, could underpin reported cases of focal as well as subarachnoid cerebral hemorrhage in COVID-19 patients but, again, this remains to be demonstrated (Heman-Ackah et al., 2020; Hernández-Fernández et al., 2020; Poyiadji et al., 2020; Sharifi-Razavi et al., 2020; Wang et al., 2020b).

Another possible pathophysiological rationale for the occurrence of cerebrovascular diseases in COVID-19 patients could be the cytokine storm mentioned above. The systemic release of SARS-CoV-2-induced pro-inflammatory cytokines such as IL-1β, IL-6, IL-8 and TNFα may not only have a negative influence on pre-existing arteriosclerotic diseases ((Goldberg et al., 2020), reviewed in (Libby et al., 2018)). It could also play an important role in tissue-factor mediated activation of the coagulation system, inter alia, resulting in thrombin generation and the inhibition or the dysfunction of physiological anticoagulant systems (Vary and Kimball, 1992; Levi et al., 1997; Franco et al., 2000; Chen et al., 2020a; Fogarty et al., 2020; Harzallah et al., 2020; Helms et al., 2020b; Tang et al., 2020; Zhang et al., 2020b). Accordingly, this could not only lead to the occurrence of cerebral ischemia but also to cerebral venous thrombosis (CVT) in COVID-19 patients as described in several case reports (Francesco et al., 2020; Hemasian and Ansari, 2020; Hughes et al., 2020; Li et al., 2020a). Ultimately, this procoagulatory state might activate the fibrinolytic system generating characteristic fibrin degradation products (FDPs) resulting in disseminated intravascular coagulation (DIC) as it was also observed in COVID-19 patients (Chen et al., 2020a; Fogarty et al., 2020; Tang et al., 2020). Another aspect that could explain a hypercoagulable state in COVID-19 patients could be a SARS-CoV-2-induced antiphospholipid syndrome which by itself is known to affect the CNS causing stroke and CVT (reviewed in (Nayer and Ortega, 2014)). In a small series of three patients, Zhang and colleagues describe the presence of anticardiolipin immunoglobulin(Ig)A, anti-β2-glycoprotein I IgA and IgG antibodies in the serum of patients with COVID-19 who developed cerebral infarctions during their hospitalization (Zhang et al., 2020b). Further studies

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reported 45% up to 88% of COVID-19 patients tested positive for lupus anticoagulant (Harzallah et al., 2020; Helms et al., 2020b). However, this might be non-specific since antiphospholipid antibodies and lupus anticoagulants are often detected particularly in elderly patients in the context of infection or related to specific medications (reviewed in (Uthman and Gharavi, 2002; Giannakopoulos and Krilis, 2013)). As a result, there has been a controversial discussion regarding the significance of these results (Connell et al., 2020; Escher et al., 2020; Tang, 2020; Tang et al., 2020). In addition, studies of Merkler et al. report an increased risk of stroke in COVID-19 patients compared to patients who had respiratory tract infection due to another viral pathogen, it can be summarized that further studies are needed to confirm this finding (Merkler et al., 2020). Finally, it is worth mentioning that, in general, the fear of contracting COVID-19 has led to a reluctance of patients particularly with mild stroke symptoms to present to emergency departments (Oxley et al., 2020; Siegler et al., 2020). Of note, Zhao and colleagues report a 37.9% decrease in hospital admissions related to stroke during the Chinese epidemic in February 2020 compared to the same period in the previous year. In parallel to that, the absolute number of patients treated by thrombolysis or thrombectomy dropped by 25.5% and 22.7%, respectively. In this regard, not only the patients’ and their families’ fear of contracting SARS-CoV-2 in hospital may result in a significant delay for stroke treatment in time. The same may apply to insufficient transportation resources during lockdown, COVID-19 screening procedures and local infectious prevention strategies. This could obviously result in potentially poorer outcomes and emphasizes the need for standardized management guidelines in stroke care during the COVID-19 pandemic (Zhao et al., 2020b).

