Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19 and the central nervous system

Safwan O. Alomari[a], Zaki Abou-Mrad[a], Ali Bydon[b,*]

[a] Neurosurgery Department, American University of Beirut Medical Center, Beirut, Lebanon
[b] Neurosurgery Department, Johns Hopkins University School of Medicine, Baltimore, MD, USA

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1. Introduction

At the beginning of December 2019, Wuhan, the capital of Hubei Province and a large city of approximately 11 million persons located in the central region of the People's Republic of China, witnessed an outbreak of a cluster of persons with viral pneumonia of unknown agent. On 7 January 2020, a group of Chinese scientists succeeded to identify the etiological agent of the epidemic as a previously unknown coronavirus, and they named it by 2019-nCoV (for 2019 novel coronavirus) [1,2]. At the beginning of January 2020, the COVID-19 virus has spread to other countries including Japan, Korea, Thailand, Iran, and the United States [3].

The novel coronavirus disease received an official name by the World Health Organization (WHO) as Coronavirus Disease 19 (COVID-19), on February 11, 2020 [4]. Later, the International Committee on Taxonomy of Viruses has suggested SARS-CoV-2 as the name of the virus that causes COVID-19 [5]. The World Health Organization declared the virus outbreak a pandemic on March 11, 2020 [6].

The primary symptoms of COVID-19 include fever, dry cough, and fatigue [7]. However, some patients diagnosed with COVID-19 have not shown these typical symptoms, at the time of diagnosis; instead, they have exhibited only neurological symptoms as the initial symptoms, such as the following: non-specific manifestations including headache, malaise and unstable walking, cerebral hemorrhage, cerebral infarction; as well as other neurological diseases [8].

Until now, we have scarce literature on COVID-19 aspects related to the nervous system. In this article, the authors discuss the neurological aspects of COVID-19 and provide a concise review of the reported literature on this field.

2. Routes of reaching the nervous system and possible pathophysiology

For a given virus, the ability to infect certain cells, tissues, or even species while not affecting others is referred to as viral tropism [9]. This viral tropism, allowing a virus to replicate in and affect certain body tissues, would then lead to the symptomatic presentation of that virus. A major factor that dictates this tissue selectivity, is the virus's ability to bind and take over specific host cell surface receptors [9]. Recent research on SARS-CoV-2 has shown that similarly to SARS-CoV, this virus can invade tissues by binding to the angiotensin-converting enzyme 2 (ACE2) receptor on certain host cells (Fig. 1A) [10]. This binding is mediated by the spike protein found on the surface of SARS-CoV-2 and was found to have up to 20 times the binding affinity of SARS-CoV [11]. While its mRNA can be found in virtually all body tissues, the ACE2 receptor is mostly expressed in lung alveolar epithelial cells, small intestine enterocytes, vascular endothelial cells, in addition to airway epithelial cells, and kidney cells [12]. More recently, it was reported that brain also expresses ACE2 receptors on glial cells and neurons and this is most prominent in the brainstem, the paraventricular nucleus (PVN), nucleus tractus solitarius (NTS), and the rostral ventrolateral medulla which all play a role in cardiovascular regulation [13].

On the other hand, viral tissue invasion does not solely rely on the presence of certain receptors and the ability to hijack them. Recent studies on the novel coronavirus have shown that, like its predecessors, a substantial part of its symptomatology can be explained by the cytokine storm it triggers, leading to a systemic inflammatory response syndrome (SIRS) or SIRS-like phenomenon (Fig. 1B) [14,15]. This inflammation is mediated by interleukins (IL-6 and IL-8) released by

* Corresponding author.
E-mail address: abydon1@jhmi.edu (A. Bydon).

