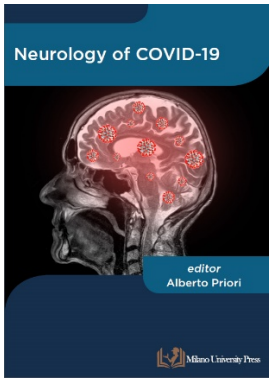

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Chapter 7. Encephalomyelitis in COVID-19

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Introduction

After the first cases of the novel coronavirus disease 2019 (COVID-19) were reported in Wuhan, China, in December 2019, the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly became a pandemic, forcing health-care systems and governments across the world to take measures to contain the infection, and simultaneously engaging the health community in a race against time to develop effective treatments[1,2]. The SARS-CoV-2 is a positive-sense, enveloped, single-stranded RNA virus that primarily affects the lungs, and the recent disease has been designated as COVID-19. As with many other flu-like syndromes, the most common symptoms of COVID-19 are fever and dry cough, whereas other manifestations, including rhinorrhea and gastrointestinal symptoms, are much less frequent[3]. Reports from China at the beginning of the outbreak, and from other countries afterwards, have clearly demonstrated that most patients (80%) have mild symptoms with no or mild pneumonia; among those patients with more significant symptoms, 15% have severe respiratory distress and 5% have respiratory failure, septic shock, and/or multi- organ failure[4,5]. Although the scientific community is still trying to understand the syndromic complexity of COVID-19, growing evidence indicates that the disease is not limited to the respiratory system and that SARS-CoV-2 has an organotropism beyond the respiratory tract, including the kidneys, liver, heart, skin, and brain. COVID-19-associated neurological manifestations range from mild symptoms such as dizziness, headache, dysgeusia, or anosmia to severe disorders such as stroke, Guillain-Barré syndrome (GBS), acute hemorrhagic necrotizing encephalopathy, meningoencephalitis, and cerebral venous thrombosis. The frequency of reported neurological signs and symptoms is variable but, in spite of this, substantial. In an early Chinese retrospective study, 36.4% of 214 COVID-19 patients had neurological symptoms which included dizziness (16.8%), headache (13.1%), impaired consciousness (7.5%), dysgeusia (5.6%), and anosmia (5.1%)[5]. In Western studies, dysgeusia and anosmia are reported in many patients[6,7]. A French study reports that 49 out of 58 (84%)

COVID-19 intensive care unit (ICU) patients had neurological signs which included agitation (69%), confusion (65%), corticospinal tract signs (67%), and dysexecutive syndrome (33%)[8]. A study from a British referral center described cases of septic or para-infectious encephalopathy, autoimmune encephalitis including acute disseminated encephalomyelitis (ADEM), and GBS[9]. An Italian study also reported a wide range of encephalopathies during the first wave, including ADEM, limbic encephalitis, necrotizing hemorrhagic encephalopathies and meningoencephalitis[10]. In general, neurological complications have been reported to be more common in older age groups and patients with pre-existing comorbidities, including diabetes mellitus, hypertension, malignancies, immunological disorders, obesity, chronic respiratory disease, coronary artery disease, and liver failure[11]. Neurological abnormalities and manifestations have been described as the presenting symptom of SARS-CoV-2 in some patients, while in most cases the neurological onset followed the classical respiratory onset. More recently, there has been growing evidence favoring a relatively high neurological involvement in the so-called Long COVID. In fact, viral infections can damage the structure and function of the nervous system, manifesting as encephalitis, toxic encephalopathy, and post-infectious demyelinating disease[11,12]. Coronaviruses can invade the nervous tissues involving immune-functioning macrophages, microglia, or astrocytes[13] and cause nerve damage through direct infection pathways (circulatory and neuronal), hypoxia, immune injury, attacking ACE2 enzymes, and other mechanisms[14]. The involvement of the nervous system can be due to a direct action of these viruses on the nervous tissue and/or to an indirect action through the activation of immune-mediated mechanisms. While the first can be verified during the acute phase of the disease, the second is mostly apparent only days, weeks, or even months after the acute phase.

