REVIEW ARTICLE

Neurological manifestations and neuro-invasive mechanisms of the severe acute respiratory syndrome coronavirus type 2

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Keywords:
cerebrovascular diseases, COVID-19, neuro-invasive mechanism, neurological manifestations, SARS-CoV-2

Received 20 April 2020
Accepted 11 May 2020

European Journal of Neurology 2020, **27:** 1578–1587

doi:10.1111/ene.14329

Background and purpose: Infections with coronaviruses are not always confined to the respiratory tract and various neurological manifestations have been reported. The aim of this study was to perform a review to describe neurological manifestations in patients with COVID-19 and possible neuro-invasive mechanisms of Sars-CoV-2.

Methods: PubMed, Web of Science and COVID-dedicated databases were searched for the combination of COVID-19 terminology and neurology terminology up to 10 May 2020. Social media channels were followed up between 15 March and 10 May 2020 for postings with the same scope. Neurological manifestations were extracted from the identified papers and combined to provide a useful summary for the neurologist in clinical practice.

Results: Neurological manifestations potentially related to COVID-19 have been reported in large studies, case series and case reports and include acute cerebrovascular diseases, impaired consciousness, cranial nerve manifestations and autoimmune disorders such as the Guillain–Barré syndrome often present in patients with more severe COVID-19. Cranial nerve symptoms such as olfactory and gustatory dysfunctions are highly prevalent in patients with mild to moderate COVID-19 even without associated nasal symptoms and often present in an early stage of the disease.

Conclusion: Physicians should be aware of the neurological manifestations in patients with COVID-19, especially when rapid clinical deterioration occurs. The neurological symptoms in COVID-19 patients may be due to direct viral neurological injury or indirect neuroinflammatory and autoimmune mechanisms. No antiviral treatments against the virus or vaccines for its prevention are available and the long-term consequences of the infection on human health remain uncertain especially with regard to the neurological system.

Introduction

In December 2019, several unexplained pneumonia cases in Wuhan, China, led to the detection of a novel coronavirus [1]. Infection with this virus caused symptoms resembling those caused by the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). Genomic characterization classified the virus as a Betacoronavirus, like MERS-CoV and SARS-CoV. Its entry into human host cells is mediated by the same receptor as in SARS-CoV, i.e. the angiotensin-converting enzyme 2 (ACE2) receptor. Therefore, the virus was named SARS-CoV-2. The

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This manuscript was handled by Prof. Didier Leys, and discussed with the other editors, but Prof. Kristl Vonck was not involved at any stage of the review process

EUROPEAN JOURNAL OF NEUROLOGY

World Health Organization named the disease coronavirus disease 2019 (COVID-19) and declared the outbreak of COVID-19 a pandemic on 11 March 2020, after the disease had spread to more than 100 countries and led to tens of thousands of cases within a few months [2]. The spectrum of clinical manifestations ranges from asymptomatic to symptoms such as fever, cough, diarrhoea and fatigue, and in some cases the infection eventually leads to severe pneumonia, acute respiratory distress syndrome (ARDS) and/or death [2]. Increasing evidence shows that infections with coronaviruses are not always confined to the respiratory tract and neurological manifestations have been reported [3]. This report provides an overview of the currently reported neurological manifestations in patients with a high likelihood of an infection with SARS-CoV-2, the currently identified risk factors and the proposed neuro-invasive viral mechanisms (Table 1).

Methods

PubMed, Web of Science and COVID-dedicated literature databases (MIT COVID-19 open research dataset, COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv) were searched for the combination of various COVID-19 terminologies (COVID-19, coronavirus, novel coronavirus, SARS-CoV-2) and neurology terminology (neurological symptoms, neurological manifestations, neurological disorders, stroke, seizures, epilepsy, multiple sclerosis, neurodegenerative, movement disorder, Parkinson's, extrapyramidal, autoimmune, encephalitis, encephalopathy, meningitis, headache, consciousness, neuropathy, central nervous system, peripheral nervous system) as well as neuroinvasive mechanisms up to 10 May 2020. Social media channels (Facebook, Twitter, Linked-in) were followed up between 15 March and 10 May 2020 for postings with the same scope. Neurological manifestations were extracted from the identified papers and combined when relevant to provide a useful summary for the neurologist in clinical practice.

