Neurological complications of COVID-19: from pathophysiology to rehabilitation. An overview

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Abstract. *Objective:* To evaluate how the SARS-COV2 is able to affect the nervous system, the main neurological manifestation, and the treatment used, including neurorehabilitation. *Methods:* Studies performed during the current year that fulfilled inclusion criteria were selected from PubMed, Scopus, Cochrane, and Web of Sciences databases. The search combined the terms "Covid 19," "rehabilitation/treatment," and "neurological complications." *Results:* The exact route by which SARS-CoV-2 can penetrate the CNS is still unknown, although a possible retrograde transynaptic pathway from peripheral nerve endings, and/or through the olfactory bulb, have been suggested. An early management of COVID-19 by a multiprofessional team is fundamental to avoid long term sequaele. Rehabilitation is recommended to improve respiratory and cardiac function, as well as to avoid long term neurological complications. *Conclusions:* As no specific conclusions in term of prognosis and treatment could be done, research and consensus paper are needed to provide NeuroCovid patients with the best treatment options, including neurorehabilitation. (www.actabiomedica.it)

Key words: COVID-19, neurocovid, pandemic, neurological complications

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), originating from Wuhan, is spreading around the world and the outbreak continues to escalate since December 2019. On 30 January 2020, COVID-19 was registered as the sixth Public Health Emergency of International Concern (PHEIC) by the World Health Organization (WHO), which was socially declared as a pandemic on 11 March 2020(1-3). At the end of January 2020, the infection spread all over Italy, but with high infection rates and mortality in the northern part, especially in Lombardy, the most industrialized and polluted region of the country. It is noteworthy that an association between severe viral respiratory disease and air pollution has been described (4).

SARS-CoV-2 is a beta-coronavirus with an average incubation period of 3-7 days (with a maximum of 14 days). COVID-19 is highly contagious with a wide spectrum of clinical manifestations, *typically involving the respiratory system* (5-7), although many patients can be totally asymptomatic. Several risk factors are associated with the complications of COVID-19, and these include older age (>65), chronic respiratory diseases, cardiovascular diseases, hypertension, diabetes, and obesity. So far, males are registered to be infected with a higher prevalence compared to females and the reason is yet undiscovered (8, 9).

SARS-CoV-2 is transmitted either via airborne small droplets (aerosols) that disperse one or two metres when speaking or coughing, or direct contact with infected nasal secretions, or by fomites (contaminated objects) (10). It has been suggested that

SARS-CoV-2 binds by glycoproteins expressed on its surface to the receptor of the angiotensin-converting enzyme 2 (hACE2) (11), which is distributed in the respiratory tract epithelium, lung parenchyma and other areas, such as the gastrointestinal tract, endothelial cells, among others (12). In addition to ACE2 receptor, SARS-CoV-2 uses the serine protease type II transmembrane serine protease for spike protein priming (13,14). Then, patients with COVID-19 present symptoms that include fever, shortness of breath, cough, sore throat, nasal congestion, dizziness, chills, muscle ache, arthralgia, weakness, fatigue or myalgia, chest tightness, excessive mucus production with expectoration, hemoptysis, and dyspnea (15-21). Severe or fatal complications include pneumonia, type I respiratory failure, sepsis, metabolic acidosis, septic shock, arrhythmia, acute cardiac injury, heart failure, acute kidney injury, bleeding, or hypoxic encephalopathy (22-25).

Growing evidence is demonstrating the involvement, both directly and indirectly, of the nervous system by the SARS-COV-2.

Aim of this review is to evaluate how the SARS-COV2 is able to affect the nervous system, the main neurological manifestation, and the treatment used, including neurorehabilitation.

Search Strategy

Studies were identified by an online search of Scopus, PubMed, Web of Science, and Cochrane databases. The search combined the following terms: "CoVID19"[MeSH Terms] OR "neurological"[All Fields] AND "complications"[All Fields] OR "neurological complications" [All Fields] AND "COVID-19 neurorehabilitation" [MeSH Terms] AND/OR "pathogenesis" [All Fields] AND "rehabilitation" [All Fields] OR"COVID19 pathogenesis and treatment " [All Fields]. Studies met specified selection criteria and were published in the current year (January-November 2020). We selected only texts in English and removed duplicates. All articles were evaluated according to the title, abstract, and text. We included studies that examined pathogenesis and treatment, including rehabilitation in patients with Neurocovid. A total of. . . articles were eventually selected for inclusion (see Figure 1) and the main findings on clinical manifestation reported and table 1.

