COVID-19: a global threat to the nervous system

Running head: Neurologic manifestations of COVID-19

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Abstract:

In less than 6 months, the severe acute respiratory syndrome-coronavirus type 2 (SARS-CoV-2) has spread worldwide infecting nearly 6 million people and killing over 350,000. Initially thought to be restricted to the respiratory system, we now understand that coronavirus disease 2019 (COVID-19) also involves multiple other organs including the central and peripheral nervous system. The number of recognized neurologic manifestations of SARS-CoV-2 infection is rapidly accumulating. These may result from a variety of mechanisms including virus-induced hyper-inflammatory and hypercoagulable states, direct virus infection of the CNS, and post-infectious immune mediated processes. Example of COVID-19 CNS disease include encephalopathy, encephalitis, acute disseminated encephalomyelitis, meningitis, ischemic and hemorrhagic stroke, venous sinus thrombosis and endothelialitis. In the peripheral nervous system COVID-19 is associated with dysfunction of smell and taste, muscle injury, the Guillain-Barre syndrome and its variants. Due to its worldwide distribution and multifactorial pathogenic mechanisms, COVID-19 poses a global threat to the entire nervous system. While our understanding of SARS-CoV-2 neuropathogenesis is still incomplete and our knowledge is evolving rapidly, we hope that this review will provide a useful framework and help neurologists in understanding the many neurologic facets of COVID-19.

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The novel coronavirus, now called severe acute respiratory syndrome-coronavirus type 2 (SARS-CoV-2), is the agent of coronavirus disease-2019 (COVID-19), that was first diagnosed on December 8, 2019 in a patient in the city of Wuhan in central China. Common symptoms of COVID-19 include fever, cough, fatigue, and shortness of breath. While most affected individuals have no or minor symptoms, some go on to develop pneumonia, acute respiratory distress syndrome (ARDS), and succumb from multiple organ failure. On January 30th, 2020, the world health organization (WHO) declared it a Public Health Emergency of international concern. It has been estimated that the number of infected individuals during the early epidemic doubled every 2.4 days, and the R_0 value, or number of people that can be infected by a single individual may be as high as 4.7-6.6.[1] After spreading throughout China, the disease took hold in Europe and the U.S., and in view of this alarming development and the rapid growth of cases, public health officials in many jurisdictions ordered people to shelter in place beginning with the state of California on March 19, 2020. As of May 29, 2020, there have been 5.88 million confirmed cases in 188 countries and 363,000 reported deaths, and most countries are in various phases of relaxing quarantine requirements while continuing some social distancing measures.

What are Coronaviruses and what makes SARS-CoV-2 so contagious? Coronaviruses, which have a diameter of approximately 100 nm, are named after their crown-like appearance on electron microscopy. They infect many animal species and are part of the family of *Coronaviridae* that contain four distinct Genera. Coronaviruses are positive strand, single stranded ribonucleic acid (+ss-RNA) viruses. They have the largest genome of all RNA viruses, approximately 30 kilobases in length. The full sequence of SARS-CoV-2 was published on January 7, 2020 and revealed that it is was a β–coronavirus, similarly to other human coronaviruses that are responsible for 15% of all cases of acute viral naso-pharyngitis, also known as "common cold".[2] However, SARS-CoV-2 contains unique sequences, including a polybasic cleavage site in the spike protein, which is a potential determinant of increased transmissibility.[3]

Coronaviruses have caused deadly outbreaks in the past. The first one caused by SARS-CoV, occurred in China in 2003 and affected approximately 8000 people, with a 10% mortality. The Middle-East Respiratory Syndrome (MERS) outbreak began in Saudi Arabia in 2012, and affected 2500 individuals with a 35% mortality. SARS-CoV-2 has approximately 80% sequence homology with SARS-CoV, but 96% homology with a bat coronavirus and 92% with a pangolin coronavirus, suggesting it arouse in animals and then spread between species to humans. The spike protein of SARS-CoV-2 binds to its cellular receptor, the angiotensin converting enzyme 2 (ACE2), which also acts as receptor for SARS-CoV. Viral entry occurs after proteolytic cleavage of the spike protein by the transmembrane protease TMPRSS2. ACE2 is expressed abundantly in lung alveolar cells, but also in many cell types and organs in the body, including the cerebral cortex, digestive tract, kidney, gallbladder, testis and adrenal gland.[4]

Experience with the neurological complications of MERS and SARS provides a framework for considering both reported and potential neurological complications with SARS-CoV-2 and COVID-19.[5-10] In both MERS and SARS significant neurological complications were fortunately extremely rare. Reported cases of neurological disease suggests a minimum incidence of ~1:200 cases (MERS) -1:1000 cases (SARS). It is important to recognize however that the total number of confirmed cases of MERS and SARS together is only ~10,500 cases. It is likely that the sheer numeracy of COVID-19 compared to MERS and SARS, with nearly 4 million cases reported worldwide to date, will bring out a broader spectrum of neurological manifestations. In MERS and SARS neurological disease could be considered in three major categories: (1) The neurological consequences of the associated pulmonary and systemic disease including encephalopathy and stroke, (2) direct CNS invasion by virus including encephalitis, and (3) post-infectious and potentially immune-mediated complications including Guillain-Barre syndrome (GBS) and its variants and acute disseminated encephalomyelitis (ADEM).