Neurological manifestations of SARS-CoV-2

Neurological manifestations were reported in 36.4% of a first large series of 214 patients with laboratory-confirmed diagnosis of SARS-CoV-2 hospitalized in three dedicated COVID-19 hospitals in Wuhan [3]. Neurological symptoms were more common in patients with severe infection according to their respiratory status (45.5% vs. 30.2% in non-severe cases) and fell into three categories: central nervous system (CNS) manifestations [dizziness, headache, impaired consciousness, acute cerebrovascular disease (CVD), ataxia and seizure], cranial and peripheral nervous system manifestations (taste impairment, smell impairment, vision impairment and neuropathy) and skeletal muscular injury manifestations. Patients with a severe respiratory infection were older, had more underlying disorders and showed fewer typical symptoms such as fever and cough. In line with these findings, a retrospective study from Wuhan looking at clinical characteristics in 113 deceased patients with COVID-19 reported disturbances of consciousness on admission in nearly one-third of the patients [4]. A recent study from two Strasbourg intensive care units (ICUs) found neurological symptoms on ICU admission in 14% (8/58) of patients with ARDS; two-thirds of patients demonstrated agitation when sedation and neuromuscular blockade were withdrawn [5]. In two-thirds of patients, corticospinal tract signs were found. Of the patients already discharged at the time of reporting, one-third had signs of a dysexecutive syndrome consisting of inattention, disorientation or poorly organized movements in response to commands. Eleven of 13 patients who underwent magnetic resonance imaging (MRI) due to signs of encephalopathy showed bilateral frontotemporal hypoperfusion on perfusion imaging and two had a small acute ischaemic stroke without clinical symptoms. In seven of these patients in whom a lumbar puncture was performed, reverse transcription polymerase chain reaction (RT-PCR) assays of the cerebrospinal fluid (CSF) samples were negative for SARS-CoV-2. In a retrospective analysis of patients admitted to a neuro-COVID unit in Italy, it appeared that patients (56/173) had a significantly higher in-hospital mortality, delirium and disability compared to neurology patients admitted in the same period without COVID-19 (117/173) [6]. A post-mortem brain MRI study from Belgium in 19 patients demonstrated brain abnormalities in eight non-survivors of COVID-19 such as haemorrhagic and posterior reversible encephalopathy syndrome related brain lesions [7].

Cerebrovascular diseases

In the initial Wuhan retrospective series, 5% of patients had new onset CVD; five patients were diagnosed with ischaemic stroke, one with cerebral haemorrhage [3]. In all of these patients signs of an increased inflammatory response were found compared to patients without CVD such as increased C-reactive protein and extremely high levels of D-dimers. Several patients with CVD were older and more likely to have common cerebrovascular risk

Table 1 Overview of studies, case series and case reports describing neurological manifestations of COVID-19 up to 10 May 2020

Type of study	Number and type of patients	Geographical region	Main neurological manifestation	Main findings	SARS-CoV-2 RT-PCR		
					Throat swab	Nasopharyngeal swab	CSF
Retrospective observational case series [3]	n = 214 consecutively hospitalized patients	Wuhan, China	CNS, PNS, cranial nerve, muscular injury	• Neurological manifestation in 36% • Impaired consciousness, acute cerebrovascular disease, ataxia, seizures, taste, smell and vision impairment, neuropathy, skeletal muscle injury • 5% new onset stroke • Neurological manifestations more common in patients with severe COVID-19 • 5% anosmia, 5% dysgeusia	+	/	/
Retrospective case series [4]	n = 113 deceased vs. n = 161 fully recovered hospitalized patients	Wuhan, China	Disorders of consciousness	• 22% conscious disorders in deceased vs. 1% in recovered patients	+	/	/
Observational case series [5]	n = 58 consecutive admission to ICU due to ARDS	Strasbourg, France	Neurological symptoms	• Neurological symptoms in 14% on admission, in 67% when NM was stopped • Agitation in 40% when NM was stopped • 67% corticospinal tract signs • In a third, signs of a dysexecutive syndrome consisting of inattention, disorientation or poorly organized movements in response to commands	+	/	7/7: –
Retrospective cohort study [6]	n = 173, n = 56 COVID-19 with neurological symptoms, n = 117 neurological symptoms without COVID-19	Brescia, Bologna, Milan, Italy	Neurological symptoms	• In COVID-19 patients + neurological symptoms: significantly higher in-hospital mortality, delirium and disability	+	+	/
Prospective case series [7]	n = 19 non-survivors of COVID-19	Belgium	Structural MRI brain abnormalities <24 h of death	• 2/19: subcortical microbleeds and macrobleeds • 1/19: PRES related brain lesions • 1/19 non-specific white matter lesions • 4/19: asymmetric olfactory bulbs without other abnormalities	+	/	/
Retrospective case series [8]	n = 4	New York, USA	New onset stroke	• 4 ischaemic stroke patients relatively early in stage of disease (1/4 TIA)	+, no further specification		
Retrospective case series [9]	n = 6	London, UK	New onset stroke	• 6/6: large vessel occlusion • 6/6: multi territorial infarcts • 6/6 elevated D-dimer levels of ≥1000 µg/l	+, no further specification		
Case report encephalitis [22]	n = 1	Japan	CNS infection	• Meningo-encephalitis • Generalized seizures and decreased consciousness • MRI: hyperintensity along the wall of R lateral ventricle and hyperintense signal changes in the R MTL and hippocampus	–	/	+
Case report acute [26]	n = 1	USA	Encephalopathy	• MRI: haemorrhagic rim enhancing lesions within the bilateral thalami, MTL, subinsular region	+	/	/