Pathogenesis and neurovirulence properties of SARS-CoV-2

Coronaviruses belong to the family Coronaviridae which consists of four genera: alpha-, beta-, delta- and gamma-coronavirus (26). Human coronaviruses 229E, OC43, NL63 and HKU1 are endemic worldwide, and are responsible for 15-30% of upper respiratory tract infections, oto-rhinitis, laryngitis and pharyngitis. Sometimes, they can cause more serious infections, such as bronchitis, bronchiolitis, exacerbation of asthma or SARS.

Respiratory viruses can penetrate the central nervous system (CNS) (neuroinvasion), affect both neurons and glial cells (a property known as neurotropism), and induce various neurological pathologies (neurovirulence) (27). The exact route by which SARS-CoV-2 can penetrate the CNS is still unknown (26). Li et al. suggest a possible retrograde transynaptic pathway from peripheral nerve endings, through the mechanoreceptors and chemoreceptors located in the lungs and respiratory tract that transmitted to the nucleus of the solitary tract. On the other hand, SARS-CoV infection has shown to cause neuronal death in ACE2 transgenic mice (28), entering the CNS through the olfactory bulb, and spreading transneuronally to other regions of the brain. Indeed, it has been demonstrated that the human coronaviruses OC43 is neuroinvasive spreading from the olfactory bulb to the brain stem and spinal cord, by the axonal transport system as a means of neuron-to-neuron propagation (27), causing flaccid paralysis and demyelination in animal models (29-32). Regulation of the ACE2-R is another valid route to facilitate cell invasion by SARSCoV-2 and its rapid replication (28). Indeed, the high expression of ACE2-R on the endothelial cells of the blood-brain barrier allows a rapid viral binding and facilitates viral entry into the CNS by damaging vasculature (33-35). When invading the cerebral vascular endothelium, the virus reduces the functionality of the ACE2-R causing an elevation of cerebral blood pressure and, as
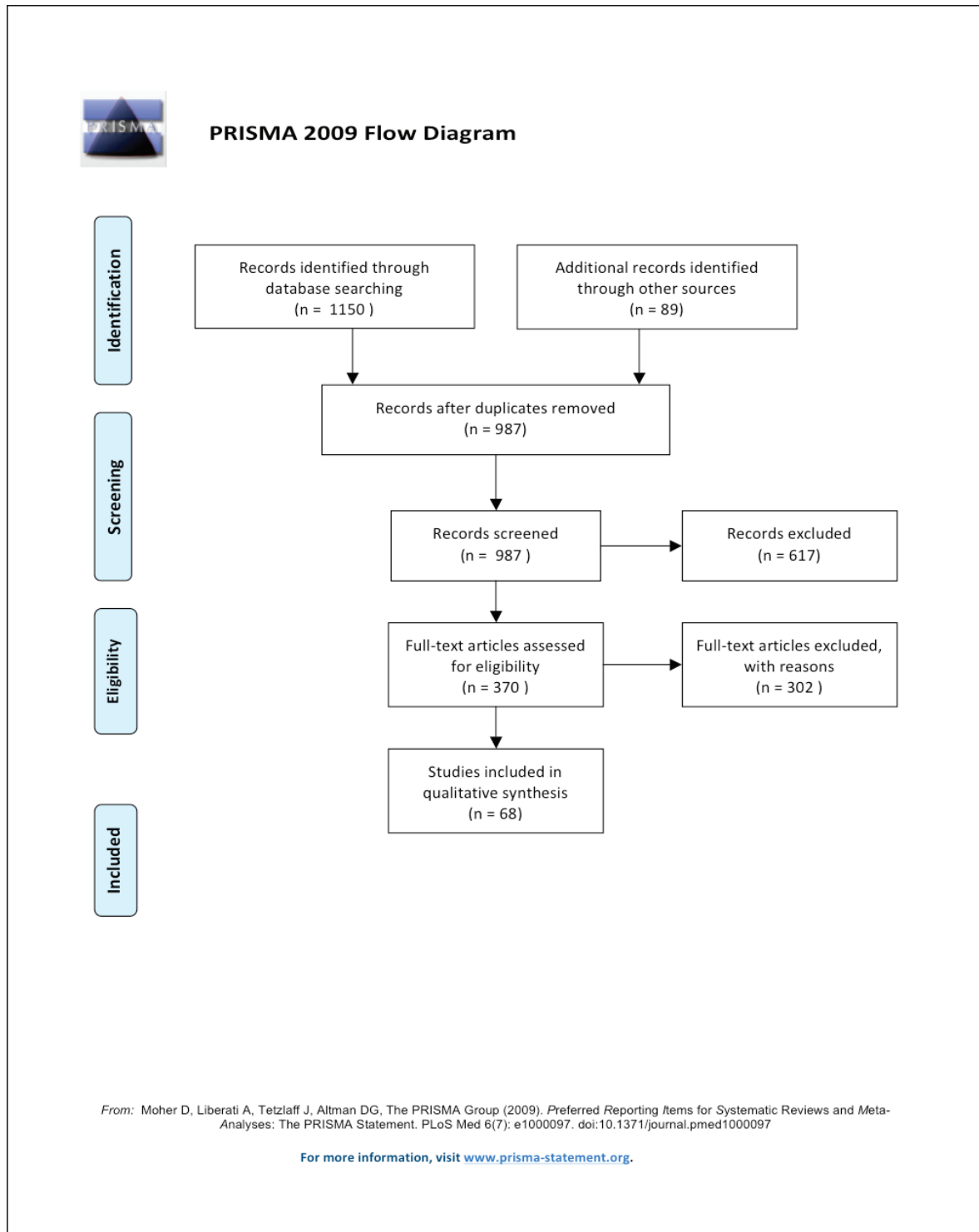
PRISMA 2009 Flow Diagram

