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REVIEW

COVID-19 SECTION

Neurological manifestations in COVID-19: how relevant is this association?

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ABSTRACT

INTRODUCTION: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first reported in December 2019 in an outbreak occurring in Wuhan, China and has spread rapidly all over the word causing a global pandemic with approximately 129 million confirmed cases and more than 2.8 million deaths worldwide as of April 2nd, 2021. With the increasing number of people affected by this disease, it has become early apparent that SARS-CoV-2 may also affect the nervous system.

EVIDENCE ACQUISITION: A great number of case reports, case series and review, often incomplete and not-peer-reviewed, about the observation of neurological symptoms in coronavirus disease-19 (COVID-19) have been published to date. In this review, we have tried to summarize the most recent evidences about the main neurological syndrome associated to the infection: delirium/confusion, encephalitis, Guillain-Barré Syndrome (GBS) and ischemic stroke.

EVIDENCE SYNTHESIS: From the huge amount of literature published in the last year, it appears that the neurological involvement of nervous system in COVID-19 is a relatively rare event as compared to the lung damage, but it is one of the most frequent extra-pulmonary complications. A supposed direct invasion of the nervous system, a para-infectious or post-infectious immune-mediated disease, or simply post-systemic effects of the viral infection, have been proposed as the main mechanisms.

CONCLUSIONS: Encephalopathy and stroke are the most serious and common syndromes associated with COVID-19, mostly related to the inflammatory and hypercoagulable status, whereas available data suggest a post-infectious immune mediated mechanism for SARS-CoV-2 related GBS. However, more extensive epidemiological and histopathological studies are warranted to confirm the casualty of this latter association.

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KEY WORDS: COVID-19; Ischemic stroke; Brain diseases.

Introduction

Coronavirus disease-19 (COVID-19) pandemic represents a worldwide public health problem with over 129 million confirmed cases and more than 2.8 million deaths worldwide as of April 2nd, 2021.[1] It is caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) which is mostly a respiratory virus with a high tropism for the lung.[2] SARS-CoV-2 became pandemic in a few months, showing a dramatic dissemination capacity. It emerged in December 2019 from Wuhan in China and it spread rapidly all over the world.[3, 4] Clinical presentations of COVID-19 range from no symptoms (asymptomatic) to severe pneumonia. The mortality for critically ill patients is

relevant, with a survival time of 1-2 weeks after intensive care unit (ICU) admission and a mortality rate of 26% in a case series of 1591 patients in Italy.[5] Although some neurological manifestations have been commonly described such as headache, dizziness, nausea and vomiting, hypogeusia and hyposmia especially in the first phase of the disease,[6] the potential invasion of the central nervous system has been supposed, given the similarity of the SARS-CoV-2 with Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome SARS coronavirus,[6, 7] but has not been proven yet. The so called "cytokine storm," together with the coagulopathy secondary to an excessive and dysregulated host immune response, may contribute to the development of acute respiratory distress syndrome (ARDS), multiorgan dysfunction and death.[8-11] A huge amount of scientific literature including case reports, case series and reviews (often with incomplete data and appeared on non-peer-review websites) about the neurological involvement during COVID-19 disease, have been published so far. In a systematic review of 901 patients affected by COVID-19 and neurological symptoms reported in case reports and series until May 2020, Ellul et al proposed different mechanisms to explain the neurological involvement, such as a supposed direct invasion of the nervous system, a para-infectious or a post-infectious immune-mediated disease.[12] Interestingly, among these 901 patients only eight were reported to have encephalitis (and only one patient in four tested presented the SARS-CoV-2 in the cerebrospinal fluid [CSF]) and nineteen were described to have Guillain-Barré Syndrome (GBS). Overall, the incidence of stroke in patients hospitalized with COVID-19 was 2-6% in cohort studies, and 96 patients with acute cerebrovascular disease were reported by the same authors, frequently associated with a pro-inflammatory hypercoagulable state.[12]