Neurological complications of systemic COVID-19.

In a review of 214 patients hospitalized in three dedicated COVID-19 hospitals in Wuhan China, 36% of patients had nervous system symptoms.[11] These were further subdivided into those thought to reflect CNS, Peripheral nervous system (PNS) and skeletal muscle injury. Overall, 25% of patients had symptoms considered evidence of CNS dysfunction including dizziness (17%), headache (13%), impaired consciousness (7.5%), acute cerebrovascular disease (3%), ataxia (0.5%) and seizures (0.5%). Confirming this low incidence of seizures, no cases of status epilepticus or new onset seizures were reported in a large cohort of over 304 hospitalized COVID19 patients in Hubei Province, China,[12] although there have been isolated case reports describing seizures at presentation in both adult and pediatric patients with COVID19.[13, 14]

In the series by Mao and colleagues[11], the patients were subdivided based on the severity of their pneumonia and pulmonary impairment, and among those with "severe" disease (n=88) the incidence of CNS symptoms was higher (31%) compared to the non-severe group (21%), although the results were not statistically significant (p=0.09). Although all the categorized CNS symptoms occurred more frequently in patients with severe disease compared to non-severe disease, only impaired consciousness (15% in severe vs. 2% in non-severe, $p<0.001$) and acute cerebrovascular disease (5.7% vs. 0.8%, p=0.03) were significantly different between the two groups. Diagnostic studies were limited, but the impairment of consciousness seems most consistent with encephalopathy. Not surprisingly, when compared to those with non-severe disease, the severe cohort were older (58$\pm$15 yrs vs. 49$\pm$15 yrs), and more likely to have comorbidities including hypertension, diabetes, malignancy, cardiac, cerebrovascular, or kidney disease (48% vs. 33%, p=0.03). The severe group also had more evidence of systemic inflammation including elevated

C-reactive protein (CRP, median 37 mg/L) and D-Dimer (median 0.9 mg/L) compared to non-severe cases, and were also more likely to have evidence of hepatic (elevated alanine and aspartate aminotransferases) and renal (elevated BUN, creatinine) dysfunction.

A second survey of 58 hospitalized patients (median age 63) with COVID-19 acute respiratory distress syndrome (ARDS) at Strasbourg University Hospital found that 69% of patients had agitation, 67% corticospinal tract signs, and 36% a "dysexecutive" syndrome with difficulty in concentration, attention, orientation and following commands.[15] All patients studied (11/11) had evidence of frontal hypoperfusion on arterial spin label and dynamic susceptibility-weighted perfusion MRI. Only seven patients had a CSF examination and none had a pleocytosis and none had detectable SARS-CoV-2 RNA detected by reverse transcriptase-polymerase chain reaction (RT-PCR). One patient did have elevated IgG levels and "mildly" elevated total protein. CSF specific oligoclonal bands (OCBs) were not detected, but one patient had "mirror pattern" OCBs in CSF and serum.

In a study of MRI abnormalities in Intensive Care Unit patients with COVID19, 21% (50/235) of patients developed neurological symptoms.[16] In this group of neurologically symptomatic patients, only 27 had MRIs performed, and of these 44% (12/27) had new acute findings. Surprisingly, 56% (15/27) had no new MRI changes. The most common new abnormalities was multifocal areas of cortical FLAIR signal (10/12), accompanied in three patients by areas of increased FLAIR signal in the subcortical and deep white matter. One patient each had new transverse sinus thrombosis and acute middle cerebral artery infarction. Five of the ten patients with cortical FLAIR abnormalities had a CSF examination, and none of these patients had a pleocytosis elevated IgG Index, or OCBs (0/3 tested), although four had an elevated protein (mean 80 mg/dl, range 60-110). RT-PCR for SARS-CoV-2 was negative in all five cases tested. In another MRI series of critically ill patients on mechanical ventilation, many were found to have confluent T2 hyperintensities and restricted diffusion in the deep and subcortical white matter, in some cases accompanied by punctate microhemorrhages in the juxtacortical and callosal white matter that resembled findings seen in delayed post-hypoxic leukoencephalopathy.[17]

The mechanism of encephalopathy in COVID-19 remains to be determined. From available studies COVID-19 encephalopathy appears to be more common in patients with more severe disease, associated comorbidities, evidence of multi-organ system dysfunction including hypoxemia, and renal and hepatic impairment and elevated markers of systemic inflammation. Virus is not detected in CSF by RT-PCR and pleocytosis is usually absent. Some patients may have altered perfusion detectable by MRI, others have leukoencephalopathy with or without punctate microhemorrhages. This group needs to be distinguished from patients with encephalitis (who have a pleocytosis) and post-infectious immune mediated encephalitis (see below).