Records identified through database searching (n = 1150)

Additional records identified through other sources (n = 89)

Records after duplicates removed (n = 987)

Records screened (n = 987)

Records excluded (n = 617)

Full-text articles assessed for eligibility (n = 370)

Full-text articles excluded, with reasons (n = 302)

Studies included in qualitative synthesis (n = 68)

Identification

Screening

Eligibility

Included

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 1. Shows the flow diagram of the study selection.

Table 1. COVID-19–related complications in the nervous system

Complication	Clinical manifestations	Auxiliary examination	Physio-pathogenesis	References
Viral meningitis/ encephalitis	Headache Altered mental status, meningeal irritation signs	CSF: positive PCR assay for SARS-CoV-2 Increased lymphocytes and proteins MRI: FLAIR hyperintensity EEG: slowing	unclear may be edema secondary to inflammatory injury versus direct viral infection	75 80-86
Acute disseminated encephalomyelitis (ADEM)	Multifocal deficits	MRI: FLAIR hyperintensity, multifocal demyelinating lesions Autopsy: ADEM-like appearance in the subcortical white matter	clusters of macrophages, axonal injury	87-89
Acute necrotizing encephalopathy (ANE)	Altered mental status	CT: hypoattenuation MRI: T2 FLAIR hyperintensity with internal hemorrhage	cytokine release syndrome	90-91
Cerebrovascular disease	Sensory or motor dysfunction	CT/MRI: ischemic or hemorrhagic change	Increased blood pressure thrombocytopenia coagulation disorders cytokine release syndrome hypoxia	38-39 47-49 52-56; 67-79
Epilepsy	Seizures	CSF: negative PCR assay for SARS-CoV-2 EEG: semirhythmic, irregular, high-amplitude delta waves	unknown	95-96
Acute myelitis	Flaccid paralysis, hypesthesia Urinary and bowel dysfunction	MRI: T2 hyperintensity	unclear	97-98
Hyposmia and hypogeusia	Loss of a sense of smell and taste	Questionnaire-based survey Cross-sectional study	transneural penetration through the olfactory bulb, or the penetration through the angiotensin converting enzyme 2 receptor, widely expressed on the epithelial cells of the mucosa of the oral cavity.	57-61
Guillain-Barré syndrome (GBS)	Flaccid paralysis	CSF: negative PCR assay for SARS-CoV-2 MRI: enhancement of affected nerve roots EMG: decreased recruitment	Cytokine storm hyperinflammation	50-51 99-105
Miller Fisher syndrome (MSF) and polyneuritis cranialis	Ophthalmoplegia, ataxia, and areflexia	MRI: relative enlargement, T2 hyperintensity, and enhancement of the affected CN Anti-GD1b antibody positive	Cytokine storm hyperinflammation	106-109
Cognitive dysfunction	Memory and executive Function deficits	No information	direct viral involvement of the CNS effect of hypoxemia.	110-111