(continued)

Table 1 *(Continued)*

Type of study	Number and type of patients	Geographical region	Main neurological manifestation	Main findings	SARS-CoV-2 RT-PCR		
					Throat swab	Nasopharyngeal swab	CSF
Retrospective multicentre study [27]	n = 304 hospitalized patients	China	Seizures/ epilepsy	• No epilepsy history • 108/304 severe COVID-19 • 0/304 acute symptomatic seizures or new onset epilepsy	Laboratory-confirmed SARS-CoV-2; no further specification		
Case report [28]	n = 1	Iran	Seizures/ epilepsy	• New onset recurrent generalized seizures • MRI/CSF normal	+	+	–
Community survey [29]	n = 1702 at home patients using radar COVID-19 app for symptom report	UK	Hyposmia and/ or anosmia, dysgeusia	• 59%: loss of smell and taste	RT-PCR positive; no further specification		
Retrospective cohort [30]	n = 42, mild COVID-19 hospitalized patients	Tel-Aviv, Israel	Hyposmia and anosmia	• 30% hyposmia and anosmia • Onset 3-4 days after symptom onset • Rapid recovery in most patients	+	/	/
Cross-sectional survey [31]	n = 59, hospitalized patients	Milan, Italy	Hyposmia and anosmia, dysgeusia	• 34%: taste or smell disorder • 19%: taste and smell disorder • 20% onset before hospital admission • More in females	SARS-CoV-2–positive; no further specifications		
Survey [32]	n = 202 outpatients with mild to moderate COVID-19 symptoms	Treviso, Belluno, Italy	Hyposmia and anosmia, dysgeusia	• 65% hyposmia • 11% as a first symptom • More frequent in women • 35% symptom of blocked nose • 3% only smell and taste symptoms	+	/	/
Prospective multicentre study [33]	n = 417 mild to moderate hospitalized COVID-19 patients	Belgium, France, Spain, Italy	Olfactory and gustatory dysfunctions	• 85.6% olfactory dysfunction and • 88.0% gustatory dysfunction (11.8%), • 12% before other symptoms • 47% facial pain • 22% dysphagia	RT-PCR positive; no further specification		
Case report [34]	n = 2	Madrid, Spain	Cranial nerve pathology, MFS	• CSF: albumin-cytologic dissociation • Cranial nerve disturbances early during infection (3 and 5 days after symptom onset)	/	+	–
Case report [35]	n = 2	USA	Cranial nerve pathology, MFS	• Ophthalmoparesis • Early after symptom onset • MRI: abnormal perineural or cranial nerve findings	+	/	–
Case report [37]	n = 1	China	GBS	• Symmetric leg weakness and areflexia • EMG: suggestive of demyelinating neuropathy • CSF: albumin-cytologic dissociation • Early after symptom onset	+	–	–
Case series [38]	n = 5	Northern Italy	Cranial nerve pathology, GBS	• 4/5 lower limb weakness and paresthesias • 1/5 facial diplegia, ataxia, paresthesia • Symptom interval: 5–10 days • 2/5: normal CSF protein	n = 4: + n = 1:	serologic+	/
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–, negative; +, positive; ARDS, acute respiratory distress syndrome; CNS, central nervous system; CSF, cerebrospinal fluid; EMG, electromyography; GBS, Guillain–Barré syndrome; ICU, intensive care unit; MFS, Miller Fisher syndrome; MRI, magnetic resonance imaging; MTL, medial temporal lobe; NM, neuromuscular blockade; PNS, peripheral nervous system; PRES, posterior reversible encephalopathy syndrome; R, right-sided; RT-PCR, reverse transcription polymerase chain reaction assay; TIA, transient ischaemic attack.

factors including hypertension and diabetes mellitus. The vast majority of patients had a severe respiratory infection. A case series from New York reported on four new onset ischaemic stroke patients relatively early in the stage of the disease [8]. A report from Queens Square, London, describes six patients with RT-PCR confirmed COVID with new onset ischaemic stroke, all due to large vessel occlusion and having elevated D-dimer levels of ≥1000 μg/l (5/6 > 7000 μg/l); two patients were under anticoagulant therapy. Patients had multi-territory infarcts; two experienced a concurrent venous thrombosis. In 5/6 stroke occurred 8–24 days after onset of COVID-19 symptoms but in one patient stroke occurred during the pre-symptomatic phase [9].