In a series of 5 consecutive COVID-19 patients with delayed awakening post mechanical ventilation for ARDS, MRI showed enhancement of the wall of basal skull arteries without enlargement of the vessel wall or stenosis. Toxic-metabolic derangements and seizures were ruled out, CSF SARS-CoV-2 RT-PCR was negative in all and they showed marked improvement in alertness 48-72 h after treatment of methylprednisolone 0.5 g/d iv for 5 days. These findings suggest that an endothelialitis rather than a vasculitis was responsible for the encephalopathy.[18] Direct infection of endothelial cells by SARS-CoV-2 and associated endothelial inflammation has been demonstrated histologically in post-mortem specimens from a variety of organs which did not include the brain.[19]

However, in an autopsy series including examination of the brain of 20 COVID-19 patient, 6 had microthrombi and acute infarctions and two focal parenchymal infiltrate of T-lymphocytes, while the others mainly had minimal inflammation and slight neuronal loss without acute hypoxic-ischemic changes in most cases. There was no evidence of meningomeningoencephalitis, microglial nodules, or viral inclusions including in the olfactory bulbs and brainstem and no demyelination. ACE2 was expressed in lung and brain capillaries. All cases had evidence of systemic inflammation.[20]

A second major manifestation of systemic COVID-19 disease is acute cerebrovascular disease. In the study by Mao and colleagues[11] this was present in 6 of the 214 (3%) hospitalized cases, but 5 of the six events occurred in those with severe disease (incidence 6%, p=0.03 vs. non-severe disease).[11] Five of the six reported events were ischemic strokes, and one was hemorrhagic. In the review of cases at Strasbourg University Hospital[15], 3 of 13 (23%) had cerebral ischemic stroke. In a single center retrospective study from China of 221 hospitalized COVID-19 patients, 13 had acute strokes including 11 ischemic, one hemorrhagic and one venous sinus thrombosis.[21] The stroke patients were older, had more comorbidities including diabetes, hypertension, and a prior stroke history and elevated inflammatory markers including D-Dimer and CRP. Another review of six consecutive COVID-19 patients admitted to the National Hospital in Queen Square with stroke noted that occlusions typically involved large vessels and often occurred in multiple vascular territories.[22] In five of six cases the strokes occurred 8-24 days after onset of COVID-19 symptoms. All patients had a highly pro-thrombotic state with very high D-dimer levels and elevated ferritin. Five of the six patients had detectable lupus anticoagulant, suggesting another potential prothrombotic mechanism for stroke in COVID19. Anticardiolipin IgA and anti-phospholipid IgA and IgM antibodies directed against β_2-glycoprotein-1 were also found in three patients with COVID-associated multiple territory large vessel infarctions.[23] Finally, a post mortem MRI study showed subcortical micro- and macro-bleeds (2 decedents), cortico-

subcortical edematous changes evocative of posterior reversible encephalopathy syndrome (PRES, one decedent), and nonspecific deep white matter changes (one decedent).[24]
Although initial reports emphasized acute cerebrovascular disease in older patients with COVID-19, a recent report described five cases of large vessel stroke as a presenting feature of COVID-19 in younger individuals two of whom lacked classic stroke risk factors.[25] These patients ranged in age from 33-49 yrs. Two of the five had diabetes one of whom had had a mild prior stroke history, and one had hypertension and dyslipidemia. The infarcts involved large vessel territories including the middle cerebral artery (3), posterior cerebral artery (1), and internal carotid artery (1). Two patients had preceding COVID-19 symptoms including fever, chills, cough, and headache; one patient had only lethargy. Surprisingly, two of the five patients had no antecedent of COVID-19-related symptoms preceding their stroke presentation. These five patients had elevated Prothrombin (range 12.8-15.2s) and Activated partial Thromboplastin Times (range 25-42.7s), elevated fibrinogen (range 370-739 mg/dl), D-Dimer (range 52-13,800 ng/ml) and ferritin (range 7-1564 ng/ml) consistent with a hyper-coagulable state and the presence of disseminated intravascular coagulation (DIC).

COVID-19 cerebrovascular disease appears to be predominantly ischemic and to involve large vessels. In older individuals it reflects the underlying severity of systemic disease as well as the hyper-inflammatory state, whereas in younger patients it appears to be due to hyper-coagulopathy. Children with a Kawasaki disease-like multisystem inflammatory syndrome (MIS) have recently been described.[26, 27] Patients with Kawasaki disease can develop cerebral vasculopathy and forms of neurological involvement, and in one series of 10 COVID-19 associated cases of MIS, two patients had meningeal symptoms.[28] As noted, it addition to hypercoagulable states, SARS-CoV-2 can infect and injure endothelial cells. However it remains to be determined whether virus-induced injury to endothelial cells (a vasculopathy) or even true vasculitis contributes to COVID19 related cerebrovascular syndromes, and this determination will require additional detailed vessel imaging and neuropathological analyses. Similarly, the number of cases is too small to determine the comparative therapeutic benefit, if any, of anti-platelet or anticoagulant drugs or immunomodulatory therapies in COVID-19 associated neurovascular syndromes.

Neuroinvasion by SARS-CoV-2.

