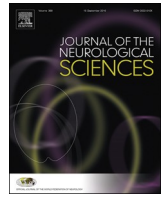




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Review Article

The neurology of COVID-19 revisited: A proposal from the Environmental Neurology Specialty Group of the World Federation of Neurology to implement international neurological registries



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ABSTRACT

A comprehensive review of the neurological disorders reported during the current COVID-19 pandemic demonstrates that infection with SARS-CoV-2 affects the central nervous system (CNS), the peripheral nervous system (PNS) and the muscle. CNS manifestations include: headache and decreased responsiveness considered initial indicators of potential neurological involvement; anosmia, hyposmia, hypogeusia, and dysgeusia are frequent early symptoms of coronavirus infection. Respiratory failure, the lethal manifestation of COVID-19, responsible for 264,679 deaths worldwide, is probably neurogenic in origin and may result from the viral invasion of cranial nerve I, progressing into rhinencephalon and brainstem respiratory centers. Cerebrovascular disease, in particular large-vessel ischemic strokes, and less frequently cerebral venous thrombosis, intracerebral hemorrhage and subarachnoid hemorrhage, usually occur as part of a thrombotic state induced by viral attachment to ACE2 receptors in endothelium causing widespread endotheliitis, coagulopathy, arterial and venous thromboses. Acute hemorrhagic necrotizing encephalopathy is associated to the cytokine storm. A frontal hypoperfusion syndrome has been identified. There are isolated reports of seizures, encephalopathy, meningitis, encephalitis, and myelitis. The neurological diseases affecting the PNS and muscle in COVID-19 are less frequent and include Guillain-Barré syndrome; Miller Fisher syndrome; polyneuritis cranialis; and rare instances of viral myopathy with rhabdomyolysis. The main conclusion of this review is the pressing need to define the neurology of COVID-19, its frequency, manifestations, neuropathology and pathogenesis. On behalf of the World Federation of Neurology we invite national and regional neurological associations to create local databases to report cases with neurological manifestations observed during the on-going pandemic. International neuroepidemiological collaboration may help define the natural history of this worldwide problem.

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1. Introduction

Coronavirus disease 2019 (COVID-19) is a severe acute respiratory syndrome (SARS) caused by the SARS-CoV-2 coronavirus that since December 2019 reached pandemic proportions causing in 5 months more than 3 million confirmed cases worldwide and over 260,000 deaths [Johns Hopkins University Coronavirus Resource Center: <https://coronavirus.jhu.edu>]. Recent publications [1–3] have described neurological manifestations in COVID-19 involving the central nervous system (CNS), peripheral nervous system (PNS) and muscle, as well as early alterations of olfaction and taste [4]. The Environmental Neurology Specialty Group of the World Federation of Neurology concluded that the potential neurological involvement in COVID-19 is a topic of major importance that necessitates a global effort to obtain the neuroepidemiological and clinical data required to quantify the magnitude of the problem, to define the full range of the neurological disease and to encourage neuropathological, physiopathological and therapeutic research. We proposed the creation of international COVID-19 neurological registries to collect and assemble data on acute, chronic and any long-latency effects on the infection on the nervous system [5]. This followed the example of the Spanish Neurological Society (Sociedad Española de Neurología, SEN) [www.sen.es] that, in the midst of one of the most severe outbreaks of COVID-19 in Europe, managed to implement a registry of de novo acute and subacute neurological manifestations in patients with confirmed SARS-CoV-2 infection.

We provide in this review updated information on the known neurological consequences of coronavirus infection in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), as well as selected published data on nervous system injury observed in animal models. We conclude with a current review of neurological manifestations reported in patients with COVID-19. Future research will define issues of congenital involvement –such as seen in maternal infections with Zika virus– or long-latency brain disorders following in utero, perinatal or early childhood infections. While presently unknown in COVID-19, we should be alert to the possibility of tardive disorders comparable to measles-associated Subacute Sclerosing Panencephalitis or Progressive Rubella Panencephalitis; as well as long-term neurological disease, for example late Parkinsonism that occurred among survivors of Encephalitis Lethargica [6] during the 1918–1920 influenza pandemic [7] and, more recently, the increased risk of narcolepsy observed in 2009–2010 after the swine flu pandemic due to influenza A with concurrent vaccination using a monovalent H1N1 influenza vaccine [8].

2. Coronaviruses

According to Henry [9], the name “coronavirus,” from the Latin *corona* (crown), was coined in 1967 by June Almeida [10] based on ultrastructural images resembling the solar corona that she obtained of human cold viruses and the avian infectious bronchitis virus [11]. Since then, a large number of avian, feline, canine, porcine, bovine and equine coronaviruses of veterinary interest has been described as etiological agents of respiratory and enteric diseases [12]. A coronavirus characterized as porcine hemagglutinating encephalomyelitis virus (PHEMV) causes respiratory symptoms and encephalomyelitis in pigs. It was first isolated in 1962 in Canada [13] but became an endemic worldwide zoonosis reported as late as 2015 at animal fairs in Michigan and Ohio, USA [14].

Coronaviruses were considered minor human pathogens until the 2002–2003 outbreak of SARS in Guangdong, China, that eventually affected 8096 people and caused at least 774 deaths worldwide (mortality rate 9.6%), according to the World Health Organization (WHO). SARS-CoV (now called SARS-CoV-1) [15,16] originated in bats (*Rhinolophus affinis*) and reached humans via badgers (*Melogale moschata*), Himalayan palm civets (*Paguma larvata*), and raccoon dogs (*Nyctereutes procyonoides*) [17]. This SARS epidemic outbreak demonstrated the

capacity of coronaviruses to infect humans and to jump across species [15–17], most likely from bat reservoirs [18–20].

Ten years later, in 2012, another outbreak of a highly pathogenic coronavirus, MERS-CoV [21,22], caused 2494 confirmed cases and 858 deaths according to WHO data (case-fatality rate: 34.4%) particularly in Saudi Arabia [23]. MERS may have also originated from bats [20] and utilized camels and dromedaries as intermediary hosts [24,25]. Evidence of camel-to-human infection occurred initially in the Arabian Peninsula [26] followed by viral spread that included nosocomial infections [23].

The current COVID-19 pandemic emerged in December 2019 in Wuhan, China. A zoonotic origin of the etiological agent, SARS-CoV-2, was confirmed with viral isolation from reservoirs in bats that infected as intermediate host the Malayan pangolin (*Manis javanica*) and other wildlife used for food in China [27,28]. These outbreaks have solidly confirmed the high infectivity and lethality of the coronaviruses that pose serious threats to Public Health around the world.

2.1. Taxonomy and structure

The coronaviruses (CoV) are members of the *Coronavirinae* subfamily. The *Torovirinae* plus the coronaviruses comprise the *Coronaviridae* family in the order *Nidovirales* [21]. CoVs are classified in four different genera: alpha, beta, gamma, and delta-CoV according to their phylogenetic links and genomic structures. The *Coronaviridae* members MERS-CoV, SARS-CoV-1, and SARS-CoV-2 all belong to the beta-coronavirus (β -CoV) genus and share highly homologous genomic sequences [21].