Acute inflammation caused by infection is often followed by a procoagulant state and has been postulated as one of the mechanisms underlying stroke [10]. Studies from the Netherlands and France suggest that blood clots throughout the body appear in 20%–30% of critically ill COVID-19 patients [11,12]. Coagulation dysfunctions including thrombocytopenia and D-dimer increase are frequently seen in patients with COVID-19 at the beginning of the so-called hyperinflammatory phase (phase III) of the disease progression and are associated with negative clinical evolution [13]. The increase in D-dimer levels appears to be higher in COVID-19 patients with CVD compared to patients without CVD (median levels of 900 μg/l) but this is a finding that will need to be further investigated and documented [3,9]. During the outbreak in 2002–2003 of SARS-CoV, a study reporting on 206 patients in Singapore mentioned five patients with thromboembolic stroke and many critically ill patients who were on low molecular weight heparine who still developed deep venous thrombosis and pulmonary embolism suggesting the presence of a procoagulant state in SARS [14]. From this series, vigilance for thrombotic complications including stroke was proposed especially in patients treated with intravenous immunoglobulin that was hypothesized to further increase viscosity in a hypercoagulable state. In two studies reporting on COVID-19 stroke patients with multiple cerebral infarcts and clinically significant coagulopathy, the detection of antiphospholipid antibodies has been reported [9,15]. Antiphospholipid antibodies abnormally target phospholipid proteins, and the presence of these antibodies is central to the diagnosis of the antiphospholipid syndrome [16]. The antibodies may arise transiently in patients with critical illness and various infections. In some patients with genetic predisposition, this may induce a permanent antiphospholipid syndrome, which needs to be investigated at least 12 weeks after the acute illness according to international guidelines [17].

Infections of the central nervous system

The neuro-invasive potential of coronaviruses (CoVs) has been documented for most of the CoVs including SARS-CoV and MERS-CoV [18–20]. The presence of SARS-CoV particles as well as the ACE2 receptor has been demonstrated in both animal and human brains and cases of direct viral CNS invasion have been reported in several human CoVs [20,21]. SARS-CoVs have been detected in the CSF of a patient with encephalitis [22]. Due to the similarity between SARS-CoV and SARS-CoV-2 and the presence of the ACE2 receptor in the CNS, the possibility was raised that SARS-CoV-2 might also lead to direct CNS infection with similar complications. Indeed, a recent report described the first case of meningo-encephalitis due to SARS-CoV-2, associated with transient generalized seizures and MRI lesions. Interestingly, SARS-CoV-2 RNA was not detected in the nasopharyngeal swab but was detected in the CSF [23].

It is hypothesized that CNS infection with involvement and dysfunction of the cardiorespiratory brainstem centres may contribute to death of infected animals or patients [24,25]. A common observation in hACE2 Tg mice that were inoculated intranasally or intracranially (even at low doses) with SARS-CoV particles was a disseminated infection of the dorsal vagal complex (nucleus tractus solitarius, area postrema and dorsal motor nucleus of the vagus) [20]. This complex contains afferent and efferent projections of the vagus nerve to the lungs and respiratory tracts indicating that the vagus nerve might be another important neuronal route for SARS-CoV-2 entry into the brain. In a similar way, studies on MERS-CoV have shown the brainstem to be heavily infected [19].

This leads to the hypothesis also made by an earlier report that death of infected animals or patients may be at least partially due to the dysfunction of the cardiorespiratory brainstem centre [24,25]. The cytokine storm with excessive levels of proinflammatory cytokines may also contribute to the lethality of the infection [18]. This is illustrated by a recent report of a COVID-19 patient with an acute necrotizing encephalopathy, a rare complication observed in infections with viruses including influenza, and related to a cytokine storm in the brain without direct viral invasion [26].

Seizures and epilepsy

A Chinese multicentre retrospective study enrolled 304 patients in China, of whom 108 had a severe condition

[27]. None of these patients had a known history of epilepsy. Neither acute symptomatic seizures nor status epilepticus were observed. In one-third of patients, brain insults or metabolic imbalances known to increase the risk of seizures occurred during the disease course without seizure observation. From this study, there was no evidence suggesting an additional risk of acute symptomatic seizures in people with COVID-19. It should be noted that electroencephalograms were not performed in the patients. In the Strasbourg ICU series, in eight patients electroencephalography detected nonspecific changes; one patient had diffuse bifrontal slowing consistent with encephalopathy [5]. A case report describes one Iranian patient who was admitted with new onset recurrent generalized seizures and tested positive for SARS-CoV-2 although no evidence for viral CNS invasion in the CSF was found and MRI was normal [28].