In contrast to encephalopathy, in which evidence for direct invasion by virus of the CNS is absent, encephalitis occurs when direct invasion of the CNS by virus produces tissue injury and neurological dysfunction. Evidence for direct invasion of the CNS was seen in patients with SARS. Xu and colleagues described a fatal case in a 39 year-old man with delirium that progressed to somnolence and coma.[10] At post-mortem SARS-CoV antigen was detected in brain tissue by

immunohistochemistry (IHC) and viral RNA by in-situ hybridization (ISH). SARS-CoV virions were seen by transmission electron microscopy of brain tissue inoculated cell culture. In a post mortem analysis of 4 SARS patients, low level infection of cerebral neurons with SARS-CoV (1-24% of cells) was seen in the cerebrum in all four cases by IHC and ISH, although none of the cases had virus detected in cerebellum.[29]

By definition encephalitis is an inflammatory process, with supportive evidence including the presence of a CSF pleocytosis and elevated protein. However, in studies of transgenic mice expressing the human SARS-CoV receptor, Angiotensin Converting Enzyme -2 (ACE2), infection with SARS-CoV was associated with viral entry into the CNS, spread within the CNS, and neuronal injury with relatively limited inflammation.[30] This suggests the possibility that in some cases of SARS-CoV-2 CNS invasion that signs of inflammation could be modest or even absent. Regardless of the presence or absence of inflammation, diagnostic studies may show evidence of either a generalized or focal CNS process including areas of attenuation on computed tomography (CT), hyperintense signal on FLAIR or T2-weighted sequences on MRI, and focal patterns including seizures on electroencephalograms (EEG). Definitive evidence supporting direct viral invasion would include a positive CSF RT-PCR for SARS-CoV-2, demonstration of intrathecal synthesis of SARS-CoV-2-specific antibodies, or detection of SARS-CoV-2 antigen or RNA in brain tissue obtained at biopsy or autopsy.

Cases meeting strict criteria for encephalitis resulting from direct SARS-CoV-2 are currently extremely rare, although several plausible case reports have now appeared. Moriguchi et al. described a 24 y.o. man with COVID-19 disease who developed nuchal rigidity, progressively decreased consciousness (GCS=6), and generalized seizures.[31] CSF showed a slight mononuclear predominant pleocytosis (12 cells/mm^3) and elevated opening pressure (>320 mm H_20). Neuroimaging showed hippocampal and mesial temporal increased FLAIR signal and the CSF RT-PCR was positive for SARS-CoV-2. Unfortunately, studies to exclude other viral etiologies of encephalitis were limited. A second case involved a 41 y.o. woman with headache, fever, a new onset seizure and photophobia and nuchal rigidity followed by hallucinations and disorientation A head CT was normal and MRI was not performed. An EEG showed generalized slowing. The CSF exam showed a lymphocytic pleocytosis (70 cells/ul, 100% lymphocytes) and elevated protein (100 mg/dL) and a positive SARS-CoV-2 RT-PCR.[32, 33]

Several cases have appeared in which patients had inflammatory features consistent with encephalitis, but who did not have evidence of direct viral CNS invasion. Bernard-Valnet et. al. reported on two patients with "meningo-encephalitis concomitant to SARS-CoV2".[34] These patients had nuchal rigidity, altered mental status, mild CSF lymphocytic pleocytosis (17-21 cells/mm^3 on initial LP), and mildly elevated CSF protein (46-47mg/dl). However, in both patients

the MRI was normal and neither patient had a positive CSF RT-PCR for SARS-CoV-2. Similarly, Pilotto et al describe a 60 y.o. man with COVID-19 developed confusion, irritability and then apathy progressing to "akinetic mutism" with nuchal rigidity.[35] The CSF showed a mild lymphocytic pleocytosis (18 cells/mm^3) and elevated protein (70 mg/dl). An EEG showed generalized slowing with an anterior predominance. The CT and MRI were normal, and CSF RT-PCR was negative twice for SARS-CoV-2. Although treated with a wide variety of medications this patient showed improvement coincident to administration of high dose methylprednisolone.[35] Another study reported on 6 critically ill patients with severe ARDS, elevated inflammatory markers and depressed consciousness and/or agitation considered to have "autoimmune meningoencephalitis."[36] No patient had a CSF pleocytosis but five had elevated CSF protein (52-131 mg/dL) and three MRI had cortical hyperintensities with sulcal effacement. There were no controls but patients were felt to have responded to plasma exchange. In one report a patient with neuropsychiatric symptoms and COVID-19 had a "hematic" CSF tap with 960 "red and white blood cells" and an elevated protein (65 mg/dL) and detectable NMDA receptor antibodies. This currently isolated case also raises the possibility that COVID-19 may trigger auto-antibody production.[37]