The coronaviruses are enveloped single-stranded ribonucleic acid (RNA) viruses with the largest known RNA genome, ranging from 26.2 to 31.7 kilobases [21]. The genome contains a 5' cap and is composed of six to ten open reading frames (ORFs). There are three main viral proteins in the envelope of the virion: the spike protein (S), the membrane protein (M) and the envelope protein (E). The spike glycoprotein mediates virus entry and determines the range of potential hosts, cell tropism and disease pathogenesis [29]. SARS-CoV-1 and SARS-CoV-2 use angiotensin-converting enzyme 2 (ACE2) as receptor to infect ciliated bronchial epithelial cells and type II pneumocytes [20], which explains the severity of the pulmonary involvement. SARS-CoV-2 has a higher affinity than SARS-CoV-1 for the ACE2 receptor, which is present in neurons and endothelial cells indicating that SARS-CoV-2 may have higher neuroinvasive potential compared to previous coronaviruses [30]. MERS-CoV uses dipeptidyl peptidase 4 (DPP4) receptor and the carcinoembryonic antigen-related cell-adhesion molecule 5 (CEACAM5) cofactor ligand to infect unciliated bronchial cells [20]. After binding to the receptor, viruses fuse their envelope with the host cell membrane and the nucleocapsids reach the target cell. The fusion involves large conformational changes of the spike protein [31].

3. Animal models of neurotropic coronavirus infections

Four decades of research on respiratory coronaviruses have demonstrated the capacity of these viruses to go beyond the respiratory system to enter the nervous system and establish persistent brain infection of animals with or without induction of neurological illness [30,32]. There is abundant experimental animal evidence that coronaviruses can reach the brain via spillage from the lungs to the circulatory system or by axonal transport and transneuronal spread from olfactory and trigeminal nerve endings in the nasal epithelium [30,32]. Some coronaviruses experimentally can spread from airway mechanoreceptors and chemoreceptors to the medullary cardio-respiratory centers [33]. Viruses can also access the nervous system via the circumventricular organs [34] that normally lack a blood-brain barrier (BBB) and via dorsal root ganglia and autonomic (including cardiac) ganglia [35] both of which have no blood-nerve barrier (BNB). Indeed, the previously mentioned swine coronavirus PHEMV can establish

ganglionic infection of sensory neurons in dorsal root ganglia after peripheral inoculation [35].

Since SARS-CoV-2 can infect the vascular endothelium of peripheral organs (kidney lung, heart, kidney, and liver) this raises the question of BBB/BNB disruption by direct infection of the endothelium of neural vasculature. Varga and colleagues [36] demonstrated SARS-CoV-2 causes infection of endothelial cells and endotheliitis; thereby, systemic vascular endotheliitis promotes vasoconstriction, edema and a pro-coagulate state [37] with important implications relevant to cerebrovascular stroke. According to Flammer et al. [38] the vascular endothelium is an active paracrine, endocrine, and autocrine organ that is indispensable for the regulation of vascular tone and the maintenance of vascular homeostasis. Endothelial microvascular dysfunction leads to vasoconstriction with subsequent organ ischemia, inflammation with associated tissue edema, and a pro-thrombotic state [37,38]. Endothelial dysfunction is also an important factor for atherosclerosis [37,38]

Experimental studies with the mouse hepatitis virus (MHV) illustrate the potential neurological effects of infection with a neurotropic coronavirus [39]. Neurotropic MHV strains induce an acute encephalitis in mice, while animals that survive the acute infection display chronic brain demyelination, which has been used to model multiple sclerosis (MS) [40]. Of interest, Yeh et al. [41] used reverse transcriptase polymerase chain reaction (RT-PCR) to demonstrate human coronavirus (HCoV OC43) RNA in the cerebrospinal fluid (CSF) and nasopharyngeal secretions of a 15-year-old boy with acute elevation of circulating anti-HCoV antibodies and evidence on Magnetic Resonance Imaging (MRI) of the brain of demyelinating lesions diagnosed as Acute Disseminated Encephalomyelitis (ADEM), although MS could not be ruled out. Moreover, human coronavirus RNA has been demonstrated in CSF [42] and in brains of patients with MS [43,44]. Arbour and colleagues [45] using RT-PCR demonstrated the presence of HCoV RNA in 44% of brain tissue samples from 90 patients with neuropathology-proven MS.

4. Neurological involvement in SARS and MERS patients

During the epidemic outbreaks of SARS in China and MERS in Saudi Arabia, neurological signs and symptoms were reported in small numbers of patients infected with the respiratory coronaviruses SARS-CoV-1 and MERS-CoV respectively. Neuropathological data from those patients are also available in limited cases, as described below.

Table 1

SARS: pathological findings (According to Gu & Korteweg, 2007 [46]).

Organs/Tissue Pathology # Cases		
Central nervous system	Edema and degeneration of neurons, positive neurons by in situ hybridization	12
Skeletal Muscles	Myofiber necrosis and atrophy, few regenerative myofibers	13
Heart	Edema and atrophy of myocardial fibers	22
Respiratory tract	Diffuse alveolar damage with varying degrees of acute exudative features including edema, hyaline membranes, organization, and fibrosis. Macrophagic or mixed cellular infiltration, multinuclear giant cells, atypical reactive pneumocytes, and vascular injury. Positive in situ hybridization in pneumocytes, lymphocytes, and macrophages	63
Spleen and lymph nodes	Lymphocyte depletion in spleen and lymph nodes with architectural disruption. Splenic white pulp atrophy. Positive in situ hybridization signals in immune cells	25
Digestive tract	Intestines: No obvious pathology, nonspecific lesions. Depletion of mucosal lymphoid tissue. Positive in situ hybridization signals in mucosal epithelial cells	19
	Liver: No specific pathology. In some cases, necrosis and apoptosis	20
Urogenital tract	Kidneys: acute tubular necrosis, in varying degrees and other non-specific features. Positive in situ hybridization signals in the epithelial cells of the distal tubules	21
Bone marrow	In some cases, reactive hemophagocytosis	9
Adrenal gland	Necrosis and infiltration of monocytes and lymphocytes	14
Thyroid gland	Destruction of follicular epithelial cells, several apoptotic cells	5
Testes	Germ cell destruction, apoptotic spermatogenic cells	7

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4.1. SARS in China 2002–2003

In 2007, Gu and Korteweg [46] reported a dozen autopsies of SARS patients; using RT-PCR on postmortem tissue they demonstrated SARS-CoV-1 viral RNA and genomic sequences in the cytoplasm of hypothalamic and cerebral cortical neurons of confirmed SARS cases. Brain edema and focal degeneration of neurons was found together with ultrastructural confirmation of viral infection of neurons and glial cells by SARS-CoV-1. Neuropathological changes included degeneration and necrosis of neurons, extensive glial cell hyperplasia, and cellular infiltrates, but demyelination was not present. Xu and colleagues [47] isolated a SARS coronavirus strain from brain tissue of a patient with SARS and symptoms of severe CNS involvement. Pathologic examination of the brain revealed necrosis of neurons and gliosis. In addition, by immunostaining tissue sections they showed that a monokine induced by interferon- Γ (Mig) was expressed in glial cells along with infiltration of CD68⁺ monocytes/macrophages and CD3⁺ T lymphocytes in the brain parenchyma. Blood levels of interferon- Γ -inducible protein 10 and Mig in the blood were highly elevated but other cytokines and chemokines were normal [47].