Histopathological studies tested the presence of the virus in the brain or the CSF with inconclusive results. Some authors reported SARS-CoV-2 RNA in brain post-mortem or in the CSF of patients with encephalopathy or encephalitis, but at very low levels, whereas other studies have not confirmed a direct viral invasion, but only a CSF inflammation.[13-15] Possibility of artifact or contamination has also been supposed.[14]

Potential routes of brain invasion were proposed by analogy with the neurotropism of other coronaviruses. First, the olfactory route based on the frequently reported symptoms of anosmia and ageusia in COVID-19 patients. However, it is still not clear if the virus reaches olfactory neurons or is restricted to the olfactory epithelium.[14] Second, the blood brain barrier (BBB), which represents a common route of entrance in the central nervous system for many viruses. However, at present no striking evidence exists for SARS-CoV-2 invasion through the angiotensin converting enzyme 2 (ACE2), the host-target of the virus spike-protein widely expressed by brain endothelial cells, or through leukocyte infection (a mechanism also known as "Trojan horse mechanism"), since several autopsy studies revealed a lack of cerebrovascular inflammation and immune cell infiltration.[14, 15]

Acute respiratory failure is the main complication in SARS-CoV-2 patients and a direct viral invasion of brainstem respiratory nuclei has been hypothesized.[8] However, no alterations in respiratory centers or carotid chemoreceptors was observed at autopsy in a patient with respiratory dysregulation,[16] not confirming evidence of central autonomic involvement.

A recently published autopsy study on post-mortem brain of COVID-19 patients revealed the presence of megakaryocytes in cortical capillaries. The authors hypothesize that these large cells may cause ischemic alterations leading to the symptoms of "brain fog" frequently reported by the SARS-CoV-2 infected patients.[17]

Many unanswered questions do still exist about SARS-CoV-2 and nervous system involvement. Here, we attempted to provide a summary of the evidence collected in the last year about the main neurological symptoms related to COVID-19, highlighting the main clinical features and the most plausible mechanisms of the underlying histopathology.

Evidence acquisition

Delirium and mental confusion

Delirium and mental confusion are frequent conditions in patients suffering COVID-19. According to the DSM-5, delirium is defined as an acute

alteration of attention, awareness and cognition (*e.g.* disorientation, language, memory deficit) with a fluctuating course, which typically develops over a short period of time, it is secondary to another medical condition and it is not related to pre-existing cognitive disorders.[18]

A Chinese study reported a prevalence of confusion of 9% among patients with COVID-19 pneumonia,[19] and delirium has commonly reported in the intensive care unit (ICU) setting. A French case-series described neurological manifestations in 85% of patients admitted for COVID-19 related ARDS; in particular, 65% of the patients had confusion, according to the Confusion Assessment Method for the ICU.[20] The same authors found that 84.3% of patients with COVID-19 admitted to an ICU had delirium and mostly the hyperactive form, dominated by agitation. Delirium was also associated with a longer duration of invasive mechanical ventilation and a prolonged length of stay in ICU.[21] Brain MRI performed in 28 patients demonstrated subarachnoid spaces enhancement in 17 of 28 patients (60.7%) and mainly white matter abnormalities in eight patients. Inflammatory status was found in 18/28 patients, including oligoclonal bands with mirror pattern and elevated IL-6 in CSF. Only one patient was found positive for CSF RT-PCR SARS-CoV-2.[21] A more recently published meta-analysis reported 27% of patients with delirium among a total of 3868 patients analyzed from 9 studies, and an independent association with mortality irrespectively of age, sex, hypertension, diabetes and dementia. Delirium may be at admission, during hospital stay, or both.[22]

The most common cause of mental confusion in COVID-19 disease is the presence of a systemic condition (such as fever, hypoxemia or hyponatremia). The more severe the form of disease and the older the patients with many comorbidities, the more likely is the delirium development.[23, 24] Interestingly, COVID-19 pneumonia, as other forms of atypical pneumonia, can induce a syndrome of inappropriate antidiuretic hormone secretion (SIADH),[25, 26] which can lead to hyponatremia and then to confusion.