Cranial nerve disturbances

Hyposmia and anosmia have been reported to occur in the early stage of COVID-19. In the above-mentioned observational studies in Wuhan anosmia occurred in 5.1% and dysgeusia in 5.6% of patients [3]. Early reports from Europe and Israel suggest that this sudden olfactory dysfunction can appear in 30%–60% of COVID-19 cases [29–31]. An Italian study investigating altered sense of smell or taste in PCR positive patients reported that 65% of patients reported this symptom and of these 11% had symptoms before other symptoms; these symptoms were more frequent in women. 35% of patients also reported a blocked nose; 3% only had smell and taste symptoms [32]. In a recent prospective study in 417 patients with mild to moderate laboratory-confirmed COVID-19, conducted in 12 European hospitals, olfactory and gustatory dysfunctions were reported in 85.6% and 88.0% of patients respectively with a significant association between the two disorders. Anosmia has been reported as a symptom due to infection with other respiratory viruses and CoVs [33]. Whilst a pathogenesis related to nasal inflammation and related obstruction seems obvious, it has been found that symptoms occur also with high prevalence in patients without nasal obstruction or rhinorrhoea suggesting a potentially direct neuro-invasion of the nervous system paths such as the olfactory bulb. The olfactory dysfunction appeared before (11.8%), after (65.4%) or at the same time as (22.8%) the appearance of other symptoms and significantly more in women. In this study, also facial pain occurred in 47% of patients and dysphagia in 22%. In at least 25.5% of patients, both olfactory and gustatory functions recovered over a 2-week period following resolution of general symptoms. In some patients, olfaction recovered but not taste, and vice versa. The authors remark that due to the short-term observations in this study it is reasonable to think that a large number of these patients will recover over the weeks following resolution of the disease. Two COVID-19 patients with polyneuritis cranialis have been reported in Spain [34]; despite full recovery there was residual anosmia and ageusia in one case. Two American COVID-19 patients with ophthalmoparesis and abnormal findings on MRI in cranial nerves were also reported [35].

Autoimmune and inflammatory syndromes

Acute neuroinflammatory immune-mediated disorders caused by CoVs have been documented; MERS-CoV caused both ARDS and acute disseminated encephalomyelitis, and was potentially related to a post-infectious Guillain–Barré syndrome (GBS) with brainstem encephalitis [36]. Recently, cases of a SARS-CoV-2 infection associated with GBS have been reported as well. The first case report concerned a patient who had recently travelled to Wuhan and presented with clinical signs of a GBS on admission [37]. The patient developed respiratory symptoms 7 days later and tested positive for SARS-CoV-2. A more recent study reviewing patients in three hospitals in northern Italy reported on five patients who had GBS after the onset of COVID-19 [38]. Four of the patients had a positive nasopharyngeal swab for SARS-CoV-2 at the onset of the neurological syndrome and one a positive serological testing. The interval between the onset of symptoms of COVID-19 and the first symptoms of GBS ranged from 5 to 10 days. Two cases of Miller Fisher syndrome (MFS) and polyneuritis cranialis during the COVID-19 pandemic were reported in Spain [34] and two cases with ophthalmoparesis in the USA [35]. In all these cases PCR was positive for the oropharyngeal swab test but negative in the CSF. It should be noted that, in the GBS and MFS cases, potentially autoimmune related neurological symptoms and COVID-19 primo-infection symptoms typically occurred in close time relationship to each other suggesting a para-infectious profile. Although not stated in the reports, it can be estimated that the neuromuscular failure associated with GBS or MFS may further compromise breathing and contribute to the severity of respiratory insufficiency.

The involvement of CoVs in chronic neuroinflammatory diseases has been suggested as well. A significantly higher prevalence of HCoV-OC43 has been detected in brains of multiple sclerosis (MS) patients

and CoVs have also been isolated from the CSF in patients with MS [39,40]. Inflammatory molecules linked to MS could originate from infection of glial cells by CoVs [41]. A direct link between any specific virus in neuroinflammatory disorders, including MS, has not yet been described. Nevertheless, many patients with autoimmune syndromes such as MS might be particularly vulnerable as they are treated with disease-modifying treatments that potentially increase infectious risk [42]. For instance, a fatal encephalitis with HCoV-OC43 has been documented in immunocompromised patients, with infected neurons at autopsy [43]. This leads to a similar concern with SARS-CoV-2 although initial reports from a series of MS patients who were infected with SARS-CoV-2 are gradually becoming available with a positive trend for patients being treated with anti-CD20 in Madrid [44]. 9/60 (15%) patients reported symptoms highly suggestive of COVID-19, mostly without serious complications; only one patient was hospitalized. To tackle the specific questions around starting/stopping disease-modifying treatments and risk/outcome for MS patients with COVID-19 the MS International Federation and MS Data Alliance have set up an initiative for global data sharing [45].