Complication	Clinical manifestations	Auxiliary examination	Physio-pathogenesis	References
Psychiatric dysfunction	depression, fear and anger post-traumatic stress disorder delirium	No information	prolonged ventilation, use of sedatives, prone positioning, human isolation extended time away from social contacts	114-115
Other complications have been descrbed secondary to COVID treatment	**neurocognitive impairment neuropathic neuropsychiatric sequelae, retinopathy ataxia, seizures, limbic encephalitis**	No information	Combined drugs effect	116-125

COVID-19, coronavirus disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; EEG, electroencephalography; EMG, electromyography.

a consequence, blood vessel rupture leading to massive intracerebral bleeding (36), although thromboembolic events may worsen the clinical picture. This could be the reason why patients taking ACE inhibitors as well as those with comorbidity, especially hypertension and diabetes, are exposed to a major risk of COVID-19 infectious and complications (37).

Another mechanism of damage is the generation of a global systemic inflammatory response (SIRS), producing increased levels of interleukin (IL)-6, IL-12, IL-15, and tumor necrosis factor alpha (TNF-α). This activates glial cells and produces a massive pro-inflammatory CNS state, leading to severe hypoxia and, consequently, cerebral vasodilation, cerebral edema and ischemia (38, 39).

What is more, the virus has been found in the brain stem (26,40), involving the nuclei that regulate the respiratory rhythm. In details, the chemoreceptors that detect changes in the concentrations of CO_2 and O_2 send the information through the nucleus of the solitary fascicle to the central regulation of breathing. Changes in these mechanisms lead to an increase or decrease in respiratory strength (41,42). In this way, stem nuclei have connections with the respiratory system, and the entry of the coronavirus into this structure could lead to death also by affecting these neuronal groups (42).

On the other hand, the virus could directly damage CNS causing viral encephalitis and/or immune-mediated diseases (43). Finally, it could not be excluded that, the SARS-CoV-2 could be latent in the CNS for a long time and might lately reappear with neurological diseases, as demonstrated for other coronaviruses (i.e. HCoV-229E and HCoV-OC43) that have been detected after a long period in various neurological diseases in humans, including multiple sclerosis (MS) (31).

Clinical manifestation of Neurocovid

The incidence of neurological complications from SARS-CoV-2 is unknown. Necropsy studies have shown the presence of cerebral oedema and neuronal degeneration in deceased patients with COVID-19 (44), suggesting an encephalopathy (45), likely due to toxic and metabolic causes and the effect of hypoxia or drugs or subclinical crises. In a first report, 86 (36.4%) out of 214 hospitalized patients with severe infection in three hospitals of Wuhan reported neurological manifestation (46). Since then, there has been growing evidence on the fact that the virus may cause numerous neurological manifestations, such as encephalopathy (47), limbic and brainstem encephalitis (48, 49), Guillain-Barrè syndrome (50-51) and stroke (52-56).

These manifestations may reflect either direct viral infection or dysregulation of the immune response, potentially leading to hyper-inflammation processes and dysfunction of the coagulation system.

Early neurological symptoms of COVID19 infection

Headache is the first most common symptom described in people with COVID-19. In a study of more than 1,000 patients, 13.6% reported mild headaches (15% of those with severe disease), 15% of patients reported myalgia, 13.7% had elevated levels of creatine kinase (19% in severe cases), with two cases of rhabdomyolysis (0.2%)(57).