Diagnostic workup to rule out parenchymal lesions of the brain which can mimic a delirium, such as cerebrovascular accidents (both ischemic and hemorrhagic), encephalitis, acute disseminated encephalomyelitis, includes: radiological exams (brain computed tomography [CT] scan and magnetic resonance imaging [MRI]), lumbar puncture and electroencephalogram (EEG). EEG, besides its value to assess the presence of epileptic seizures, sometime reported in COVID-19 patients,[23, 27] describes usually non-specific alterations.[28, 29] However, some authors found more specific patterns as an abnormal background rhythm associated to generalized and monomorphic delta slow waves, which is prevalent in frontal areas bilaterally.[30, 31]

Delirium was also observed as the first and unique manifestation of COVID-19 infection, suggesting a pathophysiological relationship between SARS-CoV-2 infection and the development of an acute state of mental confusion.[24, 32-34] To assess this matter, brain ^{18}F-FDG-PET studies were performed reporting interesting findings. Usually, delirium is associated with global cortical hypometabolism or regional cortical changes of metabolism, mostly bilateral and localized in frontal, parietal or temporal lobes.[35] On the contrary, COVID-19 patients with delirium tend to present different patterns. In a case series of 4 patients affected by encephalopathy due to SARS-CoV-2, brain FDG-PET showed a prefrontal and orbito-frontal cortex hypometabolism and a cerebellar vermis hypermetabolism.[36] Similarly, another study performed on 7 COVID-19 patients, revealed a prefrontal cortex (especially on the right side), bilateral insula, anterior cingulate and caudate nucleus hypometabolism, and cerebellar vermis, dentate nucleus and pons mild hypermetabolism.[37]

Confusion has also been observed at a late stage of COVID-19, when respiratory symptoms are resolving or even after their resolution, in a context of a post-infectious neurological syndrome.[38-40] These syndromes include encephalitis due to an antibody-mediated mechanism and autoimmune limbic encephalitis. The main characteristics of these diseases are: the presence of altered mental status, confusion, seizures; a brain MRI showing hyperintensities of the temporal lobes bilaterally, in T2 and FLAIR weighted sequences; elevated proteins in cerebrospinal fluid with no pleocytosis and, in some cases, the pres-

ence of specific antibodies (such as anti-N-methyl-D-aspartate receptor [NMDAR] antibodies); a good response to immunomodulatory therapy (corticosteroids, intravenous immunoglobulin, plasma exchange).

Encephalitis

Encephalitis represents a potentially life-threatening condition of acute inflammatory state of the central nervous system (CNS) attributable to an infectious or an autoimmune etiology. To date, the clinical pictures of COVID encephalitis are reported mainly in case reports. Moriguchi *et al* reported the first documented case of meningitis/encephalitis associated with SARS-CoV-2 in Japan.[41] A 24-year-old man was admitted to emergency department for an acute onset of impaired state of consciousness with coma (GCS 6), transient generalized seizures, signs of meningeal irritation with neck stiffness, after a prodromal symptomatology characterized by fever, asthenia and headache. Laboratory tests revealed neutrophilic leukocytosis and lymphopenia with increased C-reactive protein (CRP). A lumbar puncture demonstrated a mononuclear pleocytosis and SARS-CoV-2 RNA was detected in CSF. At brain MR, Diffusion weighted Images (DWI) showed a right lateral ventriculitis and Fluid-attenuated inversion recovery (FLAIR) images showed hyperintensity in the right mesial temporal lobe and hippocampus, without contrast enhancement. The diagnosis of encephalitis remains very often presumptive on the basis of clinical neurological features and laboratory support, and frequently the detection of the virus in CSF may be not conclusive, as reported in a case report of a Wuhan male with SARS-CoV-2 infection presenting with fever, myalgia, unconsciousness and meningeal irritation and extensor plantar response.[42] Wong *et al.* reported a rare case of a 40-year old man with a clinical brainstem dysfunction 3 days after hospital admission for a COVID-19 pneumonia; a brain MR documented an inflammatory rhombencephalitis/myelitis.[43] Poyiadji *et al.* proposed a case report of acute necrotizing encephalitis caused by SARS-CoV-2. The authors speculate about the possible alternative pathogenetic mechanism of the cytokine storm, instead of direct viral invasion of the CNS.[44]