**Guillain-Barré-Syndrome (GBS)**

Another conceivable neurological manifestation of SARS-CoV-2 may be Guillain-Barré-Syndrome (GBS) and its variants, which have been reported in a number of COVID-19 patients. GBS is an acute mostly postinfectious immune-mediated disorder affecting nerve roots and peripheral nerves. Clinically, GBS is associated with a rapidly progressive ascending symmetric peripheral paralysis, hypo- or areflexia and can ultimately necessitate mechanical ventilation (Willison et al., 2016). It is usually linked to previous infection with Campylobacter jejuni, Mycoplasma pneumoniae, Zikavirus, Ebstein-Barr-Virus or other pathogens (Jacobs et al., 1998; Cao-Lormeau et al., 2016; Krauer et al., 2017). Prior to the current pandemic, there have already been reports associating other coronaviruses with different forms of GBS (Kim et al., 2017; Sharma et al., 2019). In the context of the current pandemic a few case reports have linked GBS and its subforms to prior infection with SARS-CoV-2. The most recent attempt at
systematically reviewing reports published before May 17, 2020, found 18 cases (De Sanctis et al.). In nearly all of the cases GBS symptoms occurred following the clinical manifestation of SARS-CoV-2, i.e. fever and non-productive cough. To our knowledge there is only one case where symptoms occurred simultaneously (Zhao et al., 2020a). Interestingly, SARS-CoV-2 RNA could not be detected via RT-PCR in the CSF of any cases. Moreover, anti-glycolipid antibodies that typically occur in the serum of GBS patients were not detected (Coen et al., 2020; Toscano et al., 2020) although some of the patients were not tested for them (Padroni et al., 2020; Sedaghat and Karimi, 2020; Toscano et al., 2020; Virani et al., 2020). Typical CSF findings such as albuminocytologic dissociation were inconsistent, varying from highly (Coen et al., 2020) to mildly increased (Alberti et al., 2020) to normal protein levels (Toscano et al., 2020). In the reported cases EMG identified mainly two variants of GBS: motor-sensory demyelinating neuropathy (Alberti et al., 2020; Coen et al., 2020; Toscano et al., 2020; Virani et al., 2020) and motor-sensory axonal neuropathy (Sedaghat and Karimi, 2020; Toscano et al., 2020). Furthermore, three of the reported patients required mechanical ventilation but it is not clear whether respiratory insufficiency resulted from COVID-19 or was part of the natural course of GBS (Toscano et al., 2020). An obvious differential diagnosis would be critical illness polyneuropathy (CIP). MRI scans of the brain and spinal cord showed a variety of findings: no pathological signals at all (Sedaghat and Karimi, 2020; Toscano et al., 2020), gadolinium enhancement in the caudal nerve roots, or, in one case, bilaterally in the facial nerve (Toscano et al., 2020). In addition, there is one case in which a SARS-CoV-2-positive patient developed Miller-Fisher-Syndrome, a GBS spectrum disease characterized by ataxia, ophthalmoplegia, areflexia, and typically antibodies to gangliosides such as GQ1b. Here, an antibody directed at the ganglioside GD1b was identified in the serum and CSF analysis showed albuminocytologic dissociation. However, again SARS-CoV-2 RNA could not be detected in the CSF. The same authors report another case where a SARS-CoV-2-positive patient suffering from diarrhea developed polyneuritis cranialis. Except for albuminocytologic dissociation, all other laboratory analyses yielded non-specific results (Gutiérrez-Ortiz et al., 2020).

**Acute disseminated encephalomyelitis (ADEM)**

Acute disseminated encephalomyelitis (ADEM) is an acute monophasic usually postinfectious, immune-mediated demyelinating disorder of the CNS. As the disease is characterized by multiple white matter lesions in the brain or spinal cord, neurological symptoms can vary significantly (Noorbakhsh et al., 2008). A first case report published in 2003 established a possible link between coronavirus OC43 and ADEM when the virus was detected in the CSF.
and the nasopharyngeal secretions of a 15 year old patient (Yeh et al., 2004). As of now, there is only one definite case report of ADEM in an adult female patient who was tested positive for SARS-CoV-2. Analysis of the patient’s CSF yielded no pathological findings, including a negative test for SARS-CoV-2 RNA. MRI revealed multiple white matter lesions in accordance with an ongoing acute inflammatory demyelinating process (Zhang et al., 2020a). Another case report by Brun and colleagues describes a 54-year-old woman diagnosed with COVID-19 requiring mechanical ventilation. After sedation was discontinued, the patient presented with prolonged confusion and hemiplegia. MRI revealed homogenous bilateral Gadolinium-enhancing brain lesions suggesting ADEM-like demyelination. As a differential diagnosis, the authors discuss small-vessel CNS vasculitis. Once again, CSF RT-PCR for SARS-CoV-2 was negative (Brun et al., 2020). Of note, ADEM as a possible (para-)infectious consequence of COVID-19 is supported by post-mortem neuropathological findings by Reichard and colleagues (Reichard et al., 2020). The authors describe subcortical scattered clusters of macrophages, a range of associated axonal injury, and a perivascular ADEM-like appearance.