Encephalitis and myelitis as a possible manifestation of the disease

Different cases and reviews have consistently shown that patients with COVID-19 are at higher risk for developing CNS involvement, including meningitis, encephalitis and myelitis. In most cases, case reports or limited series of patients, it was not clear whether CNS involvement was secondary to direct infection or para-infectious immune-mediated disease. The description of encephalitis and myelitis syndromes seen with COVID-19 were, in fact, generally highly heterogenous in their presentation[9,10,15] suggesting varied underlying neuropathogenesis, and, in some instances, were not directly correlated with COVID-19. Acute presentations were potentially a consequence of systemic pro-inflammatory cytokines transcending the blood-brain barrier (BBB) or,

more rarely, due to direct viral invasion of the central nervous system (CNS)[9,15]. Later, post-infectious presentations were likely to be due to immune-mediated processes operating through cellular or antibody pathways[9,10].

The wide spectrum of clinical presentation of encephalomyelitis in patients with SARS-CoV-2 respiratory infection, however, closely resembles those phenotypes already associated with influenza and other corona-viruses[15-18], indicating that SARS-CoV-2 behaves like other viruses.

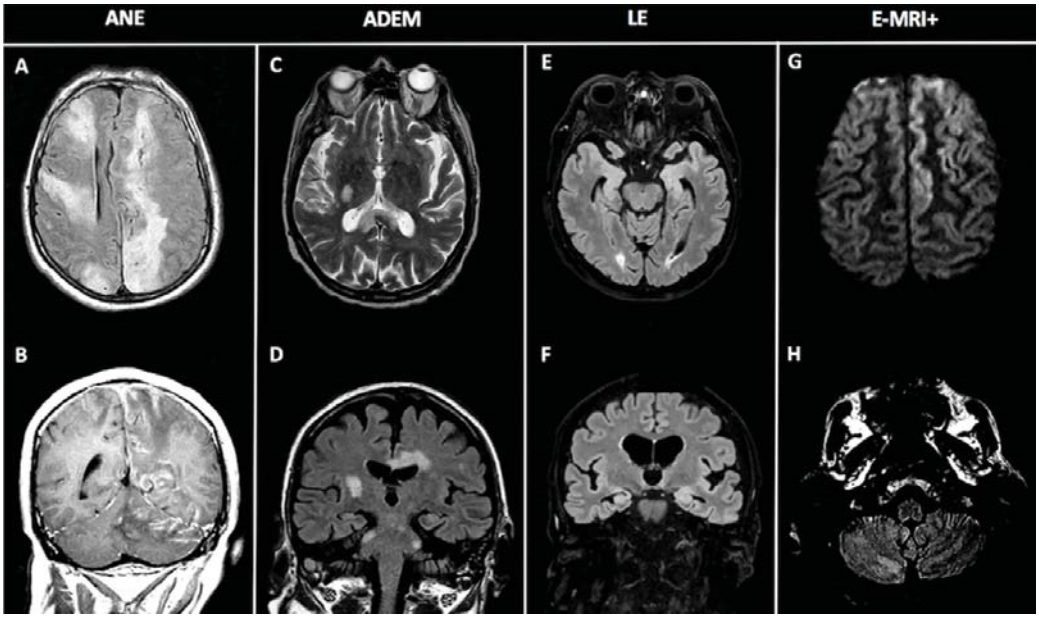
Nevertheless, the neurological complications of influenza have an estimated incidence of between 0.21 and 12 cases per million and particularly affect children[18], whereas the incidence of encephalomyelitis in COVID-19 is estimated to be at least 50 per 100,000 cases[10,20]. The trends in CNS complications in SARS-CoV and MERS-CoV proposed by Ellul and co-authors[15] had an estimated incidence of between 37 and 224 cases per 100,000 symptomatic patients. Several risk factors for encephalomyelitis as a complication of COVID-19 have been elucidated. Demographic risk factors such as old age and underlying comorbidities increased risk of complications from COVID-19 infection, including the development of encephalitis. Additionally, patients who are severely ill with COVID-19 are at a much higher risk of suffering from complications such as encephalitis and myelitis. This incidence as a complication of COVID-19 was less than 1% in the general population of COVID-19 patients but there is a notable rise to 6.7% in those who are severely ill. Although there are case reports of several patients developing encephalomyelitis weeks after initial infection with COVID-19[22], most patients develop both COVID-19 symptoms and CNS symptoms during the same period. Most often, patients present with respiratory symptoms and develop encephalomyelitis an average 14.5 days later, during their hospital stay[21,22].