SARS-CoV meningoencephalitis was demonstrated using RT-PCR in CSF to detect viral RNA in two patients with severe respiratory symptoms and generalized seizures admitted to the hospital during the severe outbreak of SARS in Hong Kong [48]; one was a 59-year-old woman in status epilepticus [49] and the second patient was a 32-year-old pregnant woman [50].

Involvement of the PNS was also reported in SARS occurring 2–3 weeks after onset of infection with features of axonal peripheral neuropathy [51,52]. A myopathy with elevated creatinine kinase was also reported [53]. Focal myocyte necrosis in skeletal muscle was found in SARS autopsy cases [46,53,54], probably caused by diffuse vasculitis [50]. A single case of olfactory neuropathy occurring 3 weeks after infection with SARS-CoV-1 was reported in Taiwan [55].

In a cohort of 206 SARS patients in Singapore [56] 5 had large-vessel strokes (2.4% or about 1 in 42 SARS infections); 4 of them were critically ill and 3 died. There was concern of enhanced thrombosis risk from using intravenous immunoglobulin (IVIg) given the observed higher incidence of deep venous thrombosis and pulmonary embolism.

A Canadian study of 22 health-care workers assessed 13–36 months after the 2003 outbreak of SARS found that chronic post-SARS-CoV infection was characterized by persistent fatigue, diffuse myalgia, weakness, depression, and non-restorative sleep with associated REM-related apneas/hypopneas, an elevated sleep EEG cyclical alternating pattern, and alpha EEG sleep anomaly [57]. These disorders

Table 2
The Neurology of COVID-19 due to SARS-CoV-2.

Neurologic diagnosis	Features	City/Country	Author [Ref]
Central nervous system symptoms			
Headache	6% to 8% (all patients) 6.5% (all patients) 13% (stroke patients)	Wuhan, China Beijing, China Wuhan, China	Various [66,68,69] Tian et al. [70] Chen et al. [71] Li et al. [62]
Agitation & Delirium	69% agitation (58 ICU patients) 65% delirium (58 ICU patients) 67% pyramidal tract signs	Strasbourg, France	Helms et al. [91]
Impaired Consciousness	22% (fatal cases vs. 1% non-fatal cases) 14.8% (severe cases vs. 2.4% non-severe cases)	Wuhan, China Wuhan, China	Chen et al. [71] Mao et al. [3]
Anosmia, hyposmia	5.1% (cases from 3 hospitals) 85.6% (cases from 12 hospitals)	Wuhan, China Europe	Mao et al. [3] Lechien et al. [4]
Dysgeusia	5.6% (cases from 3 hospitals) 88% (cases from 12 hospitals)	Wuhan, China Europe	Mao et al. [3] Lechien et al. [4]
Central nervous system diseases			
Cerebrovascular Disease	2.4% (6/214) Ischemic stroke 5 Hemorrhagic stroke 1 5.8% (13/221) Large-vessel ischemic stroke 11 Hemorrhagic stroke 1 Cerebral sinus thrombosis 1 1% to 6% (pooled analysis) 23% (3/13 ICU patients from 2 hospitals) Ischemic strokes 3 Large-vessel ischemic strokes	Wuhan, China Wuhan, China China (6 case-series) Strasbourg, France New York, US	Mao et al. [3] Li et al. [62] Aggarwal et al. [84] Helms et al. [91] Oxley et al. [129]
Frontotemporal hypoperfusion	58 ICU patients with severe COVID-19, 45 survived (33% had frontal lobe behavioral signs) 11/11 CBF-ASL-MRI frontotemporal hypoperfusion	Strasbourg, France	Helms et al. [91]
Arterial & Venous Thromboses	184 patients from 3 hospitals 31% thrombotic complications including pulmonary embolism in 81% 27% venous thromboses 3.7% arterial thromboses 3 patients with multiple arterial thromboses of legs, hands, brain, associated with anticardiolipin IgA and anti- β_2 -glycoprotein-I IgA and IgG antibodies 3 patients with multiple arterial thromboses and multi-organ failure due to coronavirus attachment to ACE2 receptors, viral invasion of endothelial cells, resulting in lymphocytic endotheliitis	The Netherlands China Zurich, Switzerland	Klok et al. [92] Zhang et al. [93] Varga et al. [36]
Subarachnoid hemorrhage	1 patient with Immune thrombocytopenic purpura	France	Zulfikar et al. [94]
Acute Hemorrhagic Necrotizing Encephalopathy	Brain MRI showed bilateral hemorrhagic rim-enhancing lesions in the thalami, medial temporal lobes, and subsular regions, probably associated with cytokine storm syndrome	Detroit, USA	Poyiadji et al. [61]
Meningoencephalitis	Seizures, neck rigidity, CSF pleocytosis (12/ μ /L). CSF-RT-PCR positive for SARS-CoV-2.	Japan	Moriguchi et al. [102]
Encephalopathy	Decreased level of consciousness with COVID-19. Negative CSF & CT brain; EEG: diffuse encephalopathy Confusion, myalgias, meningeal signs, CSF opening pressure 220 mmHg, normal CT brain.	Florida, USA Wuhan, China	Filatov et al. [103] Ye et al. [104]
Seizures	Recurrent generalized tonic-clonic seizures; normal CT/MRI, CSF-RT-PCR negative for SARS-CoV-2	Iran	Karimi et al. [105]
Myelitis	COVID-19 pneumonia, high fever (40 °C), acute flaccid paraplegia	Wuhan, China	Zhao et al. [113]
Peripheral nervous system & muscle			
Neuritic pain	8.9%	Wuhan, China	Mao et al. [3]
Guillain-Barré syndrome	First case in China 61-year-old woman First case in USA 54-year-old man Three cases from northern Italy	Shanghai, China USA Italy	Zhao et al. [108] Virani et al. [109] Toscano et al. [110]
Miller Fisher Syndrome, Polyneuritis Cranialis	50-year-old man with diplopia due to external ophthalmoplegia, ataxia and areflexia	Madrid, Spain	Gutiérrez-Ortiz et al. [112]
Neurosensory hearing loss	39-year-old man with diplopia from bilateral abducens palsy, global areflexia but no ataxia Old woman from Thailand	Bangkok, Thailand	Sriwijitalai & Wiwanitkit [113]
Myalgia	36% early symptom in > 1200 COVID-19 patients 26–51% muscle fatigue	Wuhan, China Wuhan, China	Several [62,68,69] Huang et al. [63]
Myopathies	10.7% (19.3% severe vs. 4.8% non-severe)	Wuhan, China	Mao et al. [3].
Rhabdomyolysis	33% have increased creatine kinase Early sign in 2 case reports	China Wuhan, China	Several [64–66] Jin & Tong [121] Suwanwongse et al. [122]
Irreversible respiratory failure			
Case-fatality rates (CFR)	81% of 72,314 COVID-19 infections are mild but 20% or 8255 are severe (CFR 8.0% - 14.8%) or critical (CFR 49%) Neurogenic respiratory failure due to viral brainstem invasion could explain the dismal prognosis	China Worldwide	Wu & McGoogan [124] Several [67,69,74,80,106]

conceivably may have been related to viral particles and viral genome sequences isolated from the cytoplasm of neurons in the hypothalamus [47,58].