Olfactory and taste disorders can be the initial neurological symptoms described in such patients. Nevertheless, these patients are classified as asymptomatic or pauci-symptomatic compared to patients with severe respiratory symptoms that, usually, did not report hypogeusia and hyposmia. The underlying pathogenetic mechanism that could explain the taste and olfactory disorders in SARS-CoV-2 infection are either a transneural penetration through the olfactory bulb (28), or the penetration through the ACE-R (58). Then, hyposmia and hypogeusia are considered as a possible early stage of the disease (59), and could represent a clinical screening tool to further orientate testing of pauci-symptomatic individuals (60). The prevalence of olfactory disorders in an Italian survey was described as 20% (61).

Patients with a more severe COVID-19 symptomatology are likely to have other neurologic symptoms, such as acute cerebrovascular diseases, impaired consciousness, and skeletal muscle injury.

Acute neurological complications associated to COVID19

Cerebrovascular diseases

Li et al., in a sample of 221 patients, found that 6% developed severe neurological diseases, such as ischaemic and haemorrhagic stroke, as well as cerebral vein thrombosis, with a significant proportion died as a result (62). Males are at a higher risk for stroke (62 %), with a median age of stroke onset of 63 years. Notably, a large amount of the cases present important vascular risk factors, especially hypertension and diabetes mellitus (63-66). Therefore, COVID-19 could be considered as a "stroke-trigger" with a 7.6-fold increase in the odds of cerebrovascular complications, as compared to influenza (67). Usually the onset of stroke delayed about 10 days after patients developed symptoms of COVID-19, including respiratory symptoms and fever (68,69). On the other hand, young-onset cases of stroke, without risk factors and comorbidities, are frequently related to large-vessel occlusion and occur before the onset of COVID-19 symptoms (70-72). Indeed, patients with COVID-19 appear to be particularly prone to large vessel occlusion or multi-territory involvement or involvement of otherwise uncommonly affected vessels (73-75), including for example the occlusion of the pericallosal artery (73), or the presence of multiple focal stenoses in the V4 segment of the vertebral artery (74). Then, a "protected code stroke" is necessary to be soon adopted in this frail population (76).

The pathogenesis could be explained by the binding of the SARS-CoV-2 to ACE2-R in endothelial cells increasing blood pressure which, together with the presence of thrombocytopenia and coagulation disorders, such as increased levels of D-dimers, prolonged prothrombin time and disseminated intravascular coagulation (77,78), can contribute to the increased risk of both ischaemic and haemorrhagic stroke. Other pathogenic mechanisms include the cytokine release syndrome: the virus infection predispose the patients to a systemic coagulopathy due to increased levels of fibrinogen (94%), platelet (62%) and D-dimer (100%), as well as IL-6 (100%), as a results of the excessive inflammatory state (79).

Meningoencephalitis

On March 4, 2020, the Beijing Ditan Hospital reported the first case of viral encephalitis **related to** the SARS-CoV-2 (80). A second case of meningoencephalitis was described in a 24 year-old Japanese male with the SARS-CoV-2 RNA detected only in the cerebrospinal fluid (CSF), and MRI hyperintense areas in the right lateral ventricle, the mesial region of the temporal lobe and the hippocampus (81). Further patients have been more recently reported from Strasbourg, France: agitation and corticospinal tract

signs were present in 69% and 67% of the patients, respectively(82).

The pathophysiology is unclear but may be related to either the edema secondary to the inflammatory injury or a direct viral infection of the CNS (75).

In Japan, it has been described the first patient who was sent to the emergency department because of a convulsion accompanied by unconsciousness and who was subsequently diagnosed with aseptic encephalitis with the SARS-CoV-2 RNA detected in the CSF (83). Similarly, in Los Angeles, a young woman with COVID-19 showed symptoms of meningoencephalitis without respiratory failure, and SARS-CoV-2 was found to be positive in the CSF by reverse transcription–polymerase chain reaction (PCR) (84). In addition, two patients with acute meningoencephalitis associated to SARS-CoV-2 infection were reported in Switzerland, and a case of rhombencephalitis was reported as a rare complication of acute COVID-19 infection in the United Kingdom (85,86).