Extrapyramidal and neurodegenerative disorders

Apart from the neurological symptoms described in the Strasbourg study, no reports on extrapyramidal symptoms have been published. Relevant information based on previous experimental work with CoVs that may be of interest to clinical neurological practice has been found. In 1985, it was demonstrated that mice experimentally infected with CoVs, known to cause encephalitis and demyelination, demonstrate dense deposits of viral antigen in the basal ganglia [46]. In the search for aetiological factors for Parkinson's disease, a decade later Fazzini *et al*. found significantly higher CSF antibodies to four coronavirus antigens in Parkinson patients compared to controls [47]. It is known from previous preclinical and clinical studies that drugs used in Parkinson's disease, i.e. the adamantanes, may have antiviral effects and repurposing studies for COVID-19 may be indicated [48]. Studies have shown interactions between SARS-CoV-2 proteins and human proteins from various aging related pathways [49]. The decreased ability to properly activate the stress response mechanism in the elderly can lead to phenotypes that characterize neurodegenerative diseases such as the accumulation of aggregates. Coronavirus infection may, in the long term, however, lead to accelerated aging phenotypes in survivors. Prospective studies and registries may be useful to establish connections with aging-associated disorders, such as Parkinson's disease and other neurodegenerative disorders [49].

Possible neuro-invasive mechanisms of human coronaviruses

The entry of respiratory viruses in the CNS may be mediated through a haematogenous or a neuronal retrograde route. In the first route, the virus will disrupt the nasal epithelium and reach the bloodstream and leucocytes, and – by manipulating the innate immune system – invade other tissues including the CNS. Moreover, leucocytes may act as a reservoir for viral transmission for neuro-invasive CoVs [18].

In the second route, the virus could infect peripheral neurons and access the CNS through retrograde transsynaptic neuronal dissemination [18]. The retrograde axonal transport and transsynaptic transfer are well documented for other types of coronavirus such as the swine haemagglutinating encephalomyelitis virus (HEV) and avian bronchitis virus [50,51].

SARS-CoV and MERS-CoV have been detected mainly in neurons of the brains of infected patients [19,20]. A similar neuronal tropism was also detected upon inoculation of transgenic mice in which expression of human ACE2 was targeted to epithelial cells using the human cytokeratin 18 (K18) promoter (K18-hACE2 Tg mice) [20]. Although the olfactory bulb is highly efficient at confining neuro-invasion, several viruses have been shown to enter the CNS through the olfactory route [18]. An experimental study using hACE2 Tg mice showed the olfactory nerve being the primary entry route of SARS-CoV to the brain. Subsequently, the virus rapidly spreads throughout the brain which probably contributes to high mortality in these mice [20]. This olfactory route for CNS invasion of SARS-CoV-2 remains to be proven, but it is plausible as findings of anosmia associated with COVID-19 suggest the presence of the virus in the nasal epithelium or the olfactory bulb. Moreover, anosmia and ageusia are prevalent in COVID-19 patients, even without other nasal symptoms [33]. Nevertheless, the mechanism of COVID-19 induced anosmia remains to be elucidated as it seems that ACE2 receptors are not expressed by olfactory neurons and no data have been reported yet on an association of anosmia and the presence of CNS manifestations [52,53].

Conclusion

Increasing evidence shows that infections with CoVs are not always confined to the respiratory tract.

Physicians should be aware of the possibility of neurological manifestations including acute CVDs, impaired consciousness, cranial nerve manifestations and autoimmune disorders such as GBS. Olfactory and gustatory dysfunctions are both prevalent in patients with mild to moderate COVID-19 who may not have nasal symptoms. Sudden anosmia or ageusia need to be recognized by the international scientific community as important symptoms of COVID-19. Most of the other neurological symptoms are demonstrated in patients with more severe COVID-19 disease and potentially result from widespread dysregulation of homeostasis caused by major organ system damage. However, a part of the neurological spectrum in COVID-19 patients may be due to direct viral neurological injury or indirect neuroinflammatory and autoimmune mechanisms and may occur soon in the course of the disease. Detection of the viral nucleic acid in the CSF is rare until now; detection of intrathecal synthesis of antiviral antibodies or brain autopsies on the COVID-19 patients could clarify the viral capacity for CNS invasion. Physicians should be aware that in patients with severe COVID-19 rapid clinical deterioration could be related to a neurological event such as encephalitis or stroke potentially contributing to its high mortality rate. Acute CVD is not uncommon in COVID-19 and the development of CVD is an important negative prognostic factor. There are currently no antiviral treatments against the virus or vaccines for its prevention. A study using affinity purification mass spectrometry identified 332 high-confidence SARS-CoV-2 human protein–protein interactions. The identified SARS-CoV-2 viral proteins connected to a wide array of biological processes, including protein trafficking, translation, transcription and ubiquitination regulation. Using a combination of a systematic chemoinformatic drug search with a pathway centric analysis, close to 70 different drugs and compounds, including US Food and Drug Administration approved drugs, compounds in clinical trials as well as preclinical compounds targeting parts of the resulting network, were listed. Currently, testing of these compounds for antiviral activity therapeutic value is ongoing. Some of these drugs are well known to the neurological community such as valproic acid, haloperidol and entacapone [54]. The long-term consequences of the infection on human health remain uncertain. Aging-associated disorders such as Parkinson's disease and autoimmune disorders might be a potential long-term complication of SARS-CoV-2 infections. The European Academy of Neurology has initiated an online survey to keep track as much as possible of SARS-CoV-2 neurological manifestations (https://www.ean.org/ean/eancore-covid-19).