Table 1 summarizes the pathological lesions produced by SARS-CoV-1 including, in addition to respiratory tract lesions and pneumonia with severe alveolar damage, viral injury in mucosal cells of the intestine, acute tubular necrosis, vasculitis and lymphocyte depletion in spleen and lymph nodes [46]. According to Guo et al. [54], the pathology of SARS is the result of direct injury caused by the coronavirus infection of target cells, as well as indirect injury from immune responses, circulatory dysfunction, and hypoxia. The exact route of SARS-CoV-1 infection of the human brain is unknown. Infected monocytes/macrophages migrating across the blood–brain barrier (BBB) might be involved [54].

In summary, there is solid evidence of involvement of nervous system and muscle in human infection by SARS-CoV-1 based on neuropathological studies. However, clinical series of SARS patients with neurological manifestations are unavailable.

4.2. MERS-CoV in Saudi Arabia

According to Senga et al. [59], following the prodromal symptoms of fever, chills, cough, and dyspnea present in > 70% of patients, approximately one-third of the cases infected with MERS-CoV had myalgia, malaise, and gastrointestinal symptoms. Arabi et al. [60] provided the only report of neurological involvement in 3 fatal cases observed during the epidemic outbreak of MERS in Saudi Arabia in June 2012.

The first patient was a 74-year-old man with a 3-day history of ataxia, vomiting, confusion, fever, and left hemiparesis; he became comatose and required respiratory support. CSF was normal and negative for MERS-CoV. MRI showed multiple bilateral non-enhancing areas of signal hyperintensity on T2/FLAIR in the periventricular, deep white matter, subcortical area, corpus callosum, bilateral brachium pontis, midbrain as well as in the left cerebellum and upper cervical cord. The second patient was a 57-year-old man who presented with flu-like illness, fever and a gangrenous toe who developed facial paralysis, respiratory distress, became comatose and required intubation. MRI showed bilaterally deep watershed lesions, and scattered foci in the cortical and subcortical regions of the temporal, parietal, and occipital lobes. The third patient was a 45-year-old man with cough, dyspnea, rigors, fever, and diarrhea. He was conscious and had no focal neurological signs. He developed septic shock and respiratory failure. MRI showed confluent non-enhancing T2WI/FLAIR hyperintensities within the white matter of both cerebral hemispheres and along the corticospinal tract. CSF showed white cell count of 2 cells/mm³, protein 0.85 g/L with negative RT-PCR for MERS-CoV.

Although not recognized as such by the authors, the brain MRI images are highly suggestive of acute hemorrhagic necrotizing encephalopathy (AHNE), a condition recently reported during the COVID-19 epidemic outbreak in the USA [61]. In summary, there is almost complete absence of clinical information on the neurology of MERS and no pathological data are available, except for a single postmortem needle biopsy of the brain with normal results.

5. Neurological disease in COVID-19: central nervous system

As indicated earlier, a few reports issued from the original epidemic outbreak in Wuhan, China [1–3], emphasize the occurrence of neurological involvement in patients with SARS-CoV-2. A systematic review published in the *Journal of the Neurological Sciences* [1] found only 6 articles [3,62–66] from December 2019 to March 2020 addressing the neurology of COVID-19 and concluded that these complications have not been studied appropriately, particularly because they may remain unrecognized in patients with severe illness. Also, it is unclear if some of the conditions listed here are simply concurrent or if they are

induced by the viral infection. However, given the growing reports of neurological disease of COVID-19, with others [2,67], we consider it critical to define the direct neurotropic effect as well as the indirect virus-induced secondary impact of SARS-CoV-2 infection on the nervous system. We updated the review of published reports as of April 30, 2020, including a number of pre-publication articles, and describe below the available data on the neurology of COVID-19. **Table 2** summarizes this information.

5.1. Headache and alterations of consciousness

During the early symptomatic phase of SARS-CoV-2 infection in > 1200 patients reported from hospitals in Wuhan [62–66,68,69], fever occurred in 88%–92%; cough in 67%–69%, fatigue in 26%–51%, and 36% had myalgia. In a cohort of 262 confirmed cases from Beijing hospitals [70] 6.5% had headache, compared with 6%–8% in Wuhan and 13% developed cerebrovascular disease (CVD) [62]. Chen et al. [71] studied the initial symptoms in a cohort of 113 fatalities of COVID-19 compared with 161 patients who recovered; early alteration of consciousness occurred significantly more often in fatal cases (22%) compared with 1% among those who recovered. Mao et al. [3] also found impaired consciousness in 14.8% of 214 patients hospitalized due to severe disease compared with 2.4% in non-severe infections. Therefore, early onset of headache and decreased responsiveness are indicators of potential neurological involvement in COVID-19 patients.

5.2. Alterations of smell and taste

The absence or diminished ability to smell (anosmia, hyposmia) or to taste normally (hypogeusia, dysgeusia) is a common symptom among COVID-19 patients around the world [4,72–74] and it has been suggested that anosmia could indicate the neurotropic potential of the coronavirus to invade the brain [75]. Among 214 patients with COVID-19 from 3 hospitals in Wuhan, China [3] hypogeusia was reported in 5.6% and hyposmia in 5.1%. A much higher incidence of these disorders has been described in European patients. A multi-center study involving 12 European hospitals conducted by the Young-Otolaryngologists of the International Federation of Oto-rhino-laryngological Societies (YO-IFOS) [4] recruited 417 patients with mild-to-moderate COVID-19 and found olfactory dysfunction in 85.6% and gustatory dysfunction in 88%; both symptoms were often associated, and early olfactory recovery occurred in 44% [4]. In severe COVID-19 cases, alterations of smell and taste occurred before any other complaints in 11.8% of the cases. According to Xydakis [72], the American Academy of Otolaryngology—Head and Neck Surgery and the British Association of Otorhinolaryngology have recommended adding anosmia-dysgeusia to the list of primary screening symptoms for SARS-CoV-2 infection. These symptoms often occur in the absence of nasal congestion or rhinorrhea in patients with mild or no constitutional symptoms [73,74].

Because of the frequent occurrence of anosmia-dysgeusia, Li and colleagues [75] suggested that viral neurotropism of SARS-CoV-2 could result in invasion of the olfactory nerve (cranial nerve I) [30,75], the olfactory brain and then the brain stem causing the irreversible respiratory failure typical of severe COVID-19. The neurotropism of coronaviruses has been demonstrated before. In 2007, Suzuki et al. [76] were able to identify coronaviruses in the nasal discharge of patients who failed to recover olfaction after a cold. Animal models have shown that the nasal route is a well-recognized pathway for neurotropic viruses to reach the brain [32,33,71,77]. Given the importance of the ACE2 receptor in the pathogenesis of SARS-CoV-2 neurotropism, Netland and colleagues [78] using mice transgenic for human ACE2 demonstrated that the virus enters the brain through the olfactory bulb and uses rapid transneuronal spread to reach olfactory cortex, basal ganglia and midbrain (dorsal raphe) nuclei, dorsal motor nucleus of the vagus, nucleus tractus solitarius and area postrema causing neuronal death in the absence of encephalitis. A similar pattern of brain invasion

was demonstrated in human brains from patients with SARS-CoV-1 infection [42,79]. It has been proposed that viral neurotropism could explain the severity of respiratory failure in COVID-19 [75] and the absence of dyspnea [80]. Mutations of the S protein of the coronavirus [81] or variations in population genetics for expression of ACE2 [82] could determine the divergences in the pattern of respiratory problems in COVID-19.