Acute disseminated encephalomyelitis (ADEM)

As far as we know, only three cases of ADEM associated to COVID-19 infection have been described: 1) A 40-year old woman with diffuse hyperintensities in the subcortical and deep white matter (87); 2) a 51-year-old woman who developed a coma and impaired unilateral oculocephalic response weeks after a SARS-CoV-2 infection with radiological evidence of ADEM (88); and 3) the autopsy of a 71-year-old patient diagnosed with COVID-19 showed scattered clusters of macrophages, axonal injury, and a perivascular ADEM-like appearance in the subcortical white matter (89). As for other viruses, an immunomediated reaction has been postulated to expalin the disease.

Acute Necrotizing Encephalopathy (ANE)

ANE is a rare complication recently described in patients with COVID-19 (90,91), although the disease was also described in other viral infections, including influenza. The pathogenesis is related to the cytokine release syndrome, a well-known manifestation of COVID-19. Typical MRI findings include hyperintense lesions and hemorrhage in the thalamus, brainstem, cerebellum, and cerebral white matter (92).

In such a severe complication, a treatment with intravenous immunoglobulin (IVIG) and steroids can be attempted (93).

Epilepsy

Epileptic seizures are pissible complications of COVID-19. Indeed, new-onset seizures in critically ill patients with COVID-19 should be considered as acute symptomatic seizures and the treating physician should try to determine the etiology of the seizure and manage the cause immediately and appropriately (94). Interestingly, a focal status epilepticus as the onset of COVID-19 in the context of a predisposing but well-controlled SARS-CoV-2 related postencephalitic epilepsy has been reported (94). On the other hand, a man without any history of epilepsy developing multiple episodes of seizures after infection with SARS-CoV-2 was also reported (95). In addition, an infant with both COVID-19 and rhinovirus infections presented with a few seizures, although no changes were observed at the EEG (96).

Subacute Neurological Manifestations

Myelitis

Several cases of acute trasverse myelitis have been reported after COVID-19 infection. Among them: i) a 66-year-old man presented with acute flaccid paralysis of bilateral lower limbs and urinary and bowel incontinencedue to a multifocal transverse myelitis (87); ii) a 60-year-old man developed progressive weakness of the lower limbs, bladder dysfunction, hypoesthesia below the T9 level and a moderate spastic paraparesis due to a hyperintensity lesion of the thoracic spinal cord (97); iii) a 69-yearold woman was diagnosed with acute necrotizing myelitis based on the clinical symptoms and MRI manifestations (98).

Guillain–Barre syndrome (GBS)

Cases of Guillain-Barre syndrome (GBS) as significant neurological sequelae of SARS-CoV-2 have been reported (99,100). Among the published cases,

there is a considerable variability in the onset of features of GBS and the typical respiratory symptoms. Generally, flaccid tetraparesis or tetraplegia evolved over a period of 36 hours to 4 days. The interval between the onset of symptoms of Covid-19 and the first symptoms of Guillain–Barré syndrome (GBS) ranged from 5 to 14 days, in line with the well-known "post-infectious" presentation of GBS. However, some GBS cases presented either as the same time as the symptoms of SARS-CoV-2 or before the COVID-19 onset (99). Then, Zhao et al. proposed a so-called "para-infectious" profile pattern when GBS occurs at the same time of an acute episode of infection (99), explaining some of the early onset cases of GBS with early significant respiratory involvement or in the absence of a history of any other plausible infection known to cause GBS. The pathogenesis of GBS and SARS-CoV-2 infection could be explained by the presence of antibodies against the surface glycoproteins of the pathogen, which also respond to similar native protein structures found in the surface of neurones leading (100-102). Other possible theories include the "macrophage activation syndrome," also known as *cytokine storm*, with the subsequent "hyper-inflammation" (103).

Another important point is the differentiation of GBS from critical illness polyneuropathy and myopathy, in patients with SARS-CoV-2, who have prolonged admission to intensive care (104,105).

Miller Fisher Syndrome and polyneuritis cranialis, which are variants of GBS causing cranial nerve and pharyngeal and facial weakness, have also been described as related to COVID-19 (106-108). An Italian multicentre retrospective/prospective study evaluating the neurologic manifestations of the hospitalized patients with COVID-19 found that the involvement of the CNS had a poor prognosis (109).