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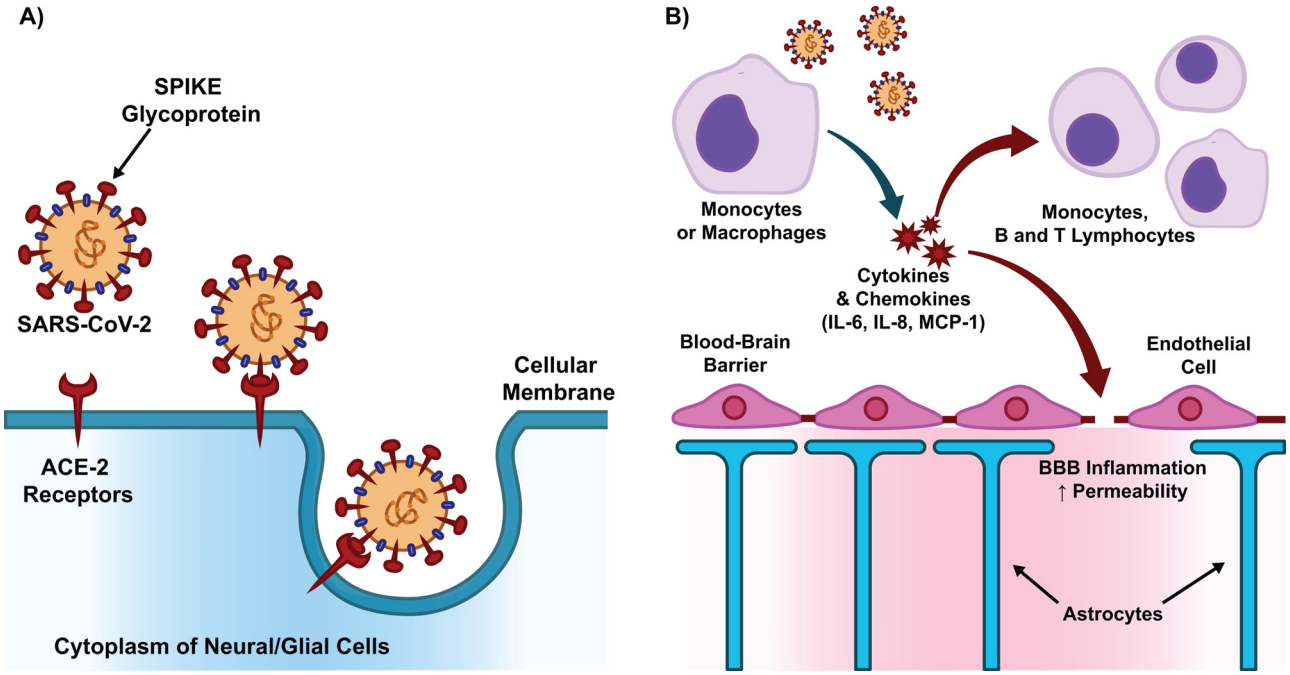

Fig. 1. Mechanisms of neurological manifestations by SARS-CoV2, A) through ACE-2 receptors and B) through cytokine release syndrome.

monocytes and macrophages to stimulate other monocytes and both B and T lymphocytes, in addition to monocyte chemoattractant protein-1 (MCP-1), a chemokine responsible for the transmigration of the monocytes across the blood-brain barrier (BBB) [16,17]. Thus, this can then lead to the inflammation of the BBB and increase its permeability which facilitates the passage of more inflammatory cytokines and chemokines into the brain and can exacerbate the neuroinflammation and neurological symptoms experienced by the patient [18].

Additionally, during previous coronavirus epidemics (SARS-CoV and MERS-CoV), animal studies on transgenic mice showed that both of these viruses were able to reach the brain when introduced intranasally [19,20]. St-Jean et al. (2004) reported that viral antigens could be detected in all brain regions, only 7 days after viral nasal inhalation in mice [21]. This brain entry is possibly mediated by the olfactory nerves and olfactory bulb which are conveniently accessible by the virus from its intranasal location. Interestingly, mice experiments with ablation of the olfactory nerves have shown a substantial decrease in coronavirus (Mouse Hepatitis Virus) neuroinvasion [22].

Finally, it is important to mention that the virus can also cause CNS damage and neurological symptoms without invading the brain itself. As respiratory viruses invade the lungs and cause inflammation, this leads to alveolar and lung tissue damage. Inflammation and edema affect the oxygen exchange that happens at the alveolar-capillary interface leading to hypoxemia and subsequently brain hypoxia with vasodilation, hyperemia and brain edema (Fig. 2) [23]. This would then manifest itself starting with headaches and, if kept unchecked, could cause a change in the level of consciousness and even coma [23]. Being a respiratory virus itself, SARS-CoV-2 has been shown to cause significant hypoxemia in many of the patients [24] and hence, this possible pathway of brain injury remains a factor in its symptomatic profile.