An unusual clinical presentation of CNS involvement in COVID-19 is focal state epilepticus with myoclonic jerks, even in the context of previous post-encephalitic (HSV) epilepsy, as described by Vollono *et al.*[45] The laboratory findings demonstrated a lymphocytopenia (560 cells/mm3) and thrombocytopenia (125,000/mm3), and a semi-rhythmic delta activity, predominantly lateralized over the left fronto-centro-temporal regions corresponding to the lesion areas, was documented on EEG. However, the specific role of the SARS-CoV-2 as a trigger of a status epilepticus seems controversial. Another interesting unusual clinical presentation of SARS-CoV-2 was represented by choreiform movements, due to putative hyperviscosity in the basal ganglia or striatum dysfunction caused by inflammation.[46]

Several concomitant and potentially misleading MRI findings were described in SARS-CoV-2 patients with meningoencephalitis, including intraparenchymal hematoma, subarachnoid hemorrhage and subdural hematoma, with the confirmation of the SARS-CoV-2 in the CSF obtained from the surgical evacuation.[47] Furthermore, a case of an anterior temporal lobe lesion with elevated choline peak and decrease of the N-acetyl aspartate peak on MR spectroscopy, initially misdiagnosed as high-grade glioma, was finally confirmed as encephalitis by the histopathological examination.[48]

Although the reported heterogeneous manifestations seem to be related to a direct damaging action of the virus, the absence of viral markers in the brain still raises some doubts. However, different possible alternative explanations have been formulated. The non-detection of the virus in CSF could be related to a suboptimal sensitivity of the available PCR tests for the detection of SARS-CoV-2, or the meningoencephalitis could be due to a post-infectious or para-infectious mechanism behind an immune-mediated etiopathology.

In support of the latter hypothesis, cases of COVID-19 encephalitis improved after treatment with plasmapheresis.[49] Moreover, anti-NMDAR antibodies were reported among COVID-19 patients. Panariello *et al.* reported a case of anti-NMDAR encephalitis in a 23-year-old Ecuadorian male with SARS-CoV-2 infection

and acute psychotic symptoms refractory to antipsychotic drugs, with subsequent altered state of consciousness. A lumbar puncture was performed with evidence of anti-NMDAR antibodies in CSF. Treatment with high doses of dexamethasone and intravenous immunoglobulin (IVIG) was started with clinical improvement.[50] Another case report documented an anti-NMDAR encephalitis in a 23-month-old infant with movement disorders and worsening encephalopathy after a diagnosis of SARS-CoV-2 mild infection.[51] A diagnosis of possible sero-negative autoimmune encephalitis in a 18-year-old woman hospitalized for fever, drowsiness, confusion, myoclonic jerks, behavioral changes and generalized tonic-clonic seizures, was formulated after COVID-19 diagnosis.[52] A brain MRI showed hyperintensities on FLAIR and T2-weighted sequences in the claustrum bilaterally, a potential marker of autoimmune encephalitis.[53] The steroid and immunomodulatory therapy undertaken on the basis of this presumed diagnosis resolved the symptoms.