5.3. Cerebrovascular disease

COVID-19 may increase the risk for venous and arterial thromboembolism associated with inflammation, hypoxia, immobilization, and diffuse intravascular coagulation.

Only three clinical series of stroke in patients with COVID-19 are currently available [3,62,84].

A report by Mao et al. [3] described 214 patients with acute COVID-19 in Wuhan included 58.9% (mean age 58.7 years) severe cases and 41.1% (mean age 49.9 years) non-severe patients. In total, 78 patients (36.4%) had neurological involvement occurring more often in the severe disease group. Six patients (2.4%) had acute cerebrovascular disease, 5 of them severe cases (5.5%) that occurred 9 days after onset (range = 1–18 days). Computed tomography (CT) of the brain confirmed 4 ischemic strokes and 1 cerebral hemorrhage. Stroke patients with severe infection were older, had more underlying vascular risk factors, especially hypertension, and showed fewer typical symptoms of COVID-19, such as fever and cough.

Also in Wuhan, Li and colleagues [62] reported 221 patients and found 11 (5%) cases with ischemic strokes mainly from large-vessel occlusion. A 32-year-old man had cerebral sinus thrombosis and another had cerebral hemorrhage (62-year-old man). Stroke affected more women (6/11) who were significantly older (71.6 ± 15.7 years) vs. 52.1 ± 15.3 years in the group without stroke; more vascular risk factors were present including history of hypertension, diabetes, and previous cerebrovascular disease. Stroke patients had leukopenia and the values of C-reactive protein (CRP) were higher (mean = 51.1 mg/L, range = 1.3–127.9 mg/L) than in non-stroke cases (12.1 mg/L, 0.1–212.0 mg/L); also, a hypercoagulable tendency was reflected in significant elevation of D-dimer values (mean = 6.9 mg/L, range = 0.3–20.0 mg/L) vs. 0.5 mg/L (range = 0.1–20.0 mg/L) in non-stroke cases ($p < .001$). Therapy included anti-platelet treatment in 6 cases and anticoagulation in 5. A total of 5 patients with stroke died (38% mortality).

A first report on 393 patients with confirmed COVID-19 from two hospitals in the disease epicenter of New York City, USA was recently published [83] but cerebrovascular disease was not mentioned. However, strokes from large-vessel occlusion in younger subjects with relatively mild COVID-19 in New York have been reported [129].

Aggarwal et al. [84] conducted a pooled analysis of the literature on the effect on COVID-19 prognosis of either new acute stroke or previous history of stroke. The analysis included 6 studies from China ranging in size from 52 to 1099 patients. Cerebrovascular disease occurred in 1% to 6% of the cohorts corresponding to a non-statistically significant increase of about 2.5-fold in odds of developing severe COVID-19 among patients with stroke compared with those without.

A number of countries have issued stroke guidelines during the COVID-19 pandemic. After the first patients with COVID-19 were hospitalized in Singapore [85], Christopher et al. [86] provided recommendations for the early recognition and treatment of stroke in patients infected with SARS-CoV-2, including the potential use of intravenous thrombolysis (TPA) or Endovascular Therapy (EVT) with mechanical thrombectomy in COVID-19 patients. A similar consensus was published in India [87].

In China, Jin et al. [88] encouraged neurologists to consider both ischemic and hemorrhagic strokes as potential complications of COVID-19. Intracerebral bleed and subarachnoid hemorrhage may be linked to arterial hypertension induced by binding of SARS-CoV-2 to ACE2

receptors and thrombocytopenia [89,90]. The risk of ischemic stroke is linked to SARS-CoV-2 infection among critically ill elderly patients with vascular risk factors, such as hypertension, diabetes mellitus, hyperlipidemia, smoking and history of previous stroke or transient ischemic attacks (TIA). Increased serum levels of D-dimer could enhance the risk of thrombosis and embolism [89,90].

5.4. Frontotemporal hypoperfusion

Helms and her colleagues [91] from Strasbourg, France, reported 58 patients with severe COVID-19 treated in two Intensive Care Units (ICUs). Neurologic findings were encountered in 84% at the time of ICU admission including agitation (69%); corticospinal tract signs (67%), such as brisk tendon reflexes, ankle clonus, and bilateral extensor plantar responses; delirium in 65% (based on the Confusion Assessment Method for the ICU, CAM-ICU); and, hyperthermia with a fever $> 38.5^\circ\text{C}$. About 12% had past neurological history of TIA, epilepsy, and mild cognitive impairment (MCI). Lumbar punctures were performed on 7 patients; in all CSF showed no cells and CSF RT-PCR was negative for SARS-CoV-2; a single case had elevated CSF protein and IgG levels. MRI showed cerebral ischemic strokes in 3/13 (23%) cases, two asymptomatic patients each had small acute ischemic strokes and 1 had a subacute stroke, probably preexisting. Linear and nodular enhancement of leptomeningeal spaces on FLAIR and T1 was noted post-contrast in 8/13 (62%) patients. Notably, arterial spin labeling (ASL)-perfusion MRI demonstrated bilateral frontotemporal hypoperfusion in 11/11 patients. Electroencephalography showed diffuse bifrontal slowing consistent with encephalopathy in 1 out of 8 cases. Of interest, 33% of the 45 survivors presented a dysexecutive syndrome suggestive of frontal lobe involvement, with alterations of attention, orientation and poorly organized movements on command.

5.5. Arterial and venous thromboses, subarachnoid hemorrhage, and coagulopathies

Evaluation of 184 patients with COVID-19 at three Dutch hospitals [92] found a high incidence (31%) of thrombotic complications, including 3 patients with stroke. Venous thrombosis occurred in 27% (95%CI 17–37%) and arterial thromboses in 3.7% (95%CI 0–8.2%). Pulmonary embolism was the most frequent thrombotic complication ($n = 25$, 81%). Advanced age and coagulopathy, defined as spontaneous prolongation of PT/PTT (prothrombin time > 3 s or activated partial thromboplastin time > 5 s), were independent predictors of thrombotic complications. The authors recommended applying strict pharmacological thrombosis prophylaxis in all COVID-19 patients admitted to ICU.

Zhang and colleagues [93] reported 3 patients from China (ages 65–70 years) with severe COVID-19 infection who developed multiple arterial thromboses associated with anticardiolipin IgA antibodies as well as anti- β_2 -glycoprotein-I IgA and IgG antibodies with negative lupus anticoagulant. Patient 1 had ischemia in the lower limbs bilaterally as well as in two fingers of the left hand; CT of the brain showed bilateral cerebral infarcts in multiple vascular territories, involving frontal, parietal, occipital lobe and bilateral basal ganglia, brain stem, and bilateral cerebellar hemispheres. Patient 2 had multiple cerebral infarctions in the right frontal lobe and bilateral parietal lobe. Patient 3 had multiple cerebral infarctions in bilateral frontal lobes, right frontal, parietal, temporal and occipital lobes, and bilateral cerebellar hemispheres.