**Acute transverse myelitis (ATM)**

Of note, acute transverse myelitis (ATM) has also been described in the context of SARS-CoV-2. ATM frequently follows infections with various pathogens, particularly viruses. ATM presents with acute paresthesia, loss of sensation, back pain as well as urinary and bowel incontinence (West et al., 2012). To date, there are two case reports of nasopharyngeal swab SARS-CoV-2-positive patients who developed ATM. Both patients showed the above-described typical clinical symptoms. One of them underwent lumbar puncture. The CSF was, however, negative for SARS-CoV-2 but showed a mononuclear lymphocytosis of 125 cells/μl. MRI of the spinal cord revealed longitudinal signal changes typical of ATM (Sarma and Bilello, 2020). The other patient was diagnosed exclusively based on his clinical symptoms. Neither CSF analysis nor MRI were performed (Zhao et al., 2020c).

**Psychiatric and neuropsychiatric presentations**

During the last SARS-CoV and MERS coronavirus epidemics psychiatric and neuropsychiatric symptoms were established as a common feature at times outlasting the infectious disease. Also neuropsychiatric symptoms occurred in caregiving health workers (Sheng et al., 2005; Su et al., 2007; Lancee et al., 2008; Mak et al., 2009; Kim et al., 2018; Lee et al., 2018). Such symptoms included emotional lability, mood disturbances, anxiety, impairment of memory, concentration or attention, sleeping disorders and confusion. In the post-infectious state, SARS-
CoV patients presented with a high point-prevalence of anxiety and depression disorders as well as post-traumatic stress disorders at roughly 15-30% even though most of the studies did not include control groups or references from the general population (Rogers et al., 2020). The current evidence for neuropsychiatric complaints in SARS-CoV-2-positive patients is scarce and incomplete regarding the long-term outcomes. In parallel to SARS-CoV and MERS, patients with COVID-19 are more susceptible to develop confusion and delirium (Rogers et al., 2020). On a note of caution, the majority of the mentioned papers have methodological problems (Rogers et al., 2020) so that further studies are required to better delineate SARS-CoV-2 related neuropsychiatric disorders.

**Conclusion**

Soon after the COVID-19 pandemic occurred it became clear that multiple organs other than the lungs are involved. In particular, a number of reports appeared describing a range of neurological disorders putatively associated with it. However, the evidence causally linking SARS-CoV-2 infection to CNS or PNS diseases is currently inconclusive. For obvious reasons, most studies were carried out in patients with SARS-CoV-2-associated acute respiratory distress syndrome (ARDS) without matched controls. Patients with such critical conditions are per se prone to develop, for instance, stroke, CIP, parainfectious GBS and critical illness myopathy (Nauwync and Huyghens, 1998; Naik-Tolani et al., 1999; Latronico and Bolton, 2011; Walkey et al., 2011; Yuki and Hartung, 2012; Nasr and Rabinstein, 2015). In general, there have only been a limited number of cases in which SARS-CoV-2 was detected in the CNS. Therefore, the nature of a potential impact of SARS-CoV-2 on the nervous system remains presently unclear – all the more so as autopsy results are partly contradictory. In addition, a structured meta-analysis is complicated by the use of different diagnostic tools, small case numbers and the fact that some of the patients suffered from additional, potentially confounding, diseases (Alberti et al., 2020; Sedaghat and Karimi, 2020; Virani et al., 2020). Currently, SARS-CoV-2 not only dominates the scientific discourse, but has also an enormous impact on our everyday life as neurologists. Concerns have arisen whether patients with autoimmune nervous system disorders, such as multiple sclerosis or immune neuropathies should be started or continued on immunomodulatory therapy potentially compromising the capacity to fight off COVID-19 and may modify the risk of developing a severe COVID-19 infection (Amor et al., 2020; Guidon and Amato, 2020; Hartung and Aktas, 2020; Louapre et al., 2020; Parrotta et al., 2020; Rajabally et al., 2020; Sormani, 2020). In general, preliminary evidence suggests MS patients are not at an increased risk to contract COVID-19 or suffer a
more severe form (Louapre et al., 2020; Sormani, 2020). Managing multiple sclerosis patients using a broadened treatment armamentarium creates additional complexity in times of COVID-19 and mandates a personalized approach relying on the unique modes of actions and risks attributable to disease modifying agents (Berger et al., 2020). Fear of infection has a direct impact on patient management and requires the responsible healthcare professional not only to search for possible SARS-CoV-2-related neurological complications or diseases, but also to effectively deliver patient care under these challenging circumstances (de Seze and Lebrun-Frenay, 2020; Kim and Grady, 2020; Tarolli et al., 2020). As recently proposed by the World Federation of Neurology, regional, national and international COVID-19 neuro-epidemiological databases are needed to better understand the connection between SARS-CoV-2 and the observed neurological diseases (Román et al., 2020).