Monti *et al.* reported a refractory status epilepticus associated with the finding of anti-NMDAR antibodies in CSF in a 50-year-old patient with fever and psychiatric symptoms and confirmed SARS-CoV-2 infection.[54]

Zambrenau *et al.* described a 66-year-old female with amnesia, confusion, and generalized crisis and asymptomatic COVID-19 infection, in which an MRI detected symmetrical T2 and FLAIR hyperintensities in mesial temporal lobes and medial thalami and upper pons, compatible with a diagnosis of limbic encephalitis.[55]

A possible clinical case of post-infectious brainstem encephalitis associated with SARS-CoV-2 was described in a 65-year-old woman with generalized myoclonus, ocular flutter with convergence spasm and hyperekplexia, with clinical improvement after steroid therapy.[56]

Medical literature also reported few cases of Acute hemorrhagic leukoencephalitis (AHLE), a rare and potential life-threatening complication of acute disseminated encephalomyelitis (ADEM), characterized by multifocal, asymmetric white matter lesions of variable size with microhemorrhages or lesions involving the splenium of the corpus callosum.[57]

Guillain-Barré Syndrome

Guillain-Barré Syndrome (GBS) is an acute inflammatory demyelinating polyradiculoneuropathy (AIDP), often with monophasic course, which usually reaches its plateau by 4 weeks. It is characterized by progressive, ascending, bilateral, flaccid limb paralysis with deep tendon hyporeflexia, frequent sensory disturbances and sometimes cranial nerve involvement. In about two-thirds of patients there are signs of autonomic dysfunction and in one-fourth of cases GBS is complicated by respiratory failure and assisted ventilation may be necessary.[58] Other GBS variants include the axonal forms (AMAN or acute axonal neuropathy and AMSAN, acute motor and sensory axonal neuropathy), the Miller-Fisher Syndrome (MFS), and the acute pandysautonomia. GBS is considered a post-infectious disorder commonly preceded by infection or other immune stimulation, that induce an aberrant immune response against peripheral nerves and spinal roots, probably due to "molecular mimicry" mechanism.[59] Diagnosis of GBS is basically clinical, while electrophysiology and CSF analysis are supportive. Specific serum anti-ganglioside antibodies have been found in association with GBS, including anti-GM1 and anti-GQ1b. Inpatient care of GBS includes intravenous immunoglobulins (IVIG) or plasma exchange (PE), which are equally effective. Outcome is variable with most patients make substantial recovery within months to years due to the resolution of immune-mediated process and endogenous repair of peripheral nerves.[59]

Increasing numbers of reports of COVID-19 associated autoimmune neuropathies have been published since the beginning of the pandemic. In a recent systematic review of 42 patients from 13 countries (mostly in Europe), from the 1st January to the 30th June 2020, Uncini *et al.* analyzed the salient features and prognosis of SARS-CoV-2 associated GBS.[60] The diagnosis of SARS-CoV-2 infection was made by RT-PCR analysis of nasopharyngeal swabs in 85.7% of cases and, when negative, by serology. The median age was 57.5 years and the majority of patients were men (64.3%). The median interval between SARS-CoV-2 symptoms and GBS

onset was 11.5 days, with a range from 3 to 28 days. For a clinical diagnostic classification, the majority of patients (71.4%) presented the classic GBS form with lower limb symmetric weakness, sensory symptoms and deep tendon hyporeflexia, whereas 4.8% had a paraparetic form, 7.1% facial diplegia with or without paresthesia, 4.8% cranial polyneuritis, 7.1% MFS and finally 4.8% ataxic neuropathy. Dysautonomic dysfunction was detected in 19.5% of cases. Twelve patients were admitted to intensive care unit after GBS diagnosis because of respiratory failure, but it was difficult to distinguish the role of SARS-CoV-2 related interstitial pneumonia from respiratory failure due to GBS. Globally, 80.5% of patients had electrophysiological features typical of AIDP, while the less common subtypes AMSAN and AMAN were detected in 13.9% and 2.8% of cases, respectively. CSF analysis was performed in 85.7% of patients and albuminocytologic dissociation was detected in 77.8% of cases. In 25 tested patients, the search of SARS-CoV-2 RNA in CSF was negative. Serum antigangliosides antibodies (tested in 52.4% of patients) were negative in 95.5% of cases and only one patient with MFS was positive for GD1b. MRI imaging showed thickening or contrast enhancement of cranial nerves and nerve roots in 40% of patients. Treatment with IVIG was performed in 87.5% of patients, while only 5% were treated with plasma exchange (PE). At follow-up, the majority of patients had a definite improvement (43.2%) or recovery (18.9%), whereas a minority has no improvement (10.8%) or minimal improvement (18.9%).[60] These data have been confirmed by a more recently published review which analyzed 52 studies for a total of 73 patients.[61]