3. Neuroinvasive potentials of coronavirus and its role in respiratory failure

There is still a debate regarding the exact role of brainstem invasion by the virus in causing respiratory failure in COVID-19 patients. Li and colleagues (2020) have suggested that SARS-CoV-2 can enter the brain, and it might be the cause of the respiratory failure in patients with COVID-19 [25]. On the other hand, Turtle (2020) has reported that respiratory failure alone does not suggest central nervous system invasion by SARS-CoV-2. Turtle relied on certain points to support his conclusion; patients with pneumonia typically develop hypoxic, or type 1 respiratory failure, with low CO2 levels and a raised respiratory rate, while brain failure typically leads to type 2 respiratory failure and involves low oxygen, high CO2 and reduced respiratory rate. He mentioned that these manifestations of type 2 respiratory failure were not reported to any great degree in any of the case series of patients from China 9. He also stated that if the neuroinvasion of the virus would be the cause of respiratory failure, the virus should be detected in the cerebrospinal fluid of these patients [26,27].

4. Among COVID-19 patients, are smokers at higher risk for brain infection?

Recently, Olds & Kabbani (2020) raised the question of nicotine associated neurological comorbidity in COVID19 patients depending on published evidence that the viral target receptor ACE2 is expressed in the brain and functionally interacts with nAChRs [29,30]. They considered neural cells and astrocytes (especially in the hypothalamus and brain stem) more prone to infection in smokers because nicotine stimulation of the nAChR was found to increase ACE2 expression within them (Fig. 3) [28–30]. ACE2 signaling pathway is believed to counteract oxidative stress and neuroinflammation, thus, disruption in ACE balance can lead to neurodegeneration of dopaminergic neurons [31] or impairment in cholinergic pathways which might participate in the progression of Alzheimer's disease [32].

We believe that this association between smoking and COVID-19 neurological manifestations, if proven, might be of great impact, since all the people worldwide are currently at high risk of being exposed to smoking and COVID-19 infection. Hence, more studies are strongly encouraged in this regard.

5. COVID-19 associated neurological manifestations

Data on COVID-19 is not yet complete or comprehensive as we are still in the midst of the active pandemic [33–36]. However, early research from Wuhan, China reported that the most common symptoms