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| Authors          | Study type                          | Definition                  | SARS-CoV2-positive Patients included | Age (years) | Female/male/diverse in % | Dizziness (%) | Headache (%) | Disorders of consciousness (%) | Ischemic stroke (%) | ICB (%) | Seizure (%) | Patients with impaired smell (%) | Patients with impaired taste (%) | Patients with impaired vision (%) |
|------------------|-------------------------------------|-----------------------------|-------------------------------------|-------------|---------------------------|---------------|--------------|-------------------------------|---------------------|---------|-------------|--------------------------------|---------------------------------|-------------------------------|
| Romero-Sánchez et al., 2020 | Retrospective observational two-center (ALBACOVID registry) | Throat swab RT-PCR or IgG/IgM antibodies against SARS-CoV-2 in a blood test | 841 | Mean 66.4 (±SD 15.0) | 56.2/43.8/0 | 51 (6.1) | 119 (14.1) | 165 (19.6) | 11 (1.3) | 3 (0.3) | 6 (0.7) | 41 (4.9) | 52 (6.2) | n.a. |
| Lodigiani et al., 2020 | Retrospective observational single-center | „laboratory-proven COVID-19“ | 388 | Median 66 (IQR 55.0-75.0) | 32.0/68.0 | n.a. | n.a. | n.a. | 9 / 362 closed cases (2.5) | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |
| Chen et al., 2020 | Retrospective case study, single-center | Throat swab RT-PCR | 274 | Median 62.0 (IQR 44.0-70.0) | 37.6/62.4/0 | 21 (7.6) | 31 (11.3) | 26 (9.5) | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |
| Shi et al., 2020 | Retrospective observational single-center | Confirmed COVID-19 | 221 | n.a. | n.a. | n.a. | n.a. | n.a. | 11 (5.0) | 1 (0.5) | n.a. | n.a. | n.a. | n.a. |
| Mao et al., 2020 | Retrospective observational multicenter | Throat swab RT-PCR | 214 | Mean 52.7 (±SD 15.5) | 59.3/40.7/0 | 36 (16.8) | 28 (13.1) | 16 (7.5) | 5 (2.3) | 1 (0.5) | 12 (5.6) | 11 (5.1) | 3 (1.4) |
| Study Reference | Study Type | Methodology | Patients | Median (IQR) | Mean (±SD) | ICMS | ICH | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |
|-----------------|------------|-------------|----------|--------------|------------|------|-----|------|------|------|------|------|------|
| Chen et al., 2020 | Retrospective observational single-center | Throat swab RT-PCR | 99 | 32.3/67.7/0 | 55.5 (±13.1) | n.a. | 8 (8.1) | 9 (8.1) | n.a. | n.a. | n.a. | n.a. | n.a. |
| Giacomelli et al., 2020 | Questionnaire-based, patient-reported, cross-sectional, single-center | n.a. | 59 | 32.2/67.8 | n.a. | 2 (3.4) | n.a. | n.a. | 14 (23.7) | 17 (28.8) | n.a. |
| Yan et al., 2020 | Questionnaire-based, patient-reported, cross-sectional, single-center | Throat swab RT-PCR | 59 | 49.2/49.2/1.7 | n.a. | 39 (66.1) | n.a. | n.a. | n.a. | n.a. | 40 (67.8) | 42 (71.2) | n.a. |
| Yang et al., 2020 | Retrospective observational single-center | Throat swab RT-PCR | 52 | 32.6/67.3/0 | 51.9 (±12.9) | n.a. | 3 (5.8) | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |
| Oxley et al., 2020 | Case series | Throat swab RT-PCR | 5 | 20.0/80.0 | 39 (IQR 35.0-46.5) | n.a. | 1 (20.0) | 4 (80.0) | 5 (100.0) | 0 (0.0) | 0 (0.0) | n.a. | n.a. |