Zulfikar and associates [94] from France, reported a 65-year-old woman with SARS-CoV-2 infection with viral pneumonia confirmed by chest CT. She developed lower-extremity purpura, epistaxis, and progressive thrombocytopenia with normal PT/PTT. One week later, she complained of right frontal headache without fever, vomiting, or focal neurologic deficits. CT of the brain showed a small subarachnoid hemorrhage in the right frontal lobe. The platelet count had decreased to

2000 per cubic millimeter and she was treated with platelet transfusion, prednisolone and eltrombopag with good results. A meta-analysis by Lippi et al. [95] confirmed the association of thrombocytopenia with severe COVID-19.

In Zurich, Switzerland, Varga and her colleagues [36] reported endothelial viral infection by SARS-CoV-2 and endotheliitis in post-mortem examinations of three patients (71-year-old man, renal transplant recipient, with history of coronary artery disease and arterial hypertension; 58-year-old woman, obese with history of hypertension; 69-year-old hypertensive man). In addition to the severe respiratory failure typical of COVID-19, they all developed multisystem organ failure and vascular complications including myocardial infarction and mesenteric ischemia requiring small intestine resection. Pathology examination demonstrated lymphocytic endotheliitis in lung, heart, kidney, small intestine and liver. Viral inclusions were revealed by electron microscopy indicating direct viral infection of endothelial cells accompanied by accumulation of mononuclear inflammatory cells. The authors [36] postulate that this mechanism could explain the widespread endothelial dysfunction associated with apoptosis and multi-organ vascular involvement observed in severe COVID-19 infections. Treatments targeted to halt viral replication or to modify ACE2 receptors [96–98] could have beneficial effects in COVID-19.

As mentioned earlier [20,84], SARS-CoV-2 infects the host by using the ACE2 receptors present in the upper airway passages and the pneumocytes in the alveolar epithelial lining, but also expressed in endothelial cells in lung, heart, kidney, intestines, and in brain, where it may protect neurons against ischemic injury [97,98]. ACE2 is the enzyme that physiologically counters the activation of the renin-angiotensin-aldosterone system (RAAS) degrading angiotensin II to angiotensin-(1–7), attenuating vasoconstriction and sodium retention [97]. The use of ACE inhibitors (ACEI) and angiotensin-receptor blockers (ARBs) during the COVID-19 pandemic was the topic of an extensive review by Vaduganathan and colleagues [97] who concluded that ACE2 may be beneficial and that the withdrawal of RAAS inhibitors in high-risk cardiovascular patients may be harmful. This is in agreement with the results of a retrospective, multi-center study in Hubei province, China [99], which included 1128 hypertensive patients with COVID-19 demonstrating that the use of ACEI/ARB was associated with lower risk of all-cause mortality.

5.6. Acute hemorrhagic necrotizing encephalopathy

Poyiadji et al. [61] from Detroit, Michigan, USA, described brain-imaging findings in a woman in her late fifties who presented with COVID-19 infection, demonstrated by a positive nasopharyngeal RT-PCR test for the SARS-CoV-2 virus. CSF showed no bacterial growth and was negative for *Herpes simplex* 1–2 virus (HSV), varicella-zoster virus (VZV), and West Nile virus. Coronavirus could not be tested in the CSF. CT brain demonstrated bilateral and symmetric hypoattenuation within the medial thalami with normal CT angiogram and CT venogram. Brain MRI showed bilateral hemorrhagic rim-enhancing lesions in the thalami, medial temporal lobes, and subinsular regions. The authors concluded that the patient presented acute hemorrhagic necrotizing encephalopathy (AHNE). This rare condition is usually considered a parainfectious disease [99]; it has been associated with influenza A (H1N1) and influenza B, parainfluenza, VZV, human herpes viruses HHV-6 and HHV-7, enteroviruses, the novel reovirus strain serotype 2 (MRV2Tou05), rotaviruses, HSV, rubella, coxsackie A9, and measles viruses, among which H1N1 and HHV-6 are the most common [99]. AHNE is not an encephalitis and the CSF usually shows no pleocytosis. It is generally accepted that AHNE may be caused by a “cytokine storm” [100] resulting in elevation of proinflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), IL-10, IL-15, IL-1 β , soluble TNF receptor, and interferon- γ (IFN- γ), plus lymphocytes, in particular CD56⁺ natural killer (NK) cells leading to brain injury through alterations of the BBB by trypsin and matrix

metalloprotease-9 without vessel wall disruption. AHNE may also occur following vaccination, in particular with the DPTw (diphtheria-tetanus-pertussis whole cell) vaccine [99]. COVID-19 fatalities have been associated with a hyperinflammatory syndrome manifested by a growing HScore [101] decreasing platelet counts, cytopenias, hyperferritinemia, and increased levels of IL-2, IL-7, granulocyte-colony stimulating factor, interferon- γ -inducible protein 10, monocyte chemo-attractant protein 1, TNF- α and macrophage inflammatory protein 1- α [100]. Proposed treatments include steroids, IVIg, and selective cytokine blockade with anakinra, tocilizumab, or Janus kinase (JAK) inhibition [99,100].

5.7. Encephalopathy, meningitis, encephalitis, and seizures

As reviewed earlier [3,65], decreased level of consciousness is a neurological manifestation indicative of a severe COVID-19 prognosis. The causes may range from metabolic encephalopathy associated with severe hypoxia, post-ictal state following seizures, to acute cerebrovascular disease caused by endotheliitis and subsequent hematological changes or a cytokine storm resulting in AHNE.

There are few reports of meningitis or encephalitis with demonstration of SARS-CoV-2 in CSF or brain. In Japan, Moriguchi et al. [102] reported the case of a 24-year-old man admitted with headache, fever, fatigue and seizures. On examination, he was in a post-ictal state and had neck rigidity. CT brain showed no brain edema or lesions. CSF showed 10 mononuclear and 2 polymorphonuclear cells per μ /L. CSF-RT-PCR was positive for SARS-CoV-2 but the nasal swab test was negative. Brain MRI showed hyperintense DWI/FLAIR images on the right mesial temporal lobe and the inferior horn of the right ventricle consistent with encephalitis and ventriculitis.

Filatov et al. [103] reported a second case of encephalopathy from Florida, USA, affecting a 74-year-old man with a previous stroke who became poorly responsive with COVID-19. CSF was normal and CSF-RT-PCR was negative. Brain imaging showed no new lesions and EEG was consistent with diffuse encephalopathy. He developed respiratory failure and required intubation and respiratory support.

In Wuhan, China, Ye et al. [104] reported a male COVID-19 patient with fever, shortness of breath and myalgias who became confused. Meningeal signs were positive and extensor plantar responses were elicited. Lumbar puncture showed an opening pressure of 220 mmHg and normal cells, protein and glucose. CSF was negative for SARS-CoV-2 and the brain CT was normal. The patient recovered and was discharged from the hospital. Two consecutive SARS-CoV-2 swab tests were negative.