Facial nerve neuropathy

SARS-CoV-2 associated peripheral facial nerve palsy has also been described. Lima *et al.* reported a case-series of eight patients with positive RNA RT-qPCR for SARS-CoV-2 in naso/oropharingeal swabs.[62] The mean age was 36 years. Facial palsy was the first symptom of SARS-CoV-2 infection in three patients, while in the remaining five cases facial weakness appeared from 2 to 10 days after the onset of other clinical manifestations. In all patients, tendon reflexes were normal and there were no sensory symptoms. CSF examination was normal in all cases, except for one patient with a mild protein elevation (50 mg/dL); in all eight patients RT-PCR for SARS-CoV-2 in CSF was negative. On MRI imaging, only one patient showed enhancement of intracanalicular portion of facial nerve. All patients were treated with steroids, five of them had full recovery, while three patients had some degrees of facial weakness after 30 days from facial palsy onset. Three mechanisms have been suggested for COVID-19 related facial nerve neuropathy: ischemia of vasa nervorum related to microthrombi and other vascular changes during SARS-CoV-2 infection, direct viral damage or demyelination triggered by the inflammatory process.[62]

Ischemic stroke

At present, there is still poor knowledge about the association between COVID-19 and stroke. One retrospective, observational analysis of consecutive COVID-19 patients admitted to Union Hospital, Wuhan, China from 16th January 2020 to 29th February 2020, reported that out of 221 patients with COVID-19, 11 (5%) developed acute ischemic stroke (AIS), one (0.5%) cerebral venous sinus thrombosis (CVST), and one (0.5%) cerebral hemorrhage.[63] Acute cerebrovascular disease (particularly ischemic stroke) was found to be more common in patients with severe COVID-19 disease compared to those with non-severe disease (5.7% *vs.* 0.8%), even though subjects in the first group were older and had more underlying comorbidities. They were also more likely to have increased inflammatory response and hypercoagulable state.

A New York case series reported five cases of patients with SARS-CoV-2 infection and a large vessel occlusion stroke.[64] Patients were all younger than 50, two of them with no risk factors, and they had a mean NIHSS of 17 on admission. A larger retrospective, observational case series of the Mount Sinai Health System in New York City over a three-week period (March-April 2020), found 53% SARS-CoV-2 positive out of 45 patients with large vessel occlusion stroke.[65] COVID-19 positive patients were significantly younger as compared to those tested

negative for SARS-CoV-2 (mean age of 59 years vs 74 years). Moreover, a doubling in the number of patients with large vessel occlusion stroke was observed as compared to the same previous year period and in the 15 months preceding the outbreak. This data was confirmed by other reports, strengthening the observation that COVID-19 associated ischemic strokes are more severe events, with worse functional outcome and higher mortality than non-COVID-19 related ischemic strokes.[66] However, it has also been hypothesized that the stay-at home recommendations and the general fear of the hospital during the COVID-19 pandemic, may have prevented patients with minor stroke from presenting to the hospital.[66] Nevertheless, a recent study in Barcelona reported that initial stroke severity was not different between patients with stroke admitted in March 2019 and March 2020.[67]