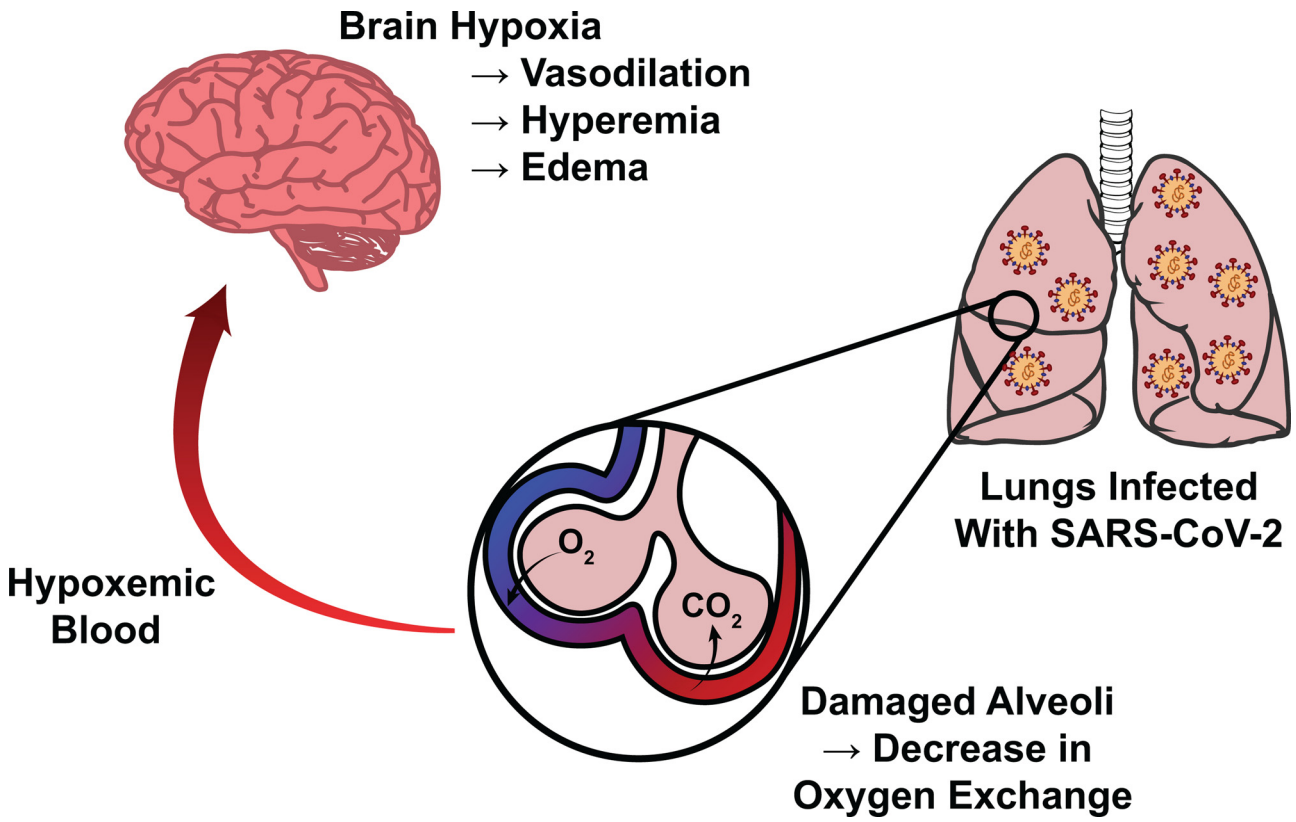

Fig. 2. Indirect brain injury in COVID-19 patients.

that appeared among patients with COVID-19 included fever (98.6 %), fatigue (69.6 %), and a dry cough (59.4 %) [37]. While these symptoms are typical of respiratory viruses, other sources additionally reported neurological symptoms and manifestation in up to 36.4 % of 814 retrospectively studied COVID19 patients (Table 1) [8].

5.1. Acute transverse myelitis

Acute transverse myelitis, also referred to just as transverse myelitis (TM), is a rare neurological disturbance consisting of an inflammation of the spinal cord. Patients with TM may present with sensory changes, weakness and autonomic dysfunctions [38]. While no preceding infection was found in some of the reported cases, transverse myelitis is usually associated with common viral infections such as Varicella Zoster (VZV), Herpes viruses (HSV-2 and Cytomegalovirus) and enteroviruses [39]. In February of 2020, in Wuhan, China, an elderly patient presented to the hospital with fever and fatigue with no previous contact with COVID-19 patients [40]. He was found to have COVID-19 based on PCR tests of his nasopharyngeal secretions. After a week of hospitalization, he developed lower extremity weakness and paresthesia progressing to paralysis, along with urinary and bowel incontinence. He was diagnosed with post-infectious acute transverse myelitis. IgM antibodies of the most common infectious organisms associated with TM (Mycoplasma pneumoniae, Ebstein-Barr Virus, and Cytomegalovirus) were negative, and it was concluded that the cause of his post-infectious TM was SARS-CoV-2 virus. Although this case report provides a strong basis for COVID-19 associated transverse myelitis, it is worth noting that CSF serological tests and a spinal cord MRI were not performed [40].

In addition, Munz et al. (2020) reported a case of a 60-year-old COVID-19 patient who developed multifocal transverse myelitis 10 days after developing COVID-19 pneumonia symptoms. T2-weighted MRI of the spine showed evidence of transverse myelitis [41,42]. All work-up tests for the typical viral causes of transverse myelitis came back negative. The patient was able to improve on multiple empiric treatments, such as intravenous immunoglobulins, steroids, and antivirals [41].

5.2. Viral encephalitis and meningitis

Encephalitis and meningitis can be caused by viruses like Herpes Simplex Virus, Rabies and others [43]. They can present with an acute onset fever, nausea and vomiting along with neurological manifestations; including headache, altered level of consciousness, behavioral disturbances, seizures, photophobia, or hemiparesis [43,44]. While treatable in most cases, early detection and appropriate treatment are important to avoid the development of long-term and more severe complications. If left untreated, mortality rates can reach up to 70 % as reported in certain cases of herpes related encephalitis and meningitis [45]. Recently, during the COVID-19 pandemic, a 24-year-old man was transferred to the University of Yamanashi Hospital in Japan after being found unconscious in his home [46]. He reported typical signs of meningitis and encephalitis. CSF was found to be positive for SARS-CoV-2, while his nasopharyngeal secretions were negative. This case provides evidence of the neuroinvasive potential of SARS-CoV-2 and its role in the development of meningitis/encephalitis. Besides, it also raises the concern of having patients with COVID-19 that have negative nasopharyngeal swabs for the virus. Another case of COVID-19-associated encephalitis was reported by Efe et al. (2020) in Turkey [47]. A 35-year-old female patient was found to be positive for SARS-CoV-2 after undergoing a left anterior temporal lobectomy for refractory seizures [47]. This patient's pre-operative magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) result were suggestive of high-grade glioma, however, a biopsy taken during her surgery was nondiagnostic. Knowing that encephalitis may often be indistinguishable from other CNS pathology on MRS [48], Efe et al. thus reported that their patient could have a case of COVID-19-associated encephalitis mimicking a glioma [47].