Table 1. Nervous system manifestation in SARS-CoV-2 positive patients. The table shows a selection of observational and case studies that describe neurological manifestations in SARS-CoV-2 positive patients. The study listing is based on the number of included patients. A selection of frequently mentioned neurological complaints in the context of a SARS-CoV-2 infection was made. ICB = intracranial hemorrhage, IQR = interquartile range, SD = standard deviation, n.a. = data not given or not available to the authors.
| Portal of entry into the CNS                  | Mode of action                  | Authors                                      |
|---------------------------------------------|---------------------------------|----------------------------------------------|
| Endothelium of cerebral vessels              | hematogenously via viral budding| Paniz-Mondolfi et al., 2020; Varga et al., 2020 |
| Nasal mucosa and olfactory bulb              | via retrograde axonal transport | Laurendon et al., 2020; Meng et al., 2020    |
| Vagus nerve                                  | via retrograde axonal transport | Li et al., 2020b; Machado and Gutierrez, 2020|
| Myeloid cells                                | hematogenously via Trojan horse transit | Chen et al. 2020d; Merad and Martin, 2020; Moore and June, 2020 |

*Table 2. Potential portals of entry for SARS-CoV-2 into the CNS.*
| Authors                        | Number of patients | Age/ gender | Analysis                                                                 | Manifestation                                                                 | Imaging                                                                 |
|-------------------------------|--------------------|-------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Moriguchi et al., 2020        | 1                  | 24y/m       | Nasopharyngeal swab SARS-CoV-2 RT-PCR *negative*                            | Pneumonia, headache, fatigue, fever, sore throat, neck stiffness, consciousness disturbance, multiple generalized seizures | Cranial MRI: FLAIR-hyperintensity right mesial temporal lobe and hippocampus. DWI-hyperintensity along the wall of the inferior horn of right lateral ventricle |
| Xiang et al., 2020            | 1                  | 56y/m       | CSF specimen SARS-CoV-2 RT-PCR *positive*                                  | COVID-19, encephalitis                                                       | Cranial CT-scan: no abnormal findings                                  |
| Duong et al., 2020            | 1                  | 41y/f       | Nasopharyngeal swab SARS-CoV-2 RT-PCR *positive*                            | Headache, fever, lethargic, seizure, neck stiffness, photophobia, confusion, hallucinations | Cranial CT-scan: no abnormal findings                                  |
| Huang et al., 2020            | 1                  | 41y/f       | CSF specimen SARS-CoV-2 RT-PCR *positive*                                  |                                                                             | Serial chest X-ray and chest CT were normal                              |
| Paniz-Mandolfi et al., 2020   | 1                  | 74y/m       | Nasopharyngeal swab SARS-CoV-2 RT-PCR *negative*                            | COVID-19, fever, confusion, agitation, new onset of atrial fibrillation       | Cranial CT-scan: patchy subcortical and periventricular hypodensities unchanged from a scan 6 months earlier |
| Wichmann et al., 2020         | 4                  | n.a.        | Minced lung tissue SARS-CoV-2 RT-PCR *positive*                             | COVID-19                                                                     | n.a.                                                                   |

Table 3. Cases in which SARS-CoV-2 was detected in the central nervous system (CNS). N.a. = data not given or not available to the authors.
Abbreviated Summary

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may be involved in or contribute to a plethora of neurological diseases. However, this hypothesis remains controversial. We aim to provide an overview of the currently available evidence for the occurrence of SARS-CoV-2 in the human nervous system and the potentially ensuing sequelae.
SARS-CoV-2

**Neurological manifestations**
- Dizziness, headache, disorders of consciousness, ischemic stroke, intracranial hemorrhage (ICH), seizure, impaired smell/taste, vision, meningoencephalitis, Guillain-Barré-Syndrome (GBS), acute disseminated encephalomyelitis (ADEM), acute transverse myelitis (ATM), psychiatric symptoms

**Portal of entry into the CNS**
- Endothelium of cerebral vessels hematogenously via viral budding
- Nasal mucosa and olfactory bulb via retrograde axonal transport
- Vagus nerve via retrograde axonal transport
- Myeloid cells via Trojan horse transit

**Detection in the CNS**
- RT-PCR from cerebrospinal fluid (CSF): 4 cases
- RT-PCR from brain tissue: 5 cases

Graphical Abstract

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