A more recently published report on a large cohort of patients from 54 health care facilities found a low occurrence (1.3%) of ischemic stroke among COVID-19 patients (103 out of 8163 analyzed).[68] In comparison, 199 patients (1.0%) developed acute ischemic stroke among 19513 patients in whom COVID-19 infection was not diagnosed. Mean age of ischemic stroke patients with and without COVID-19 (68.8±15.1 *versus* 71.0±14.9) and prevalence of vascular risk factors were similar among the two groups. On the other hand, the proportion of patients with prior cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, atrial fibrillation and congestive heart failure) was significantly higher among COVID-19 patients with AIS compared to those without stroke. Interestingly, ischemic stroke patients with and without COVID-19 were treated similarly in the acute phase, as regards intravenous thrombolysis (1.0% versus 1.0%; P=0.98) or mechanical thrombectomy (1.0% *versus* 1.0%; P=0.98). The risk of discharge to destination other than home or death doubled with occurrence of AIS in COVID-19 patients. Other authors confirmed that hypertension, dyslipidemia and diabetes are the main risk factors associated to ischemic stroke in COVID-19 patients.[69]

The three main mechanisms reputed to be responsible for the occurrence of ischemic strokes in COVID-19 are: hypercoagulable state, vasculitis, and cardiomyopathy.

Lee *et al.* reported that 20-55% of patients hospitalized due to COVID-19 had laboratory evidence of coagulopathy, with increased levels of D-dimer to above twice normal, slight prolongation of prothrombin time (1-3 times above normal), mild thrombocytopenia, and also decreased fibrinogen levels in late disease.[70]

Antiphospholipid antibodies (anticardiolipin and anti-β-glycoprotein I antibodies) have been documented in COVID-19 patients with multiple hemispheric infarcts and with concomitant elevation of prothrombin time, activated partial thromboplastin time (aPTT), fibrinogen, D-dimer, and CRP.[71] In a French study, 45% of patients with COVID-19 had a positivity of Lupus anticoagulant, while 10% presented anticardiolipin antibody.[72] In another study, lupus anticoagulant was documented in 91% of COVID-19 patients who had an elevated aPTT, but the incidence of venous thromboembolism was low in this group.[73] The meaning of these findings is unclear. SARS-CoV-2 causes clinical COVID-19 by its affinity for the ACE2 receptors that are expressed in the lungs, heart, kidneys, and small bowel. These receptors are also abundant in the vascular endothelium,[74] where infection elicits an inflammatory response (a lymphocytic "endothelitis") that has been postulated as one of the substrates for the thrombotic complications of this infection.[75] Vessels may not only be inflamed by a direct local effect of SARS-CoV-2 on the ACE2 receptors in the vascular endothelium, but also by a systemic immune response to the pathogen ("cytokine storm"). In the case of COVID-19, several cytokines, including IL-1B, IFN-γ, IP10, and MCP1 have been found to be markedly elevated, especially in patients with severe disease and high rates of mortality.[76]

While the relevance of microvascular thrombosis is becoming increasingly clear, a substantial proportion of patients with severe COVID-19 also develops large vessel occlusion.

Some of the proposed mechanisms are paradoxical embolism from deep venous thrombosis, or cardiogenic embolism from intracardiac thrombus in patients with "cardiomyopathy." There may be a direct invasion by the virus,

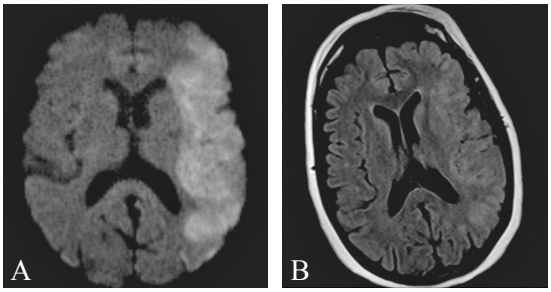

Figure 1.—Brain MR images in a patient with COVID-19 and an acute ischemic stroke in the territory of left medium cerebral artery: A) DWI-weighted sequence; B) FLAIR-weighted sequence.