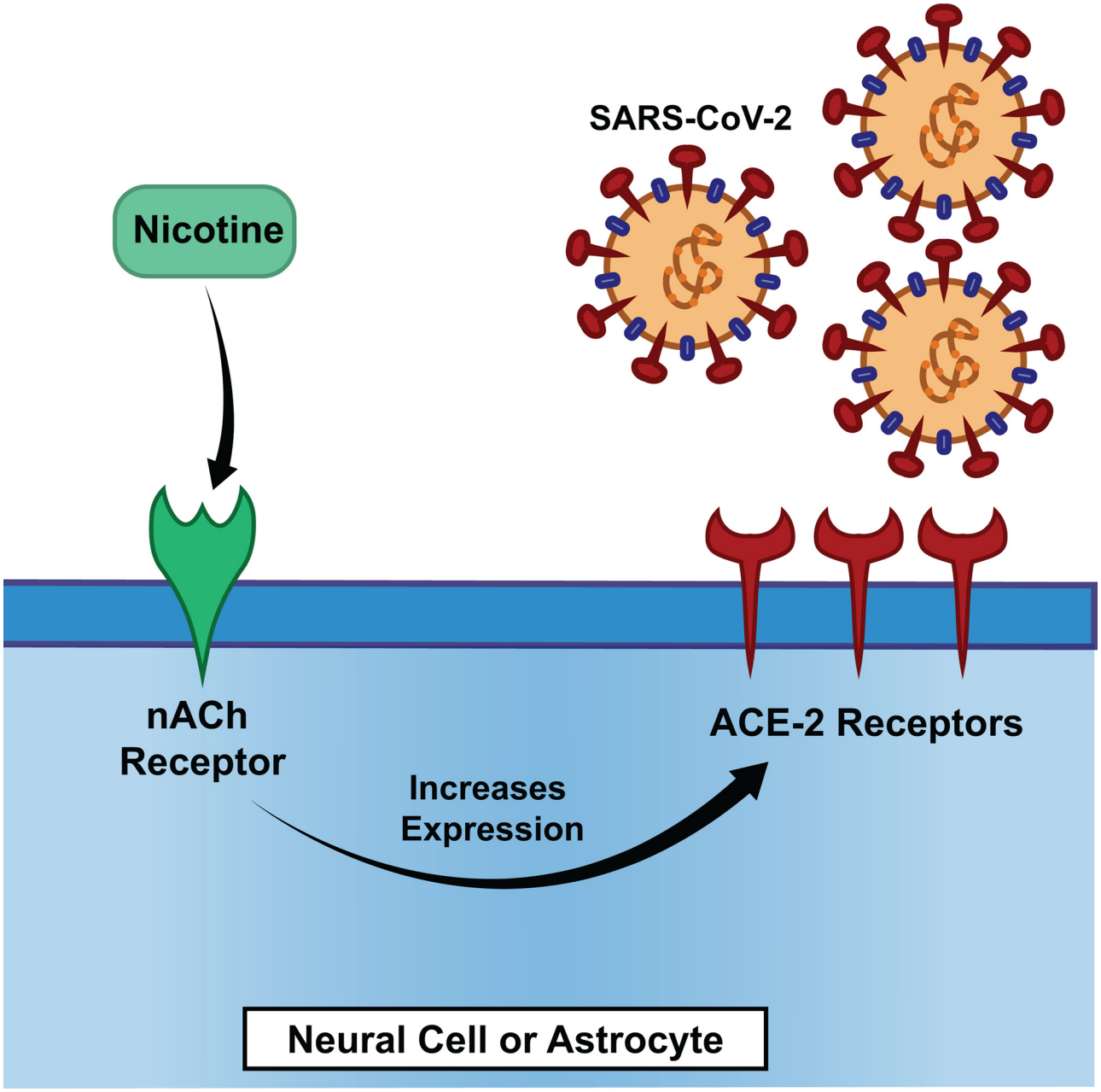

Fig. 3. Smoking aggravates CNS manifestations of COVID-19.

Moreover, Mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) was reported in a COVID-19 patient [49]. MERS is an encephalitis/encephalopathy syndrome that is associated with viral infections [50,51]. This was the first reported case of MERS associated with coronavirus infection, which adds to the expanding list of differential diagnoses to be considered in a COVID-19 patient with neurological signs, most notably; cerebellar ataxia and disturbance in consciousness [49,52,53].