In Iran, Karimi et al. [105] reported a previously healthy 30-year-old woman with COVID-19 who was admitted to hospital with recurrent generalized tonic-clonic seizures. CSF and brain MRI were normal. CSF-RT-PCR for SARS-CoV-2 was negative. Seizures were treated and the patient was discharged.

In summary, the paucity of reports of encephalitis or meningitis in COVID-19 is unexpected given the high neurotropic potential of SARS-CoV-2 [106]. The few cases of meningoencephalitis conceivable may be the consequence of the extremely high fatality rate of respirator-dependent COVID-19 patients, perhaps caused by direct injury of the respiratory centers in the brainstem. Detailed post-mortem neuropathological studies [107] should answer this dilemma.

6. Neurological disease in COVID-19: peripheral nervous system & muscle

Compared with the reports of CNS involvement in COVID-19 the bibliography describing PNS and muscle pathology is more limited.

6.1. Guillain-Barré syndrome

Zhao et al. [108] from Shanghai, China, reported the first case of Guillain-Barré syndrome (GBS) associated with COVID-19 in a 61-year-

old woman who had returned from Wuhan; she did not report fever or respiratory symptoms but complained of weakness of both legs and severe fatigue. On examination she had symmetric weakness and areflexia of both legs and feet (Medical Research Council, MRC 4/5) that progressed over the next 3 days (MRC 3/5). Lymphocytopenia and thrombocytopenia were noted. CSF cell counts were normal with elevated protein (124 mg/dL). Nerve conduction studies showed delayed distal latencies and absent F waves consistent with demyelinating neuropathy. With a diagnosis of GBS she was treated with IVIg. On day 8, oropharyngeal swabs were positive for SARS-CoV-2, suggesting a parainfectious profile for GBS, instead of the classic postinfectious one.

In the U.S., a 54-year-old male with confirmed COVID-19 and a history of fever, cough and *Clostridium difficile* colitis of recent onset developed difficulty breathing and weakness and diminished reflexes of arms and legs eventually diagnosed as GBS [109].

Toscano and colleagues [110] reported 5 patients with GBS from three hospitals in northern Italy during the COVID-19 outbreak. Patient 1: A 77-year-old woman with abrupt onset of paresthesias in legs and hands that progressed in 36 h to areflexic tetraplegia without bulbar signs. Seven days earlier she had fever, cough, and had developed pneumonia positive for SARS-CoV-2. NCV/EMG confirmed an axonal variant of GBS. The first CSF was normal but the second one showed high protein (101 mg/dL); CSF-RT-PCR was negative twice. During IVIg treatment, she developed bulbar symptoms with dysphagia and tongue weakness, which required assisted ventilation. Patient 2: A 23-year-old man with a 2-day history of mastoid pain, complete facial weakness, ageusia and leg paresthesias. Ten days earlier, the patient had fever and sore throat. On exam he had complete bilateral facial palsy, areflexia and sensory ataxia. EMG confirmed lower-extremity axonal sensory-motor neuropathy with sural nerve sparing and decreased facial nerve cMAP. CSF protein was high (1123 mg/dL) with negative virus test and anti-ganglioside antibodies. He was treated with IVIg with some improvement. Patient 3: A 55-year-old man with 10 days of fever, cough and COVID-19 pneumonia; he developed neck pain, paresthesias in the 4 limbs and lower leg weakness. On day 12, he developed areflexic tetraparesis with severe axonal neuropathy. CSF showed elevated protein (123 mg/dL) and a negative coronavirus test. He developed facial diplegia and respiratory failure with IVIg and required assisted ventilation due to neuromuscular impairment. Patient 4: A 76-year-old man with a 5-day history of cough and anosmia evolving into COVID-19 pneumonia. He was admitted with low-back pain and leg weakness that progressed rapidly to areflexic tetraparesis. CSF was normal with a negative virus test. IVIg treatment produced motor improvement more evident in the arms but he was still unable to walk. Patient 5: A 61-year-old man with a one-week history of asthenia, anosmia and ageusia. Noticed problem climbing stairs and leg paresthesias and was unable to stand up on awakening. He had generalized areflexia and paraparesis. COVID-19 oropharyngeal test was negative and CSF was normal with negative coronavirus CSF-RT-PCR. Anti-ganglioside antibodies were negative. On the second day of IVIg therapy, he developed flaccid tetraplegia with facial weakness and dysphagia; he eventually required tracheostomy and assisted ventilation. Serum SARS-CoV-2 antibodies were positive on admission. In sum, GBS occurred 5 to 10 days after onset of COVID-19 symptoms, a typical interval. Clinical neurophysiology was consistent with axonal-type GBS in 3 cases and demyelinating-type in 2 patients. Post-Gadolinium MRI showed enhancement of caudal nerve roots in 2 patients and the facial nerve in one. All patients were treated with IVIg and Patients 1 and 3 received two cycles. A similar treatment was used in GBS patients during the MERS outbreak [111].

6.2. C. Miller Fisher syndrome, polyneuritis cranialis

Gutiérrez-Ortiz and her colleagues [112] from Madrid, Spain, reported two patients with clinical manifestations of PNS involvement in COVID-19. Patient 1 was a 50-year-old man with a 2-day history of

fever, vertical diplopia, perioral paresthesias, anosmia, ageusia, and unsteadiness. He had a broad ataxic gait and global areflexia. On neuroophthalmologic examination he showed right hypertropia in all fields of gaze, severe limitation of adduction and down-gaze movements of right eye, plus left eye nystagmus on left gaze consistent with right internuclear ophthalmoparesis and right fascicular oculomotor palsy. Anti-ganglioside antibody GD1b-IgG was positive as well as the SARS-CoV-2 test. CSF showed no cells and a protein of 80 mg/dL. CSF-RT-PCR was negative for COVID-19. He was diagnosed with Miller Fisher syndrome (external ophthalmoplegia, ataxia and areflexia) with good response to IVIg.

Patient 2 was a 39-year-old man with acute onset of diplopia. He had history of diarrhea and fever, ageusia, and overall fatigue; he tested positive for COVID-19. Neuroophthalmologic exam was consistent with bilateral abducens palsy. He had global areflexia but no motor weakness. All CSF tests were negative including SARS-CoV-2; CT brain was normal. Two weeks later he had made spontaneous recovery of the diplopia, the ageusia and the areflexia. He was diagnosed with polyneuritis cranialis or with incomplete Miller Fisher syndrome *sine* ataxia. As with the GBS patient reported above, the cranial nerve involvement appears to be parainfectious (not due to direct viral neurotropism) but immune-mediated with presence of GD1b antibodies and positive response to IVIg.

A single case of de novo neurosensory hearing loss was reported in a woman with COVID-19 from Thailand [113].