Encephalitis

SARS-CoV-2 infection has been associated with a wide clinical spectrum of encephalitis, characterized by heterogeneous clinical presentation and outcomes. As far as encephalitis-related symptoms are concerned, the most common included loss or decreased level of consciousness and altered mental state or delirium, while seizures, headaches, and limb weakness were reported in 15-37% of cases[21,22]; other less common symptoms were aphasia, ataxia, and myoclonus. Patients who suffer from encephalitis as a complication of COVID-19 had much poorer outcomes compared to the general population of COVID-19 patients, including admission to intensive care facilities, use of ventilators, and a high rate of mortality. Common magnetic resonance imaging (MRI) brain findings include diffuse white matter hyperintensities and hemorrhagic lesions on fluid-attenuated inversion recovery and T2 sequences (see Figure 7.1) whereas other less common MRI findings include cerebral edema and venous thrombosis. Several cases with encephalitis as a complication of COVID-19 showed

normal brain imaging results likely due to milder encephalitis or imaging conducted before brain changes developed[22].

Figure 7.1: Brain Magnetic Resonance Imaging findings according to encephalitis phenotypes



A and **B** Case of acute necrotizing encephalitis (ANE) characterized by FLAIR diffuse bilateral hyperintensities. **B** with linear Gadolinium-enhancement on coronal T1. **C** and **D** A case of ADEM with T2 and FLAIR hyperintensities (involving corpus callosum, bilateral cerebellar peduncles and right thalamus) on axial (C) and coronal (D) plane. **E** and **F** A case of limbic encephalitis (LE) characterized by increased T2-FLAIR signal within bilateral mesial temporal lobes and (E) and coronal (F) planes. **G** and **H** A case of unspecific alterations defining the group of E-MRI+: DWI hyperintensities on frontal superior and medium gyrus and FLAIR hyperintensity on right cerebellar tonsil. ADEM: acute disseminated encephalomyelitis; ANE: acute necrotizing encephalitis; E-MRI+: encephalitis with MRI alterations; LE: limbic encephalitis.

Electroencephalography (EEG) in some patients showed patterns of general slowing while sharp waves and epileptiform activity were uncommon findings. Analyses of cerebrospinal fluid (CSF) showed mild pleocytosis and/or hyperproteinorrachia in almost all cases, whereas most COVID-19 studies failed to detect SARS-CoV-2 in the CSF samples of the COVID-19 patients with neurological manifestations[21]. To date, few cases of encephalitis have showed the presence of SARS-CoV-2 in CSF, despite negative peripheral and respiratory findings[23]. There may be various reasons for this. The virus may be cell-bound without entering the CSF or have concentrations below the level of detection of the testing method.