5.3. Infectious toxic encephalopathy

Infectious toxic encephalopathy, also known as acute toxic encephalitis, is a rare type of reversible brain dysfunction syndrome associated with cerebral edema, with no evidence of inflammation on cerebrospinal fluid analysis. Metabolic disorders, systemic toxemia, and hypoxia are considered contributing factors during the process of acute infection [54–56]. It has a wide clinical presentation. Patients with a mild form of the disease may develop headache, dysphoria, or delirium. While more severe forms may lead to disorientation, paralysis, loss of consciousness and even coma. Acute viral infection is a known cause of this disease. COVID-19 infection has been suggested as a cause of this disease depending on many findings. First, patients with COVID-19 may suffer from severe hypoxia and viremia [57], which might eventually lead to toxic encephalopathy. Moreover, around 40 % of patients with COVID-19 develop neurological symptoms and other brain dysfunction symptoms [8]. Added to that, brain edema has been detected in autopsy studies of brain tissue of COVID-19 patients [58]. Collectively, these proposals provide evidence that COVID-19 could cause infectious toxic encephalopathy, although more detailed researches are still required.

5.4. Acute hemorrhagic necrotizing encephalopathy

Acute Hemorrhagic Necrotizing Encephalopathy (ANE) occurs most commonly in the pediatric age group but reported to be in adults as

Table 1
Coronavirus related neurological manifestations.

Author(s) (Year)	Neurological Complication(s)	Time Till Onset of Complication(s)	Comments
Zhao, K., et al. (2020)	Acute Transverse Myelitis	7 days	CSF serological tests and spinal cord MRI were not done due to the pandemic.
Munz, M., et al. (2020)		10 days	
Moriguchi, T., et al. (2020) [46]	Viral Meningitis/Encephalitis	9 days	The patient had nasopharyngeal secretions negative for SARS-CoV-2, but his CSF tested positive.
		14 days	
Efe, I., et al. (2020) [47]		Not reported	Patient developed Mild encephalitis/encephalopathy with a reversible splenial lesion (MERS).
Hayashi, M., et al. (2020) [49]			
Guo, Y.-R., et al. (2020) [57]	Infectious Toxic Encephalopathy	N/A	No reports directly associating SARS-CoV-2 with Infectious Toxic Encephalopathy, but the association is suggested based on the hypoxemia caused by COVID-19.
Mao, L., et al. (2020) [8]		Median 1 – 2 days	
Xu, Z., et al. (2020) [58]		N/A	
Poyiadji, N., et al. (2020) [62]	Acute Hemorrhagic Necrotizing Encephalopathy (ANE)	3 days	Brain MRI consistent with ANE in the setting of COVID-19, with the workup for other possible etiologies being negative.
Dixon, L., et al. (2020) [63]		10 days	
Sachs, J.,et al. (2020) [65]	Leukoencephalopathy	16 days	Association between leukoencephalopathy and COVID-19 remains uncertain with hypoxemia being the most likely possible cause.
Lang, M., et al. (2020) [67]		Mean of 26 days	
Radmanesh, A., et al. (2020) [68]		Mean of 27 days	
Yeh, E.A., et al. (2004) [70]	Acute Disseminated Encephalomyelitis (ADEM)	5 days	Not a case of COVID-19. However, this case was one of the first to show a coronavirus-associated ADEM. HCoV-OC43 is phylogenetically related to SARS-CoV-2 [71].
Wang, D., et al. (2020) [37]	Acute Cerebrovascular Disease	N/A	No reports directly associating it with SARS-CoV-2. However, respiratory-related infections are independent risk factors for acute cerebrovascular disease.
Cavalcanti, D., et al. (2020) [79]		Median of 7 days	
Yaghi, S., et al. (2020) [80]		Mean of 10 days	
Valderrama, E.V., et al. (2020) [81]		7 days	
Helms, J., et al. (2020) [82]	Agitation, confusion, diffuse corticospinal tract signs and dysexecutive syndrome	N/A	Observational study on 58 patients with SARS-CoV-2 infection.
Filatov, A. et al. (2020) [83]	Encephalopathy	N/A	Reported in an elderly patient with multiple comorbidities, however.

well. Characteristic radiological features include multiple symmetric lesions with thalamic involvement. Cerebral white matter, brain stem, and cerebellum are other reported areas to be involved [59].

Acute necrotizing encephalopathy (ANE) is a rare complication of viral infections (including influenza viruses). Intracranial cytokine storms, with subsequent blood-brain barrier breakdown, is the most accepted theory behind ANE after viral infections [60]. Recent evidence showed that patients with severe COVID-19 might have a cytokine storm syndrome [61].