causing a myocarditis, with resultant injury and even death of cardiomyocytes. This may be due to the affinity of the virus for ACE2 receptor and its ensuing downregulation, leading to myocardial dysfunction.[77] The heart may also be indirectly affected by the systemic inflammatory state during the severe phase of the infection related to the cytokine storm.[78] There is also an increased cardiac stress due to respiratory failure and hypoxemia from ARDS, leading to stress cardiomyopathy. In addition, stimulation of the sympathetic nervous system could predispose to stress cardiomyopathy, cardiac arrhythmias and heart failure with preserved ejection fraction.[79, 80]

Treatment of COVID-19 ischemic stroke patients during the acute phase is challenging. Caution for stroke team members to avoid COVID-19 exposure, during clinical evaluation and conduction of imaging and laboratory procedures is mandatory. Practical guidelines and intra-hospital pathways must be set up in order to offer the best treatment (intravenous thrombolysis and mechanical thrombectomy) to stroke patients with suspected or confirmed COVID-19 infection (Figure 1).[81, 82]

Evidence synthesis

Delirium and confusion are common symptoms in COVID-19 patients but most frequently related to other underlying medical conditions such as hyponatremia, hypoxia, and fever. However, some evidence also suggests a specific SARS-CoV-2 related inflammatory effect on CNS.

The rarity of cases clinically consistent with encephalitis and the paucity of histopathological evidence of SARS-CoV-2 CNS direct invasion, suggests that SARS-CoV-2 is a possible but rare cause of brain infection.

The clinical picture of COVID-19 associated GBS seems to resemble that of classic GBS. Available data suggest a post-infectious immune mediated mechanism, although it is not possible to exclude a coincidental association and more extensive epidemiological studies are warranted. Since most of the described patients were asymptomatic for SARS-CoV-2 respiratory symptoms, the SARS-CoV-2 testing is mandatory in all patients with suspected GBS during the pandemic, in order to provide eventual rapid case isolation.

Facial nerve palsy seems to be a rare complication related to COVID-19, but a casually concomitant event cannot be ruled out.

Ischemic stroke represents the most frequent and severe complication during SARS-CoV-2 infection. A hypercoagulable state, endothelitis due to the "cytokine storm" and cardiomyopathy are the most likely hypothesized mechanisms, although the classical vascular risk factors are also determinants.

COVID-19 ischemic stroke patients have higher risk for severe disability and death compared with patients without COVID-19. Intra-hospital dedicated pathways need to be organized in order to avoid delay in thrombolysis or endovascular thrombectomy.

Conclusions

The exact role of SARS-CoV-2 in development of neurological manifestations during COVID-19 is still unclear. SARS-CoV-2 detection is lacking in the brain, but it has been localized in vasculature and immune cells. Anosmia, delirium, encephalopathy and stroke are the most frequently associated conditions. Loss of smell seems to be due to SARS-CoV-2 infection of the olfactory epithelium, rather than to the direct invasion of neuronal cells. Delirium is often related to systemic abnormalities such as hyponatremia, hypoxia or fever although some evidence suggests that it is caused by SARS-CoV-2 related microvascular and inflammatory mechanisms. Encephalopathy and stroke are the most serious

and common syndromes associated with COVID-19, mostly related to the inflammatory and hypercoagulable status.

In conclusion, comparing to the respiratory manifestations, neurological syndromes are rare. However, the continuing pandemic will highly increase the number of patients with neurological complications (stroke and encephalitis among the most serious), and we could expect a rise of the global disability prevalence in the next future. Acute stroke treatment pathways will need to be redesigned in order to guarantee the rights to the access and delivery of care to critically ill COVID-19 patients.

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