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

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Abstract

Introduction: 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, WebOfScience and Covid-dedicated databases were searched for the combination of COVID-19 terminology and neurology terminology up to May 10th 2020. Social media channels were followed-up between March 15th and May 10th 2020 for postings with the same scope. Neurological manifestations were extracted from the identified manuscripts 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 auto-immune disorders such as Guillain-Barré Syndrome often present in patients with more severe COVID-19. Cranial nerve symptoms such

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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 regards 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, ie. the angiotensin-converting enzyme 2 (ACE2) receptor. Therefore, the virus was named SARS-CoV-2. The WHO named the disease coronavirus disease 2019 (COVID-19) and declared the outbreak of COVID-19 a pandemic on 11 March 2020, after the disease 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 neurologic 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).

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Methods

Pubmed, WebOfScience 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 terminology (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 May 10th 2020. Social media channels (facebook, twitter, linked-in) were followed-up between March 15th and May 10th 2020 for postings with the same scope. Neurological manifestations were extracted from the identified manuscripts 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 3 categories: central nervous system (CNS) manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, 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 less 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 2 Strasbourg intensive care units found neurological symptoms on ICU admission in 14% (8/58) of patients with ARDS; 2/3 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, 1/3 had signs of a dysexecutive syndrome consisting of inattention, disorientation or poorly organized movements in response to commands. 11/13 patients who underwent MRI due to signs of encephalopathy, showed bilateral frontotemporal hypoperfusion on perfusion imaging and two had a small acute

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ischemic stroke without clinical symptoms. In 7 of these patients in whom a lumbar puncture was performed, RT-PCR assays of the 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 when compared to neurology patients admitted in the same period without COVID-19 (117/173)[6]. A postmortem brain MRI study from Belgium in 19 patients, demonstrated brain abnormalities in 8 non-survivors of COVID-19 such as hemorrhagic and posterior reversible encephalopathy syndrome related brain lesions[7].

1. *Cerebrovascular diseases*

In the initial Wuhan retrospective series 5% of patients had new onset cerebrovascular disease (CVD); 5 patients were diagnosed with ischemic stroke, 1 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 CRP and extremely high levels of D-dimers. Several patients with CVD were older and more likely to have common cerebrovascular risk factors including hypertension and diabetes mellitus. The vast majority of patients had a severe respiratory infection. A case series from New York, reported on 4 new onset ischemic stroke patients, relatively early in the stage of the disease[8]. A report from Queens Square, London describes 6 patients with RT-PCR confirmed COVID with new onset ischemic stroke, all due to large vessel occlusion and having elevated D-Dimer levels of >1000 microg/l (5/6 >7000 microg/l); 2 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 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% to 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 microg/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 5 patients with thromboembolic stroke and many critically ill patients who were on LMWH who still

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developed deep venous thrombosis and pulmonary embolism suggesting the presence of a pro-coagulant state in SARS[14]. From this series, vigilance for thrombotic complications including stroke was proposed especially in patients treated with intravenous immunoglobulins 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]. These 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].

2. *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 its 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 centers 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 virus 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

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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].

3. Seizures and epilepsy

A Chinese multicenter 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 or status epilepticus were observed. In 1/3 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 EEGs were not performed in patients. In the Strasbourg ICU series, in 8 patients EEG 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].

4. Cranial nerve disturbances

Hypo- and anosmia have been reported to occur in the early stage of COVID-19. In the abovementioned observational studies in Wuhan anosmia occurred in 5.1% and dysgeusia in 5.6% of patients[3]. Early reports from Europe and Israel suggested that this sudden olfactory dysfunction can appear in 30 to 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 both disorders. Anosmia has been reported as a symptom due to infection with other respiratory viruses and CoVs[33]. While 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 rhinorrhea 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 (22.8%) as the

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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 ophtalmoparesis and abnormal findings on MRI in cranial nerves were also reported[35].

5. *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 COVID-19. A more recent study reviewing patients in three hospitals in northern Italy, reported on 5 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 neurologic 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 5-10 days. Two cases of Miller Fisher syndrome and polyneuritis cranialis during the COVID-2 pandemic were reported in Spain[34]; two cases with opthalmoparesis 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 auto-immune 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.