Chronic and Secondary Neurological Complications

More and more patients that recover from COVID-19 may complain of lasting neurological sequelae that may have been overlooked at the time of acute illness. Some patients after COVID-19

infection may develop a cognitive decline, including memory and executive function deficits. Moreover, older patients with a more severe disease course can also have confusion and apraxia/ataxia (110) due to a direct viral involvement of the CNS (111) or the effect of hypoxemia. Post-extubation dysphagia has been reported in 3% to 62% of patients requiring mechanical ventilation for ARDS (112,113). The pathophysiological mechanisms of dysphagia could be related to mechanical causes, diminished proprioception, laryngeal injury and peripheral or CNS damage.

Moreover, depression, fear and anger as well as post-traumatic stress disorder have been described as psychiatric problems during the SARS epidemic, for patients, relatives and healthcare workers. The further elements of prolonged ventilation, use of sedatives, prone positioning, human isolation, and extended time away from social contacts may contribute to these and other psychiatric problem, including severe delirium (114,115).

Other complications have been described secondary to COVID treatment. Many of the medications for SARS-COV2 infection (azithromycin, corticosteroids, biologic agents as tocilizumab, antivirals as remdesivir, ribavirin, lopinavir/ritonavir, favipiravir, or antimalarials as hydroxychloroquine and chloroquine) have significant drug interactions and side effects. Lopinavir/ritonavir and azithromycin interact with many common medications in patients with prior strokes including antihypertensives, antiplatelets, statins, and anticoagulants (116-118). These also carry an increased long-term risk of neurocognitive impairment (118-121). Ribavirin and interferon alpha may have both neuropathic and neuropsychiatric sequelae, while interferon caries a risk of retinopathy.[122,123] Similarly, antimalarials also carry the risk of neuropsychiatric side effects and less commonly ataxia, seizures, and limbic encephalitis (124). Effects of remdesivir are still under investigation (125).

Treatment options: focus on rehabilitation

With the recent COVID-19 outbreak, there is a crucial need to understand the neurotropic potential of the COVID-19 virus to prioritize and individualize

the treatment protocols based on the severity of the disease and predominant organ involvement. By now, no specific therapies are available, and the main measures are represented by prevention, isolation and social distancing, hygienic handwashing measures, and the use of masks.

Thousands of clinical trial results and articles have published in this process to provide treatment methods for the disease (126-128). According to level 1 evidence, the most effective SARS-Co-V-2 pharmacologic treatments include remdesivir for mild to severe disease, and a triple regimen therapy consisting of lopinavir-ritonavir, ribavirin and interferon beta-1b for mild to moderate disease. Also, dexamethasone significantly reduced mortality in those requiring respiratory support. Convalescent plasma from blood donors with anti-SARS-CoV-2 antibodies may benefit patients with COVID-19 by providing immediate passive immunity via transfusion, or when used to manufacture hyperimmune immunoglobulin preparations. Nonetheless, optimal product characteristics, volume of transfusion, and timing of administration, as well as real efficacy, remain to be determined (128).

Moreover, several vaccines for COVID-19 are in clinical trials (NCT04398147; NCT04456595; NCT04466085; NCT04368728) (129), and others under administration in many countries, including Italy (here starting from December 27).

About non pharmacological therapies, early rehabilitation plays an important role in neurological sequelae preventing complications on the respiratory system, restoring respiratory and physical independence, promoting weaning from mechanical ventilation, maintaining and improving the virus-damaged system functions, in order to improve prognosis, quality of life, and facilitates the return to daily activities and work (130,131). Therefore, it is necessary a staging based on the disease severity and organ involvement by SARS-CoV-2 to decide if aggressive or conventional treatment modalities has to be accomplish. However, clinicians are particularly cautious about risks associated with early intervention of rehabilitative techniques, holding a conservative attitude. Then, the extraordinary measures to prevent the spread of this disease urgently imposed a new organization of all ward included rehabilitation (132). By now, there is no evidence for early rehabilitation treatment of COVID-19, a lack of experience in acute management of COVID-19 patients, and the absence of guidelines recommendations.

To this end, a recent EAN expert consensus statement for the management of patients with neurological diseases during the COVID-19 pandemic have been recently published to guide harmonization of highquality healthcare across Europe in the face of current challenges (133).