Poyiadji et al. (2020) were the first to report a case of ANE in a COVID-19 patient.

A female in her fifties presented with a 3-day history of fever, cough, and altered mental status. Laboratory work-up was negative for influenza, with the diagnosis of COVID-19 made by detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) PCR. CSF bacterial culture showed no growth after 3 days, and tests for herpes simplex virus 1 and 2, varicella-zoster virus, and West Nile virus were negative. Testing for the presence of SARS-CoV-2 in the CSF was unable to be performed. CT scan demonstrated symmetric hypoattenuation within the bilateral medial thalami, and CT angiogram and CT venogram were negative. Brain MRI showed hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions. These imaging findings were consistent with ANE and they concluded that ANE was caused by SARS-CoV2. The authors reported that the patient was treated by intravenous immunoglobulin but high-dose steroids were not initiated due to concern for respiratory compromise [62]. More recently, Dixon et al. (2020) reported another case of ANE in a 53-year-old COVID-19 patient with aplastic anemia [63]. The patient present 10 days after onset of symptoms and was shown to have swelling in the brainstem on CT scan. Brain MRI showed multiple symmetric hemorrhagic lesions in the brainstem and different nuclei. The patient died 8 days after hospital admission [63].

5.5. Leukoencephalopathy

Leukoencephalopathy is the name given to the group of diseases that affect the white matter of the central nervous system [64]. Since the beginning of the COVID-19 pandemic, many reports have showed radiological evidence of white matter injury in patients with SARS-CoV-2 infections [65,66]. Sachs et al. (2020) first reported a case of COVID-19-associated leukoencephalopathy in a 59 year-old patient that deteriorated 16 days after developing COVID-19 symptoms. MRI and CT of the brain revealed diffuse white matter lesions in addition to microhemorrhages in the corpus callosum. However, the authors did not provide a solid evidence that leukoencephalopathy was specifically due to the COVID-19 infection [65]. Lang et al. (2020) reported 6 COVID-19 patients who showed symmetric T2 FLAIR hyperintense signal with restricted diffusion in the deep white matter, and sparing of the subcortical U-fibers on brain MRI [67]. The authors concluded that hypoxemia experienced by COVID-19 patients was the contributing factor for the development of delayed post-hypoxic leukoencephalopathy [67]. More recently, Radmanesh et al. (2020) also reported similar radiological features in 11 COVID-19 patients [68]. Although it is mandatory to rule out other etiologies in these critical patients, such as hemorrhagic encephalopathy, sepsis-associated encephalopathy, posterior reversible encephalopathy syndrome in addition to other toxic and metabolic causes [68], leukoencephalopathy should be considered in COVID-19 patients.

5.6. Acute disseminated encephalomyelitis (ADEM)

Acute Disseminated encephalomyelitis (ADEM) is an autoimmune demyelinating disease of the CNS characterized by a sudden and widespread inflammation. It affects mainly children and younger adults, and it is usually triggered by viral infections, but unlike viral encephalitis, it is not due to viral neuroinvasion [69]. No cases of ADEM

in patients with COVID-19 have been reported in the literature yet. However, there is a case of a 15-year old boy that presented to the Children's Hospital of Buffalo with signs and symptoms of ADEM while also reporting a history of an upper respiratory tract infection a week before [70]. This patient was given a presumed diagnosed of ADEM (MS could not be ruled out) and was found to have Human Coronavirus OC43 (HCoV−OC43) in his CSF and nasopharyngeal secretions by RT-PCR. This was the first reported case of coronavirus-associated demyelinating disease in a pediatric patient. While SARS-CoV-2 is not yet associated with such cases, HCoV−OC43 is a member of the beta-coronavirus family to which SASR-CoV-2 also belongs. In addition, the two viruses were shown to be closely related phylogenetically and are two of the only seven known human coronaviruses [71].

5.7. Acute cerebrovascular disease

Although we have evidence that respiratory-related infections are an independent risk factor for acute cerebrovascular events [72,73], evidence specific to SARS-CoV-2 infection is still far from conclusive. Strokes were reported to have an incidence close to 2% in hospitalized patients with COVID-19 [8].