The available studies suggest that SARS-CoV-2 can rarely produce a true encephalitis or meningoencephalitis with associated evidence of direct viral invasion of the CNS. The failure to detect virus in CSF in the other reported cases, despite evidence of inflammation as evidenced by CSF pleocytosis and elevated protein, raises the possibility that some cases of COVID-19 encephalitis may occur in the absence of direct virus invasion, and could potentially result from immune-mediated inflammatory mechanisms (see below). It is important to realize that techniques including detection of intrathecal SARS-CoV-2 antibody synthesis or of viral antigen or nucleic acid in brain tissue may establish evidence for viral invasion when CSF RT-PCR studies are negative. For example, detection of intrathecal antibody synthesis is significantly more sensitive than CSF nucleic acid amplification tests for diagnosis of both West Nile Virus neuroinvasive disease and EV-D68 associated acute flaccid myelitis (AFM).[38-40] In the case of EV-D68-associated AFM, nasophayngeal and throat swabs are frequently positive for virus by RT-PCR when obtained early after disease onset, yet CSF RT-PCR tests are only positive in a small minority (<3%) of cases.[41] The sensitivity of SARS-CoV-2 RT-PCR in properly performed nasopharyngeal swabs for detection of acute COVID-19 is high, but data is currently too limited to evaluate sensitivity of this technique in CSF in patients with neurological disease.

Post-infectious and immune-mediated complications of SARS-CoV-2.

The identification of post-infectious complications of SARS-CoV-2 would be expected to temporally lag behind those resulting from acute infection. Occasional cases of Guillain-Barre syndrome (GBS) and its variants and of acute disseminated encephalomyelitis (ADEM) were reported after MERS and SARS.[5, 7, 9] Reports are now appearing of similar associations with COVID-19 and GBS, and with GBS variants including the Miller-Fisher syndrome. [42-47] The largest series to date, describes five patients.[48] In this series, all patients developed GBS 5-10 days following COVID-19 symptom onset. The clinical presentation included bilateral multi-limb flaccid weakness with areflexia. Three patients had associated respiratory failure and two had associated facial weakness. MRI showed caudal root nerve enhancement in two cases and enhancement of the facial nerve in a third case. The CSF was normocellular in all five cases, and had an elevated protein consistent with albumino-cytological dissociation in three cases. Electrophysiological studies showed reduced compound motor amplitudes and prolonged distal latencies, and the overall pattern was felt to be consistent with demyelination in 2 and axonal neuropathy in three cases. Fibrillation potentials were seen by EMG acutely in three patients and later in a 4th patient. None of the patients had SARS-CoV-2 detected in the CSF by RT-PCR. Antiganglioside antibodies were absent in the three tested patients. All patients received intravenous immunoglobulin (IVIG) and one plasma exchange, although improvement was noted in only two cases (one "mild improvement" only).

Cases of Acute Necrotizing Encephalopathy (ANE) have been reported in COVID19.[49, 50] One patient was a 50 y.o. woman with COVID-19 confirmed by nasopharyngeal RT-PCR who developed altered mental status and MRI and CT findings typical of ANE including bilateral thalamic lesions. Unfortunately, CSF studies were limited and CSF RT-PCR testing for SARS-CoV-2 was not performed. A second case occurred in a 59 y.o. woman with aplastic anemia who developed seizures and reduced consciousness ten days after onset of her COVID-19 symptoms.[50] The mechanism behind ANE remains unknown, and either direct viral or post-infectious inflammatory processes have been postulated to play a role, and many cases have been reported after upper respiratory infections including influenza. Some patients have mutations in RAN binding protein-2 (RANBP2), indicating that host genetic factors may also play a role in susceptibility.

Rare cases of Acute Disseminated Encephalomyelitis (ADEM) were associated with MERS.[6] The first case of "COVID-19 associated disseminated encephalomyelitis" was reported in a 40 y.o. woman.[51] This individual had COVID-19 symptoms followed 11 days later by dysarthria, dysphagia, facial weakness and a gaze preference. A Chest x-ray showed pneumonia and a NP RT-PCR was positive for SARS-CoV-2. Head CT showed multiple areas of patchy hypoattenuation and a MRI showed areas of increased FLAIR and T2 signal in the subcortical and deep white matter that were felt to be consistent with demyelination. Her CSF was normal. A second reported case

was in a 54 y.o. woman who developed seizures and neurological deterioration (GCS 12) and had chest x-ray lesions consistent with COVID-19 and a positive NP RT-PCR for SARS-CoV-2.[52] Her MRI showed multiple periventricular T2 hyper-intense, non-enhancing, lesions in the white matter of the cerebrum, brainstem, and spinal cord consistent with multifocal demyelination. Her CSF studies were unremarkable including a negative CSF RT-PCR for SARS CoV-2. She was treated with high dose dexamethasone and her symptoms gradually resolved. A single case of acute flaccid myelitis has also been described in COVID-19.[53] This patient developed upper limb weakness and a flaccid areflexic lower limb paralysis, urinary and bowel incontinence, and a T10 sensory level. Unfortunately, neither spine imaging nor CSF studies were available so the mechanism remains unknown. The most convincing example of ADEM-like pathology associated with COVID-19 was in a 71 y.o. who developed symptoms immediately following coronary bypass graft surgery that progressed to respiratory failure and a hyper-inflammatory state. A postmortem exam showed brain swelling and disseminated hemorrhagic lesions and subcortical white matter pathology with perivenular myelin injury but also necrotic blood vessels and perivascular inflammation. The lesions had features of both acute hemorrhagic leukoencephalitis and of acute disseminated encephalomyelitis.[54]