In addition, the presence of heme products owing to the breakdown of erythrocytes in the CSF can interfere with the PCR tests used for detecting SARS-CoV-2. Viruses can be associated with limited viremia in blood and CSF. SARS-CoV-2 RNA can only be detected from blood in 1% of the actively infected cases. It is interesting to note that the absence of the virus in the CSF could not definitely exclude a direct viral invasion, as demonstrated for other infectious diseases such as West Nile virus or enterovirus infections[24]. However, the clinical courses and CSF alterations in most patients argue against any direct CNS damage and conversely make a claim for neuroinflammatory and, in rarer cases, autoimmune responses as major players in COVID-19 encephalitis.

For these reasons, several authors have suggested the use of high-dose steroid treatment (such as methylprednisolone 1 g for 5 days) that has been demonstrated to be effective in reducing the CSF markers of inflammatory response[22]. Immunoglobulin administration or plasmapheresis are indicated, according to the current guidelines, in patients fulfilling criteria for autoimmune encephalitis, particularly in those rare cases presenting an antibody-mediated form of disease[24]. This particular approach in COVID-19 disease is still much debated, as most cases did not present CSF alterations suggestive of an immune-mediated inflammatory CNS response.

Acute transverse myelitis

Acute transverse myelitis is clinically characterized by sensorimotor disturbances, bladder/bowel dysfunction, and/or autonomic dysfunction attributable to the spinal cord. It typically manifests as a rapid disease progression from within a few hours to up to 21 days, with a sensory level, bilateral pyramidal signs, and bladder/bowel dysfunction. Acute demyelinating diseases of the CNS, such as multiple sclerosis, neuromyelitis optica spectrum disorder, and acute disseminated encephalomyelitis are other frequently encountered causes of acute myelitis. There is evidence that inflammatory reactions to infectious disease might exacerbate autoimmune diseases, making diagnostic differentiation difficult[25,26]. Many viruses can be directly implicated in the etiopathogenesis of acute transverse myelitis, including varicella-zoster, herpes simplex, Epstein-Barr, West Nile, Dengue, Japanese encephalitis, Zika, influenza, echovirus and hepatitis B, mumps, measles, and rubella viruses[5]. However, it is usually difficult to differentiate between a viral-induced and an immune-mediated transverse myelitis. Not surprisingly, several reports have linked the SARS-CoV-2 virus to the pathogenesis of acute transverse myelitis (ATM)[27,31]. Most patients had typical features of ATM with acute onset of paralysis, sensory level, and sphincter deficits due to spinal cord lesions demonstrated by imaging. Male and females were similarly affected, and mean age was 49 years, with two peaks at 29 and 58 years, but pediatric cases were also described. The main clinical manifestations were quadriplegia and paraplegia. MRI showed localized ATM lesions affected

≤3 cord segments in one-third of cases, whereas most patients had longitudinally-extensive ATM (LEATM) involving ≥4 spinal cord segments[31]. Most cases had a latency of 10 days to 6 weeks that may indicate post-infectious neurological complications mediated by the host's response to the virus, but in one-third a brief latency (15 hours to 5 days) suggested a direct neurotropic effect of SARS-CoV-2.

Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) has also been described after SARS-CoV-2 as well as other coronavirus infections, including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses[32]. ADEM affected predominantly women (2 out of 3) ranging in age from 27 to 64 years (mean age 43 years). The onset of ADEM cases was delayed after the onset of COVID-19 symptoms, which were more severe in terms of respiratory function compared to other encephalitis. Lesions revealed by MRI included cervicothoracic spinal cord lesions down to the conus medullaris, lesions in pons and medulla-cord junction, multiple T1 post-Gd enhancing white matter lesions plus bilateral edema of the optic nerves, hyperintense FLAIR lesions in the medial temporal lobe, bilateral lesions involving cerebral white matter, corpus callosum and brainstem. Indeed, immunomodulatory treatment showed high efficacy in the typical ADEM[22].