One of the early studies in this field was done by Muhammad et al. (2011) on experimental mouse models and suggested that influenza virus can aggravate ischemic brain injury via triggering a cytokine cascade and can increase the risk of cerebral hemorrhage after treatment with tissue-type plasminogen activator [74]. The infection of CoV, especially SARS-CoV-2, has been widely reported to cause cytokine storm syndromes, which may be one of the factors that CoV causes acute cerebrovascular disease [15,61]. In addition, critically ill patients with severe SARS-CoV-2 infections often show elevated levels of D-dimer and severe platelet reduction, which may render these patients prone to acute cerebrovascular events [37].

Interestingly, several recent reports showed that COVID-19 patients have a propensity to develop a hypercoagulable state [75–78]. A brief report of three COVID-19 patients, who were young (mean age of 34 years) and previously healthy, with only one of the three having a risk factor for hypercoagulability (oral contraceptives) eventually developed cerebral venous thrombosis following their infection [79]. In addition, a retrospective cohort study in New York City, showed that COVID-19 patients had higher National Institutes of Health Stroke Scale scores at admission, in addition to higher peak D-dimer values and a significantly higher mortality rate when compared with non-infected patients with strokes [80,81].

5.8. Other reported neurological manifestation

Helms et al. (2020) published their observational study on 58 patients about neurologic features in severe SARS-CoV-2 infection; they reported agitation was present in 40 patients (69 %), diffuse corticospinal tract signs, including hyperreflexia, bilateral extensor plantar reflexes and ankle clonus, were present in 39 patients (67 %). A total of 26 of 40 patients were noted to have confusion according to the Confusion Assessment Method for the ICU and 15 of 45 (33 %) had a dysexecutive syndrome consisting of disorientation, inattention, or poorly organized movements in response to command [82].

6. Neuro-investigations

6.1. Radiology

In addition to the previously mentioned imaging findings of COVID-19 patients with neurological complications, Helms et al. reported that 13 patients underwent Magnetic resonance imaging (MRI) of the brain because of unexplained encephalopathic features. Leptomeningeal enhancement was noted in 8 patients. 3 patients had radiological findings of stroke as the following: 2 patients had a small acute ischemic stroke with focal hyperintensity on diffusion-weighted imaging and an overlapping decreased apparent diffusion coefficient, and 1 patient had a subacute ischemic stroke with superimposed increased diffusion-weighted imaging and apparent diffusion coefficient signals. Interestingly, these patients with documented stroke on imaging were asymptomatic with no neurological manifestations, making the neurological course of the disease unpredictable and choosing the appropriate time to proceed with neurological imaging more challenging. To note, Bilateral frontotemporal hypoperfusion was noted in all 11 patients who underwent perfusion imaging [82].

6.2. Electroencephalography

Although there are no other reports on electroencephalography findings in COVID-19 patients, it is worth mentioning that Helms et al. reported in their paper that in the 8 patients who underwent electroencephalography, only nonspecific changes were detected; and only one patient had diffuse bifrontal slowing consistent with encephalopathy [82]. Similarly, Filatov et al. (2020) reported EEG findings of bilateral slowing and focal slowing in the left temporal region with sharply countered waves in patients with COVID-19 associated encephalopathy [83].

6.3. Cerebrospinal fluid (CSF) studies

Helms et al. reported that CSF samples obtained from 7 patients were all negative for SARS-CoV-2 and none showed cells. However, examination of CSF samples revealed oligoclonal bands were present in 2 patients, with an identical electrophoretic pattern in serum. Protein and IgG levels were elevated in 1 patient [82]. These findings might support the theory that the SARS-CoV-2 can cause neurologic manifestations indirectly, probably by triggering a reaction, rather than by direct invasion of the nervous system, although CSF was found to be positive for SARS-CoV-2 in another report [46].

7. Conclusion

As the number of patients with COVID-19 is increasing worldwide, it is necessary to stress on the importance of the atypical clinical presentations (including those related to the nervous system) of COVID-19 infection, since they might be the initial manifestations. Patients with COVID-19 infection should be evaluated early for neurological symptoms. Timely analysis of cerebrospinal fluid and early appropriate management of infection-related neurological complications might be the key to improve the prognosis of critically ill patients.

Since health-care providers might under-recognize these cases with atypical presentations, and these patients may represent a hidden source of the spread of the virus, we believe that literature on this regard should be sent by the international and local health committees to all health-care providers during this COVID -19 pandemic, to make sure that all providers are well informed and aware of these cases. Moreover, awareness campaigns addressing this issue should be directed to the population.

Since we have a scarce literature on this regard, more studies are deeply needed to enable the concerned committees to make evidence-based guidelines for prevention, early detection and appropriate management of these cases.

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Declaration of Competing Interest

None.

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