The rarity of post-infectious potentially immune-mediated cases following COVID-19 other than GBS and its variants, and the general paucity of details, makes their status unclear. The cases of ADEM-like illness are hard to distinguish from some of the patients with acute encephalopathy and associated MRI white matter lesions, but can be differentiated from cases of encephalitis by the absence of CSF pleocytosis. GBS is a common neurological disease even in the absence of COVID-19, and identifying the magnitude of the COVID-19 risk and association will require better epidemiological data. However, the 5 cases of GBS occurring in a population of 1000-1200 COVID-19 patients seen over a one month period by Toscano et al in Northern Italy suggest an incidence that is much higher than that can be expected in the general population (~1/100,000 person-years).[55] The mechanism of pathogenesis will need to be identified, and the efficacy of conventional therapies including IVIG and plasma exchange evaluated.

Other COVID-19 related neurological disorders.

One of the more striking reported symptom manifestations in patients with COVID-19 is loss or perturbation of smell (anosmia or hyposmia) and/or taste (dysgeusia). The frequency of these symptoms, their specificity as a potential diagnostic clue for COVID-19 infection as opposed to influenza or other symptomatologically similar diseases, and their implication for understanding viral pathogenesis all remain uncertain. In the Wuhan COVID-19 series impairment of smell was noted in 5% and of taste in 6% of the 214 hospitalized patients.[11] It is likely that the frequency was under-represented due to incomplete evaluations in these hospitalized sick patients. A later study of 31 patients suggested that disorders of taste occurred in 81% of COVID-19 cases (46%

anosmia, 29% hyposmia, 6% dysosmia) and disorders of taste in 94% (ageusia 45%, hypogeusia 23%, dysgeusia 26%).[56] The average duration of smell and taste disorders in the COVID-19 cases was 7.1 ±3.1 days. A multi-center European study of 417 cases with "mild-to-moderate" COVID-19 disease found a similarly high frequency of olfactory dysfunction (86%), with 80% of those affected having anosmia and 20% hyposmia.[57] ~70% of patients had recovered within 8 days of symptom onset. It has been suggested that olfactory and/or gustatory dysfunction may be indicative of neuro-invasion and provide a route from the nasopharynx or oropharynx to cardiorespiratory centers in the medulla, based on studies of transgenic mice expressing the human SARS virus receptor (ACE2) and infected with SARS-CoV, however no evidence supporting host entry via this pathway yet exists in man.[30] The transient nature of the dysfunction in most patients would seem to make direct viral infection and subsequent killing of olfactory or gustatory neurons unlikely. MRI of the olfactory bulb was normal in one RT-PCR confirmed patient with anosmia.[58]

In the Wuhan COVID-19 series 11% of patients were reported to have evidence of skeletal muscle injury (defined as a CK >200 U/L and skeletal muscle pain).[11] Injury was significantly more common in patients with "severe" disease (19%) compared to non-severe disease (5%)($p<0.001$). Unfortunately, almost no clinical details were provided beyond the presence of associated muscle pain. Subsequently two reports have appeared of rhabdomyolysis as either a presenting feature or a late complication of COVID-19.[59, 60] One patient had limb pain and weakness with a peak CK of ~12,000 U/L and myoglobulin >12,000 ug/L, and the other had a peak CK of 13,581 U/L. Neither patient had muscle biopsy performed. The mechanism of injury remains to be determined.

Immunopathogenesis of SARS-CoV-2 and implication for management and treatment of neurologic manifestations

One of the most puzzling features of SARS-CoV-2 infection is that is asymptomatic or associated with minor symptoms in approximately 80% of patients, especially children and young adults, whereas 20% will develop COVID-19 with various degrees of severity. Can knowledge gathered on SARS-CoV inform us about the immunopathogenesis of SARS-CoV-2? A successful production of type I IFN response is a key first line defense for suppressing replication of many neurotropic viruses at the site of entry and dissemination. SARS-CoV suppresses type I IFN response and downstream signaling using multiple strategies and this dampening is closely associated with disease severity.[61]

Since SARS-CoV-2 shares an overall genomic similarity of 80% with SARS-CoV and uses the same receptor, it is reasonable to expect that the innate immune mechanisms involved in pathogenesis will be similar for the two viruses. SARS-CoV has developed multiple strategies to evade the

innate immune response in order to optimize its replication capacity.[62] It appears likely that SARS-CoV-2 uses the same strategy. The magnitude of the immune response against SARS-CoV-2 needs to be precisely calibrated to control viral replication without triggering immunopathogenic injury. A hyperinflammatory response likely plays a major role in ARDS and in a subset of children may contribute to the development of a Kawasaki-like multisystem inflammatory disorder[20]. In a mouse model of SARS, rapid SARS-CoV replication and delay in IFN-I signaling led to inflammatory monocyte-macrophage accumulation, resulting in elevated lung cytokine/chemokine levels and associated vascular leakage and lethal pneumonia. This "cytokine storm", in turn, was associated with decrease T cell counts and suboptimal T cell responses to SARS-CoV infection.[63]