Acute necrotizing hemorrhagic encephalopathy

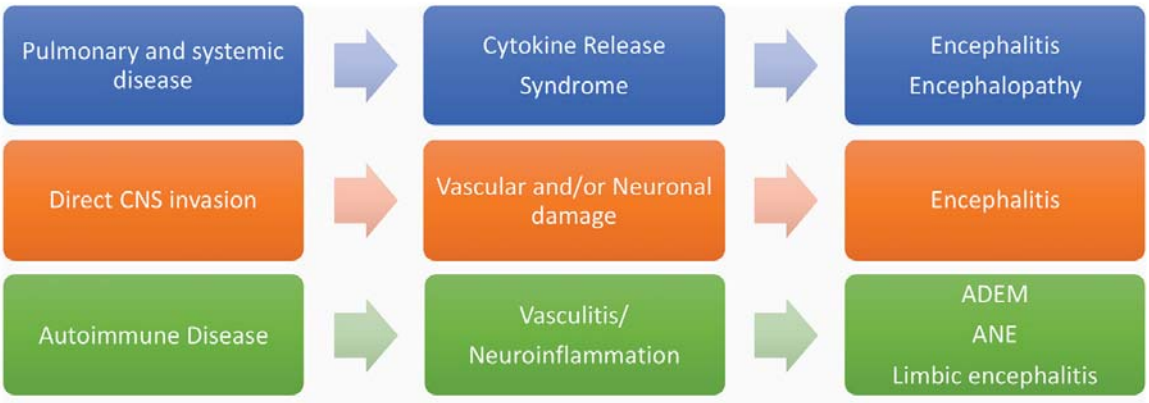
Acute necrotizing encephalopathy (ANE) is a rare neurological complication secondary to para-infectious and hyperimmune response to SARS-CoV-2 infection. This clinico-radiological syndrome affects patients with severe COVID-19 infection and occurs between one to two weeks after the onset of the upper respiratory tract infection[33,34]. The true incidence is unknown due to under-recognition of the syndrome and difficulties in obtaining timely neuroimaging studies due to patients' disease severity. Neurological manifestations of coma and persistent encephalopathy dominated clinical presentation, followed by seizures and focal deficits[22,33,34]. Neuroimaging findings in most patients showed patchy bilateral periventricular hypoattenuation on CT. MRI imaging showed multifocal diffusion restriction, periventricular confluent T2/FLAIR hyperintensities, and diffuse microhemorrhages. The pathophysiology of COVID-19-related ANE is unclear. Although the exact pathophysiology remains obscure, the lack of the typical features of viral and post-viral encephalitides in most ANE cases argues against the hypothesis that the virus directly damages the CNS and, as such, prompts speculation that, after a latent period following the infectious illness, SARS-CoV-2 might induce a secondary, parainfectious process that is responsible for many neurological manifestations. Several mechanisms were hypothesized, including hypercoagulable state from systemic inflammation,

the so-called "cytokine storm", post-infectious immune-mediated responses, direct viral-induced endotheliopathy leading to angiopathy, and microthrombosis. Viral particles have been isolated from the endothelium of various tissues, including the brain. "Cytokine storm"-mediated immunoglobulin G (IgG) production and breakdown of the blood-brain-barrier (BBB) are likely contributory mechanisms[22].

Mechanisms of COVID-19-related encephalomyelitis

There are three proposed mechanisms of the pathophysiology of encephalomyelitis as a complication of COVID-19 (Figure 7.2). The most important mechanism for the acute forms of encephalomyelitis is the systemic inflammation caused by the SARS-CoV-2 virus[36,38], which resembles Cytokine Release Syndrome (CRS).

Figure 7.2: Main mechanisms involved in encephalomyelitis



ADEM: acute disseminated encephalomyelitis; ANE: acute necrotizing encephalitis; CNS: central nervous system.