Disclosure of conflicts of interest

None of the authors has a conflict of interest for this study.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in the study.

References

1. 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.
2. Guan WJ, Ni ZY, Hu Y, *et al*. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; **382:** 1708–1720.
3. Mao L, Jin H, Wang M, *et al*. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020. https://doi.org/10.1001/jamaneurol.2020.1127
4. Chen T, Wu D, Chen H, *et al*. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020; **368:** m1091.
5. Helms J, Kremer S, Merdji H, *et al*. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med* 2020. NEJMc2008597.
6. Benussi A, Pilotto A, Premi E, *et al*. Clinical characteristics and outcomes of inpatients with neurological disease and COVID-19. *medRxiv*. https://doi.org/10.1101/2020.04.28.20082735
7. Coolen T, Lolli V, Sadeghi N, *et al*. Early postmortem brain MRI findings in COVID-19 non-survivors. *medRxiv*. https://doi.org/10.1101/2020.05.04.20090316
8. Avula A, Nalleballe K, Narula N, *et al*. COVID-19 presenting as stroke. *Brain Behav Immun* 2020. https://doi.org/10.1016/j.bbi.2020.04.077
9. Beyrouti R, Adams ME, Benjamin L, *et al*. Characteristics of ischaemic stroke associated with COVID-19. *J Neurol Neurosurg Psychiatry* 2020. https://doi.org/10.1136/jnnp-2020-323586
10. Grau AJ, Urbanek C, Palm F. Common infections and the risk of stroke. *Nat Rev Neurol* 2010; **6:** 681–694.
11. Klok FA, Kruip MJHA, van der Meer NJM, *et al*. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020. https://doi.org/10.1016/j.thromres.2020.04.013
12. Poissy J, Goutay J, Caplan M, *et al*. Pulmonary embolism in COVID-19 patients: awareness of an increased prevalence. *Circulation* 2020. https://doi.org/10.1161/CIRCULATIONAHA.120.047430
13. Nile SH, Nile A, Qiu J, Lin L, Jia X, Kai G. ArCOVID-19: pathogenesis, cytokine storm and therapeutic potential of interferons. *Cytokine Growth Factor Rev* 2020. https://doi.org/10.1016/j.cytogfr.2020.05.002
14. Umapathi T, Kor AC, Venketasubramanian N, *et al*. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). *J Neurol* 2004; **251:** 1227–1231.
15. Yan Z, Meng X, Shulan Z, *et al*. Coagulopathy and antiphospholipid antibodies in patients with Covid-19.