The same pattern is found in 522 patients with COVID-19, where the number of total T cells, CD4+ and CD8+ T cells were dramatically reduced, especially in those requiring ICU care, and T cell numbers were negatively correlated to serum IL-6, IL-10, and TNF-α concentration. Conversely, patients in the disease resolution period showed reduced IL-6, IL-10, and TNF-α levels and restored T cell counts.[64] These data were corroborated by other groups who also noticed a decrease in type 1 Interferon response in severely affected patients.[65, 66] It has been suggested that reduced and delayed IFN gamma production ("too little and too late") in the lung and depletion of both CD4 and CD8 T-cells may combine to potentiate viral injury, by reducing control of viral replication and enhancing the up-regulation of pro-inflammatory cytokines including TNF alpha, IL-6 and Il-10 ("cytokine storm") and that it may be the immune dysregulation as much or more than the direct viral infection that results in pulmonary epithelial cell injury, and similar mechanisms could be operative in the CNS.[67]

What are the possible mechanisms for the apparent immune dysregulation seen in those patients and could they have a role in the neuropathogenesis of COVID-19? The source of cytokines found in the serum in unclear, but they could be produced by lung macrophages. IL-6 could also come from infected neurons, as seen in a transgenic mouse model of SARS-Cov.[30] A high level of circulating cytokines, in turn, could lead to lymphocytopenia. TNF-α, a pro-inflammatory cytokine may cause T cell apoptosis via interacting with its receptor, TNFR1, which expression is increased in aged T cells.[68, 69] IL-6, that has both pro and anti-inflammatory properties, contributes to host defense in response to infections. However, continual synthesis of IL-6 has been shown to play a pathological role in chronic inflammation and infection.[70, 71] IL-10, an inhibitory cytokine that prevents T cell proliferation, can also induce T cell exhaustion. Interestingly COVID-19 patients have high levels of the PD-1 and Tim-3 exhaustion markers on their T cells.[64]In turn, decreased numbers of CD4+ and CD8+ T lymphocytes will considerably weaken the cellular immune response to SARS-CoV-2 in severe cases, allowing further viral replication. This can be compounded by the use of corticosteroids. Of note, a study in convalescent SARS-CoV patients showed that CD8+ T cell responses were more frequent and had

a greater magnitude of response than CD4+ T cells.[72] Finally, one autopsy series of COVID-19 patients showed histological features suggestive of secondary hemophagocytic lymphohistiocytosis (sHLH), also known as macrophage activation syndrome. This syndrome is characterized by an imbalance of innate and adaptive immune responses with aberrant activation of macrophages, and a blunted adaptive immune response.[20]

This dysregulated immune response may have a role in the pathogenesis of the COVID-19 encephalopathy. High levels of circulating pro-inflammatory cytokines can cause a confusion and alteration of consciousness, whereas a weakened T cell response may be unable to eliminate virus-infected cells in the brain causing further neurologic dysfunction. Careful studies of the CSF cytokine profile and T cell response to SARS-CoV-2 as well as post mortem studies including CNS and muscle tissues are urgently needed to better understand the neuropathogenesis of COVID-19. These will help inform whether therapeutic strategies aimed at blocking pro-inflammatory cytokines including the Il-6 inhibitors tocilizumab and sarilumab could have a beneficial effect on encephalopathy or whether corticosteroids that dampened the adaptive cellular immune response to viruses are contra-indicated. As we strive to find medications to counter the deleterious inflammatory state triggered by SARS-CoV-2, lessons can also be learned from COVID-19 outcomes in patients with neurological diseases such as multiple sclerosis or myasthenia gravis treated with immunomodulatory therapies.

Although we are only starting to grasp the complexity of SARS-CoV-2 biology, it is already apparent that COVID-19 causes a global threat to the entire nervous system, both through its worldwide distribution and multifactorial pathogenic mechanisms (Figure 1). As we hope for a vaccine or a cure, neurologists will play an important role in diagnosing, investigating and treating the many neurologic manifestations of COVID-19 (Table 1).[73]

Legend to Figure 1: Mechanisms of SARS-CoV-2 Neuropathogenesis

SARS-CoV-2 pathogenic effects on the nervous system are likely multifactorial, including manifestations of systemic disease, direct neuro-invasion of the central nervous system (CNS), involvement of the peripheral nervous system (PNS) and muscle, as well as through a post-infectious, immune-mediated mechanism. MOF: multi-organ failure; GBS: Guillain-Barre syndrome, *CNS inflammation (CSF pleocytosis and proteinoracchia) with no evidence of direct

viral infection of CNS; *CNS inflammation (CSF pleocytosis and proteinoracchia) with no evidence of direct viral infection of CNS;§ direct evidence of viral invasion (RT-PCR+, biopsy); § direct evidence of viral invasion (RT-PCR+, biopsy).