CoVs' involvement 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 CSF in patients with MS[39,40]. Inflammatory molecules linked to MS could originate from infection of glial cells by CoVs[41].

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A direct link between any specific virus in neuro-inflammatory 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 (DMTs) that potentially increase infectious risk[42]. For instance, a fatal encephalitis with HCoV-OV43 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 series of MS patients that 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 COIVD-19, mostly without serious complications; only one patient was hospitalized. To tackle the specific questions around starting/stopping DMTs and risk/outcome for MS patients with COVID-19 the MS international federation (MSIF) and MS Data Alliance have set up an initiative for global data sharing[45].

6. *Extrapyramidal and Neurodegenerative disorders*

Apart from the neurological symptoms described in the Strasbourg study, no reports on extrapyramidal symptoms have been published. We did find relevant information based on previous experimental work with CoVs that may be of interest to clinical neurological practice. 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 search for etiological 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 pre-clinical and clinical studies that drugs used in Parkinson's disease, ie. the adamantanes, may have anti-viral effects and repurposing studies for COVID-19 may be at place[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 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

Entry of respiratory viruses in the CNS may be mediated through a hematogenous 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

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tissues including the CNS. Moreover, leukocytes 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 is well documented for other types of coronavirus such as the Swine Hemagglutinating Encephalomyelitis Virus (HEV) and avian bronchitis virus[50,51].

SARS-CoV and MERS-CoV have been detected mainly in neurons of 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 leading which likely contributes to high mortality in these mice[20]. This olfactory route for CNS invasion of SARS-CoV-2 remains to be proven, but is plausible as findings of anosmia associated with COVID-19 suggests 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 has 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 cerebrovascular diseases, impaired consciousness, cranial nerve manifestations and auto-immune 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. The sudden anosmia or ageusia need to be recognized by the international scientific community as important symptoms of the COVID-19. Most of the other neurological symptoms are demonstrated in patients with more severe COVID-19 disease and are potentially resulting 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

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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 cerebrovascular disease 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 FDA 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 auto-immune 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 of possible of SARS-CoV-2 neurological manifestations (https://www.ean.org/ean/eancore-covid-19)

Data availability satement

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

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Type of study	Number & type of patients	Geographical region	Main Neurological manifestation	Main findings	SARS-CoV-2 RT-PCR		
					throat swab	naso phary ngeal swab	CSF
retrospective observational case series[3]	n=214 consecutive 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 • 1/3: 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 <24h of death	• 2/19: subcortical micro- 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 ischemic 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	+, no further specification		

				levels of $\geq$1000 microg/l			
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: hemorrhagic rim enhancing lesions within the bilateral thalami, MTL, subinsular region	+	/	/
retrospective multicenter 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 @home patients using radar COVID-19 app for symptom report	UK	hypo- 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	hypo- and anosmia	• 30% hypo-anosmia • onset 3,3 days after symptom onset • rapid recovery in most patients	+	/	/
cross-sectional survey[31]	n=59, hospitalized patients	Milan, Italy	hypo- 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	hypo- and anosmia, dysgeusia	• 65%: hypo-anosmia • 11% as a first symptom • more frequent in women. • 35: % symptom of blocked nose • 3%: only smell and taste symptoms	+	/	/
prospective multicenter 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	/	+	-

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				onset)			
case report[35]	n=2	USA	cranial nerve pathology, MFS	• ophtalmoparesis • 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 +	/	-

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

Legend: RT-PCR: real-time reverse transcription polymerase chain reaction assay, CSF: cerebrospinal fluid, +: positive, -: negative, CNS: central nervous system, PNS: peripheral nervous system, vs: versus, ICU: intensive care unit, ARDS: acute respiratory distress syndrome, NM: neuromuscular blockade, LP: lumbar puncture, MRI: magnetic resonance imaging, PRES: posterior reversible encephalopathy syndrome, R: right-sided, MTL: medial temporal lobe, MFS: Miller-Fisher Syndrome, GBS: Guillain-Barré Syndrome

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