N Engl J Med 2020. https://doi.org/10.1056/NEJMc2008597
16. Tsai LK, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. *Acta Neurol Taiwan* 2005; **14:** 113–119.
17. Martirosyan A, Aminov R, Manukyan G. Environmental triggers of autoreactive responses: induction of antiphospholipid antibody formation. *Front Immunol* 2019; **10:** 1609.
18. Desforges M, Le Coupanec A, Dubeau P, *et al*. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses* 2019; **12:** 14.
19. 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.
20. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. 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.
21. Ding Y, He L, Zhang Q, *et al*. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. *J Pathol* 2004; **203:** 622–630.
22. Hung EC, Chim SS, Chan PK, *et al*. Detection of SARS coronavirus RNA in the cerebrospinal fluid of a patient with severe acute respiratory syndrome. *Clin Chem* 2003; **49:** 2108–2109.
23. 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.
24. Xia H, Lazartigues E. Angiotensin-converting enzyme 2 in the brain: properties and future directions. *J Neurochem* 2008; **107:** 1482–1494.
25. 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.
26. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology* 2020; **31:** 201187.
27. Lu L, Xiong W, Liu D, *et al*. New-onset acute symptomatic seizure and risk factors in Corona Virus Disease 2019: a retrospective multicenter study. *Epilepsia* 2020. https://doi.org/10.1111/epi.16524
28. Karimi N, Sharifi Razavi A, Rouhani N. Frequent convulsive seizures in an adult patient with COVID-19: a case report. *Iran Red Crescent Med J* 2020; **22:** e102828.
29. Menni C, Valdes A, Freydin MB, *et al*. Loss of smell and taste in combination with other symptoms is a strong predictor of COVID-19 infection. *medRxiv* 2020. 2020.04.05.20048421
30. Levinson R, Elbaz M, Ben-Ami R, *et al*. Anosmia and dysgeusia in patients with mild SARS-CoV-2 infection. *medRxiv* 2020. 2020.04.11.20055483
31. Giacomelli A, Pezzati L, Conti F, *et al*. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. *Clin Infect Dis* 2020. https://doi.org/10.1093/cid/ciaa330
32. Spinato G, Fabrris C, Polesel J, *et al*. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. *JAMA* 2020. https://doi.org/10.1001/jama.2020.6771
33. Lechien JR, Chiesa-Estomba CM, De Siati DR, *et al*. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol* 2020. https://doi.org/10.1007/s00405-020-05965-1
34. Gutierrez-Ortiz C, Mendez A, Rodrigo-Rey S, *et al*. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. *Neurology* 2020. https://doi.org/10.1212/WNL.0000000000009619
35. Dinkin M, Gao V, Kahan J, *et al*. COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. *Neurology* 2020. https://doi.org/10.1212/WNL.0000000000009700
36. Kim JE, Heo JH, Kim HO, *et al*. Neurological complications during treatment of Middle East respiratory syndrome. *J Clin Neurol* 2017; **13:** 227–233.
37. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain–Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol* 2020; **19:** 383–384.
38. Toscano G, Palmerini F, Ravaglia S, *et al*. Guillain–Barré syndrome associated with SARS-CoV-2. *N Engl J Med* 2020. https://doi.org/10.1056/NEJMc2009191
39. Arbour N, Day R, Newcombe J, Talbot PJ. Neuroinvasion by human respiratory coronaviruses. *J Virol* 2000; **74:** 8913–8921.
40. Burks JS, DeVald BL, Jankovsky LD, Gerdes JC. Two coronaviruses isolated from central nervous system tissue of two multiple sclerosis patients. *Science* 1980; **209:** 933–934.
41. Edwards JA, Denis F, Talbot PJ. Activation of glial cells by human coronavirus OC43 infection. *J Neuroimmunol* 2000; **108:** 73–81.
42. Willis MD, Robertson NP. Multiple sclerosis and the risk of infection: considerations in the threat of the novel coronavirus, COVID-19/SARS-CoV-2. *J Neurol* 2020; **267:** 1567–1569.
43. Morfopoulou S, Brown JR, Davies EG, *et al*. Human coronavirus OC43 associated with fatal encephalitis. *N Engl J Med* 2016; **375:** 497–498.
44. Montero-Escribano P, Matıas-Guiu J, Gomez-Iglesias P, Porta-Etessam J, Pytel V, Matias-Guiu J. Anti-CD20 and Covid-19 in multiple sclerosis and related disorders: a case series of 60 patients from Madrid, Spain. *Multiple Sclerosis and Related Disorders* 2020. https://doi.org/10.1016/j.msard.2020.102185
45. MS International Federation. COVID-19 and MS: Global Data Sharing Initiative. https://www.msif.org/covid-19-ms-global-data-sharing-initiative/ (accessed 10/05/2020)
46. Fishman PS, Gass JS, Swoveland PT, Lavi E, Highkin MK, Weiss SR. Infection of the basal ganglia by a murine coronavirus. *Science* 1985; **229:** 877–879.
47. Fazzini E, Fleming J, Fahn S. Cerebrospinal fluid antibodies to coronavirus in patients with Parkinson's disease. *Mov Disord* 1992; **7:** 153–8.
48. Cimolai N. Potentially repurposing adamantanes for COVID-19. *J Med Virol* 2020.
49. Lippi A, Domingues R, Setz C, Outeiro TF, Krisko A. SARS-CoV-2: at the crossroad between aging and neurodegeneration. *Mov Disord* 2020; **35:** 716–720.

50. Li YC, Bai WZ, Hirano N, *et al*. Neurotropic virus tracing suggests a membranous-coating-mediated mechanism for transsynaptic communication. *J Comp Neurol* 2013; **521:** 203–212.
51. Matsuda K, Park CH, Sunden Y, *et al*. The vagus nerve is one route of transneural invasion for intranasally inoculated influenza A virus in mice. *Vet Pathol* 2004; **41:** 101–107.
52. Fodoulian L, Tuberosa J, Rossier D, Landis BN, Carleton A, Rodriguez I. SARS-CoV-2 receptor and entry genes are expressed by sustentacular cells in the human olfactory neuroepithelium. *bioRxiv* 2020: 2020.03.31.013268
53. Brann DH, Tsukahara T, Weinreb C, *et al*. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *bioRxiv* 2020. 2020.03.25.009084
54. Gordon DE, Jang GM, Bouhaddou M, *et al*. A SARS-CoV-2-human protein–protein interaction map reveals drug targets and potential drug-repurposing. *Nature* 2020. https://doi.org/10.1038/s41586-020-2286-9