Table 1. Neurologic Conditions associated with SARS-CoV-2 infection

Disease entity	Presentation	Supportive Neurodiagnostic testing	Pathogenesis
Encephalopathy	Altered mental status	MRI: non-specific EEG: abnormal (slow) CSF: nl cells and Pro CSF SARS-CoV-2 RT-PCR: NEG	Multiple organ failure Hypoxemia Systemic Inflammation Endothelialitis
Encephalitis	Altered mental status and CNS dysfunction	MRI: non-specific (? WM changes) EEG: abnormal (slow, +focal) CSF: pleocytosis & elev. Pro CSF SARS-CoV-2 RT-PCR: NEG	CNS Inflammation
Viral Encephalitis	Altered mental status and CNS dysfunction	MRI :new abnormality EEG: abnormal (slow, ±focal) CSF: Pleocytosis and elev. Pro CSF SARS-CoV-2 RT-PCR: POS Brain Tissue: POS (Ag or RNA)	Brain parenchymal Neuro-invasion
Viral Meningitis	Headache, nuchal rigidity	MRI: meningeal enhancement, CSF: pleocytosis & elev. Pro CSF SARS-CoV-2 RT PCR: POS	Subarachnoid invasion
Stroke	Focal motor or sensory deficit	MRI: ischemia or bleed, abnormal coagulation factors increased inflammatory markers	Coagulopathy
Anosmia/Ageusia	Olfactory or taste dysfunction	Abnormal smell/taste tests	? Peripheral vs Central neuro-invasion
ADEM	Head ache, acute neurologic symptoms	MRI: hyperintense FLAIR lesions with variable enhancement	Post-infectious
Guillain-Barre Syndrome	Flaccid muscle weakness	CSF: increased protein, nl WBC CSF SARSCoV-2 RT-PCR: NEG EMG/NCS: abnormal	Post-infectious
Muscle injury	Myalgia	CPK elevated	Myopathy or Myositis?

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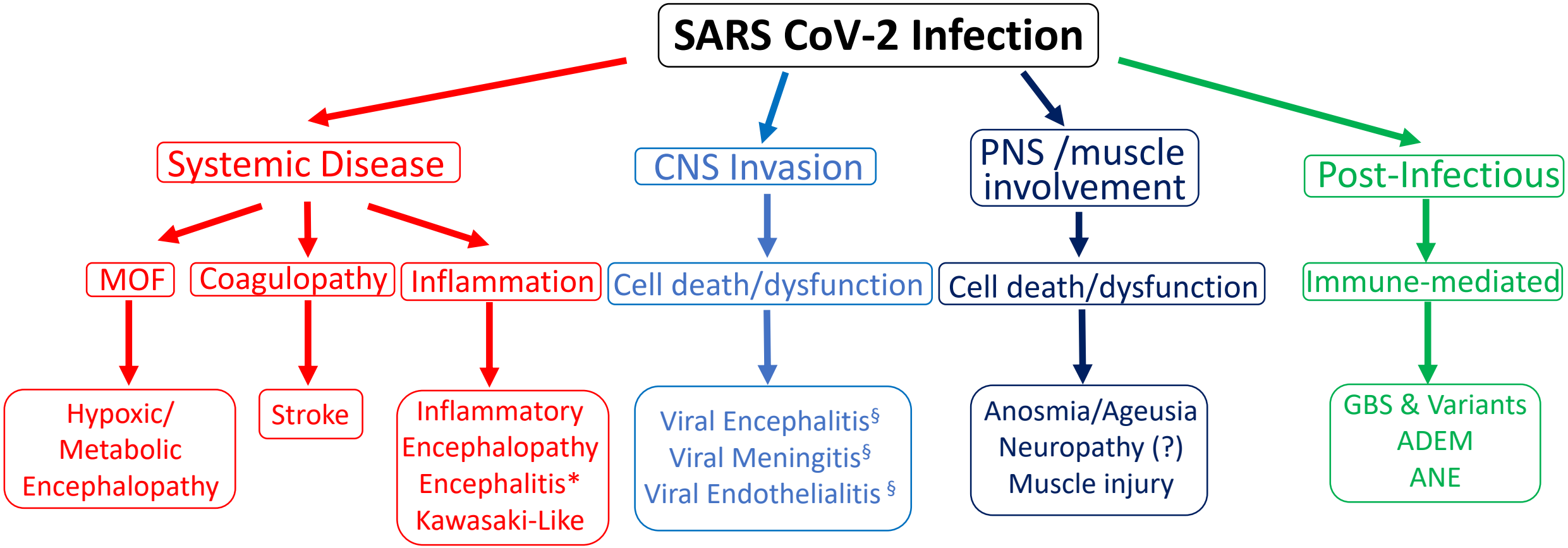
SARS CoV-2 Infection
Systemic Disease
CNS Invasion
PNS /muscle involvement
Post-Infectious
MOF
Coagulopathy
Inflammation
Cell death/dysfunction
Cell death/dysfunction
Immune-mediated
Hypoxic/ Metabolic Encephalopathy
Stroke
Inflammatory Encephalopathy Encephalitis* Kawasaki-Like
Viral Encephalitis§ Viral Meningitis§ Viral Endothelialitis §
Anosmia/Ageusia Neuropathy (?) Muscle injury
GBS & Variants ADEM ANE