6.3. Myelitis

Zhao et al. [114] from Wuhan, China, reported a case of a 66-year-old man with fever and fatigue for two days from COVID-19 pneumonia. After high fever at night (40 °C), he developed acute flaccid paralysis of the legs along with urinary and bowel incontinence. He had decreased strength in the arms (MRC 3/5) with normal bilateral reflexes in upper extremities and flaccid paralysis in the legs (MRC 0/5) with bilateral hyporeflexia but without pathologic reflexes. Sensation was intact in the arms but was globally impaired in both legs with a T10 sensory level. CT brain revealed basal ganglia and paraventricular lacunar infarctions. CSF and MRI were not done due to pandemic preventive measures. A possible cytokine storm in response to SARS-CoV-2 infection was diagnosed based on the high fever, leukocytosis, low serum iron (1.80 μmol/L, normal = 10.6–36.7 μmol/L), elevated serum ferritin (> 2000 ng/mL, normal = 21.81–274.6 ng/mL) and high levels of CRP, serum amyloid protein, procalcitonin, and interleukin-6. Following treatment, muscle strength in both upper limbs recovered (MRC 4/5) with minimal improvement in the legs (MRC 1/5). Possible infectious causes of myelitis were ruled out [115], including *Mycoplasma pneumoniae* [116], *Chlamydia pneumoniae*, Epstein-Barr virus (EBV), influenza A-B virus, parainfluenza virus, adenovirus, coxsackieviruses, cytomegalovirus (CMV), and respiratory syncytial virus. Tuberculosis infection was negative. The authors postulated that myelitis was the result of direct SARS-CoV-2 given that ACE2 receptors are expressed on the surface membranes of spinal cord neurons [117] combined with a cytokine storm syndrome [99,100].

6.4. Myasthenia Gravis (MG)

The International MG/COVID-19 Working Group [118] published the guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic.

6.5. Myopathies

As mentioned earlier, fatigue occurred in 26%–51% of patients with COVID-19 in China [63], 36% had myalgia and increased creatine kinase (CK) was present in 33% of patients [64–66]. There are no reports

of electromyography or muscle histopathology. Viral myositis occurred with MERS [119] and SARS [42,47–49]. Rhabdomyolysis was reported in patients with acute renal failure during SARS [120] and there are two reports [121,122] during COVID-19. Guidon and Amato [123] published a guide for the management of immune therapies and support groups for patients with neuromuscular disorders during the COVID-19 emergency.

7. Conclusions

We conclude from this comprehensive review of current literature that patients with COVID-19 frequently suffer substantial neurological involvement. According to the analysis of 72,314 cases from China [124], the large majority of SARS-CoV-2 infections (81%) are mild and subjects recover entirely, while about 20% (8255 cases) develop respiratory symptoms ranging from severe (case-fatality rate, CFR 8.0%–14.8%) to critical (CFR 49%) particularly among elderly subjects with multiple risk factors. However, many severe cases occur in young people after trivial symptoms of the infection [125].

Although the a priori impression is that CNS injury occurs predominantly as a result of metabolic and inflammatory responses occurring in elderly patients admitted to intensive care units (ICU), a direct viral attack might be a more likely explanation for the extremely high mortality. Vincent & Taccone [126] point out that once old age, frailty, disability, comorbidities, or lack of personnel and equipment are discounted, most ICU patients can be supported by invasive mechanical ventilation until the lungs recover [127]. This is not to the case with COVID-19.

We hypothesize that SARS-CoV-2, like other human coronaviruses, has neurogenic properties that result in anosmia in 85.6% of the cases [4] occurring shortly after the virus reaches ACE2 receptors in the nasal epithelium at the time of contagion. Given the relative absence of nasal congestion and rhinorrhea [66,67], anosmia likely results from viral presence in the olfactory bulbs [69]. In about half of the cases (44%), the defense mechanisms control the infection and early olfactory recovery occurs [4]. In some of the remaining patients, the viral neurotropism of SARS-CoV-2 probably invades the brain via axonal transport and transneuronal spread from the olfactory nerves to the rhinencephalon finally reaching the brainstem causing the irreversible respiratory failure of severe COVID-19, typically characterized by lack of dyspnea [74].

Concurrently, the virus proliferates and attaches to ACE2 receptors present in the upper airway and in pneumocytes in the alveolar epithelial lining, as well as in endothelial cells of the lungs, heart, kidney, and intestine [91–93], resulting in generalized endotheliitis [91] that causes severe pneumonia, multi-organ collapse including heart failure, hepatorenal syndrome, coagulopathy and thrombotic state. Widespread viral invasion of the vascular endothelium apparently may increase the risk of blood clots that leads to concomitant cardiovascular and cerebrovascular events, perhaps the most serious complications of COVID-19 infection. The immune response to the viral proliferation has been poorly studied but includes the effects of the cytokine storm syndrome [100]. While the acute and residual effects of SARS-CoV-2 infection have come into focus, as of this writing there are no reports of the long-latency effects observed in subjects acutely infected with non-coronaviruses.

8. Recommendations

It is clear that information on the neurology of COVID-19 is fragmentary at best due to the emergency arising from local outbreaks worldwide with massive numbers of patients challenging the health services. The same is true of the pandemic at large, and, as expressed by Lipsitch and colleagues [128], epidemiological studies are needed to provide solid information on total numbers of cases, including mild ones, risk factors and timing of transmission, severity and attack rate; as

well as risk factors for severe outcomes including death, and timing and intensity of infectiousness determined by viral shedding studies.

There is an urgent need to understand the neurotropic potential of SARS-CoV-2 and the frequency of these complications; the traditional methods of neurology including the time-honored clinicopathological correlation should provide much-needed answers. The Environmental Neurology Specialty Group of the World Federation of Neurology (ENSG-WFN) issued an appeal [5] to neurological societies around the globe to develop national or regional COVID-19 neuroepidemiological databanks. Neurologists and physicians at the front line of this pandemic are asked to report to each society all cases of new-onset, acute, delayed and long-latency neurological disorders associated with SARS-CoV-2 infection during the current COVID-19 pandemic. The worldwide response to this pandemic encourages us to believe that regional neurologists and physicians, government authorities, and scientists with expertise in Public Health, epidemiology, infectious diseases, virology, neurosciences and other relevant fields will be willing to advise and assist neurological societies to achieve the goal of creating national and regional databases. This will also encourage much needed peer-reviewed publications on the neurology of COVID-19. We will work to assure that the results of the national registries are collected, posted and become freely available at the WFN website [https://wfneurology.org]. This global effort should help the world understand the neurological impact of COVID-19.

Authors' contribution

This paper is the result of a Delphi-type consensus of the listed members of the Environmental Neurology Specialty Group of the World Federation of Neurology (ENSG-WFN) with the participation of all authors via e-mail and telephone. Jacques Reis, Gustavo Román, Peter Spencer, and Alain Buguet coordinated the meetings. Initial data collection and drafts by Peter Spencer, manuscript redirection and literature review by Gustavo Román; final drafts by Gustavo Román with additional contributions from all other authors. Miguel Láinez provided valuable input on the experience of the registry and database of the Spanish Neurological Society during the outbreak. All authors provided input for the scientific content of the paper and submitted bibliographic references, suggestions, and edits.

Declaration Competing of Interest

The authors are all members of the Environmental Neurology Specialty Group (ENSG) of the World Federation of Neurology and declare no competing interests.

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