This is a potentially fatal complication of various infectious (e.g., influenza, SARS, Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis) and non-infectious diseases (e.g., multiple organ dysfunction syndrome, multiple sclerosis). It is triggered by an initial release of proinflammatory cytokines from activated T and/or B cells[37]. The release of cytokines activates bystander immune cells and endothelial cells to produce proinflammatory molecules. CRS-driven neurological disturbances have been described following CAR-T cell therapy and are termed immune effector cell-associated neurotoxicity syndrome (ICANS). There are various clinical manifestations of ICANS and these include encephalopathy (confusion or delirium), expressive aphasia or language disturbance, motor weakness, tremor, headache, seizures, depressed level of consciousness, and,

more rarely, diffuse cerebral edema[39,40]. Some neurological signs/symptoms such as expressive aphasia appear to be very specific to ICANS. Symptoms may progress to seizures or depressed level of consciousness/obtundation to the point of requiring intubation for airway protection. There have been rare cases of diffuse cerebral edema, often developing rapidly over hours with few antecedent clinical warning signs. However, most ICANS symptoms are transient and can fully resolve within the first 3-4 weeks of treatment; persistent abnormalities are uncommon[39]. Severe ICANS occurs almost exclusively in patients who develop CRS and almost always after the first fever. ICANS can occur at the same time as CRS or days later after CRS abates. Brain MRI in ICANS revealed the presence of acute T2/FLAIR hyperintensities suggestive of interstitial edema of varying severity and small (mm-scale) ischemic strokes[39]. More importantly, proinflammatory cytokines such as IL-6 have been shown to lead to endothelial damage and BBB dysfunction in this clinical entity and there is evidence that severe ICANS is associated with elevated CSF protein levels, likely reflecting increased blood-CSF barrier permeability. Accordingly, SARS-CoV-2 infection also activates the innate immune system, causing the release of large amounts of inflammatory cytokines. This causes the phenomenon known as "cytokine storm," which results in systemic inflammatory response syndrome[41]. Evidence to support this theory has been demonstrated by a recent study on CSF. Patients with encephalitis showed increased CSF levels of IL-8, IL-6, TNF-α, and β2-macroglobulin[42]. A second mechanism is direct invasion of the SARS-CoV-2 virus into the brain parenchyma that could cause the development of encephalitis[43,44]. SARS-CoV-2 could enter the brain parenchyma via a trans-synaptic propagation or via hematogenous invasion. In trans-synaptic propagation, SARS-CoV-2 binds to the angiotensin II (ACE-II) receptor on the cell membrane of peripheral nerve cells and enters cells via receptor-mediated endocytosis. It then uses active axonal machinery to travel retrogradely to the CNS[46]. One such route is via the olfactory epithelium, where SARS-CoV-2 invades the olfactory primary sensory neurons and travels to the cribriform plate of the ethmoid bone. From there, it crosses into the anterior cranial fossa and may later spread throughout the brain parenchyma to cause encephalitis[45].

During hematogenous invasion, SARS-CoV-2 crosses the BBB to enter the brain parenchyma. SARS-CoV-2 first invades vascular endothelial cells that express the ACE-II receptor[2,32]. It then interacts with ACE-II on surrounding neurons, glial cells, and other vascular cells, beginning a cycle of viral budding. This causes damage to both vascular and neuronal tissue, compromising the BBB and allowing the SARS-CoV-2 virus to enter the CNS.

Alternatively, hematogenous invasion could also occur through the infection of leukocytes[45]. Lymphocytes, monocytes, and granulocytes all express the ACE-II receptor, making way for possible infection with SARS-CoV-2. Once infected, these leukocytes travel in the blood vessels and cross the BBB,

entering the CNS and taking the SARS-CoV-2 virus with them, where they can infect other cell types within the CNS to cause encephalitis. However, it has been suggested that direct invasion of SARS-CoV-2 into the CNS may be less likely to be the main mechanism causing encephalomyelitis in COVID-19, as most of these patients have had a negative CSF PCR against SARS-CoV-2[2,4,45].

A third proposed mechanism for encephalomyelitis as a complication of COVID-19 is molecular mimicry[46]. In response to infection with SARS-CoV-2, there is an expansion of host antibodies and lymphocytes. Although these immune molecules are supposed to be specific for SARS-CoV-2 viral antigens, some of them are cross-reactive and can attack self-antigens[47]. When cells in the vascular endothelium and brain parenchyma are affected, there is widespread damage to the CNS, which may cause the development of encephalitis[32,46]. There have also been reports of acute hemorrhagic necrotizing encephalopathy which is known to develop via molecular mimicry, further supporting the theory of molecular mimicry as the pathophysiology of encephalitis as a complication of COVID-19[32].

Conclusive remarks

A variety of neurological manifestations have been reported in COVID-19, which include encephalopathy, encephalitis, and myelitis. Various clinical presentations have been described among which altered mental state and delirium are the most frequent, though these are not always clearly detected. The incidence is relatively low, but higher compared to other viral infections. Different mechanisms have been proposed according to onset and the relationship with COVID-19 symptoms. Most encephalitis, closely related to the onset of respiratory problems were likely due to a cytokine release syndrome. Direct invasion of SARS-CoV-2 is an unlikely mechanism but a few neuropathological studies have shown that this might happen in selected cases. Many cases of encephalomyelitis have occurred after the onset of COVID-19 and were likely immune-mediated. Different mechanisms have been identified but the heterogenous clinical picture still needs to be better understood. A key challenge in any epidemiological investigation is the precise definition of patients' clinical phenotypes. Clinicians should be aware that the diagnostic work-up should be as detailed and exhaustive as possible in order to rule out causes other than SARS-CoV-2 infection before including cases in epidemiological analyses. This requires, for example, a distinction between patients with clear evidence of brain inflammation (encephalitis) and patients with encephalopathy, and a careful characterization of all patients with suspected disease of the spinal cord by CSF examination, neurophysiological studies and, when needed, spinal imaging. Although this careful characterization is not always easy to achieve, especially in severely affected individuals, it should be noted that such a rigorous diagnostic approach was not applied in many of the studies published to date, with the obvious consequence

of phenotypic heterogeneity which compromised the reliability of the findings. A useful experimental approach would be, at least, a large-scale case-control study to compare homogeneous groups of patients with confirmed SARS-CoV-2 infection with non-infected individuals; however, this approach would present design challenges, as exposure to SARS-CoV-2 is high in the general population and widespread antibody testing would be needed to ascertain seroprevalence. In addition, neuropathological examination of patients with COVID-19 after death should be performed, as this approach might provide clues as to the mechanisms underlying nervous system injury. Finally, although an emphasis has been put on recovery from the acute phase of the infection, the potential long-term neurological effects of COVID-19 should not be overlooked. If SARS-CoV-2 invades the CNS, neurological manifestations could recur in predisposed individuals after the virus has remained latent for a long time. Longitudinal neurological assessments of patients after recovery will be crucial in understanding the natural history of SARS-CoV-2 in the CNS and monitoring for potential neurological sequelae. Evidence from animal and human studies of other coronaviruses suggests that, in some at-risk individuals, the inflammatory response elicited in acute or chronic infection might trigger or accelerate subclinical mechanisms that underlie the earliest stages of many neurological diseases. Accordingly, longitudinal studies should include careful neurological, imaging, laboratory, and neuropsychological evaluation in order to determine the interplay between central and systemic infection driving CNS damage and neurological alterations.

Take-home message

- COVID-19 infection is associated with increased risk of encephalitis and myelitis through different mechanisms.
- The spectrum of SARS-CoV-2-related encephalitides includes inflammatory-mediated and rare antibody-mediated forms.
- A prompt diagnosis of encephalitis and myelitis in COVID-19 is pivotal for early treatment.
- High-dose steroid treatment should be discussed on the basis of clinical and biological features as treatment options for non-infectious encephalitis/myelitis concomitant COVID-19 disease.

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