Moreover, an expert panel with early experience managing patients with COVID-19 outlines the clear need for rehabilitation intervention in both the acute and post-acute phases of the disease (134). Some physicians are in the opinion that the current treatment plan should not allow physical therapists to provide treatment to COVID-19 patients in ICU, as this may increase the risk of cross infection, and that management of these patients should focus only on life support, antiviral therapy, and hormone therapy. It is believed that early rehabilitation will interfere with the clinical treatment, increase patient oxygen consumption, and may not cause any benefit, leading to the current situation where most critically ill patients are not offered the opportunity of early rehabilitative intervention. On the contrary, early rehabilitation of critically ill patients with COVID-19 is believed of some help when performing such an intervention on cognitive status, respiratory function, cardiovascular function, and musculoskeletal function (135).

Indeed, to manage the three major areas, i.e. positioning, early mobilization, and respiratory management, patients present a better prognosis, *as per* exercise capacity, muscle strength, and walking ability at discharge, as well as reductions in the duration of mechanical ventilation, length of the ICU stay, and length of hospital stay.

The new frontiers of rehabilitation, namely telemedicine, offer the opportunity to follow a rehabilitation program to those who are in hospitals lacking of rehab services or at home. In particular, "telemental health" is a new frontier of providing mental health assessment and treatment at a distance (136,137). Despite the distance, the tool could allow to perform psychology session on-time by creating and maintaining a psychologist/patient trusted relationship

(136,137). A motor program with scheduled exercise could be also provided to the patients and virtual physical training program could be followed by several cross-platform tools. Although the initial doubtfully in this new kind of approach, the "cyberhealth psychotherapy" can encourage the patient to be more compliant with the rehabilitation daily schedule and motivated to recover their functions (138). Therefore, a multidisciplinary team is critical to achieve successfully the rehabilitation outcome and an early rehabilitation has become an indispensable part of multidisciplinary management of the critically ill patients. Even recent guidelines on pulmonary rehabilitation community-dwelling state that COVID-19 patients could be managed with telehealth programs to deliver the required rehabilitation input in the form of tele-rehabilitation (139).

In order to ensure that post-discharged COVID-19 patients were appropriately monitored and provided with the required input, a proposed pathway by the Hull University Teaching Hospital NHS Trust was developed. The care pathway aimed to evaluate the post recovery type of rehabilitation and the clinical needs of patients following infection with the SARS-Cov-2 virus in order to set in a multidisciplinary tele-rehabilitation component (139-142).

Cardiac and respiratory long-term complications are frequent after Covid-19, and they should be properly treated, as they can affect also the nervous system. Moreover, patients following stroke or other neurological complications may have cardiorespiratory failure, and thus they should be provided with respiratory rehabilitation, besides neurorehab. Curci et al. showed that post-acute COVID-19 patients suffered from dyspnoea and shortness of breath even for minimal activities, affecting motor rehabilitation (136). Nonetheless, patients with COVID-19 do not present only with respiratory and cardiological dysfunctions, but also with nutritional, internal and neurological injuries, accompanied by motor complications cognitive impairment, critical-illness–related myopathy and neuropathy, dysphagia, joint stiffness and pain, and psychiatric problems (anxiety, depression, fear and anger as well as post-traumatic stress disorder) caused by both prolonged immobilization and cerebral hypoxemia (111, 143-147). As a consequence, a

multidisciplinary approach is fundamental to properly manage these frail patients.

In stroke patients with COVID-19, a longer period of immobility is known to delay functional recovery. Thus, the reduced assistance from physical and occupational therapists due to COVID-19 infection could be bypassed by facilitating devices of neurorehabilitation. Prospective techniques can be used to stimulate neurorestoration and maintain muscle strength and required minimal supervision (148). For example, transcutaneous electrical stimulation (TENS) devices of sensory and peripheral nerves improves early poststroke lower-extremity impairment and late motor function (149), improves the flaccid limb (150), and prevents post-stroke spasticity in lower limbs (151) as well as improves hand dexterity in patients with moderate to severe hemiparesis (152). Another simple, effective and feasible method could be the Mirror Therapy (MT) (153), using a mirror that is positioned between the affected and unaffected limbs reflecting the movement of an unaffected limb and giving the illusion of movement of the affected limb. This process facilitates the mirror neurons involved in imitative learning through interaction with the neural motor area (154, 155).

In patients with stroke, virtual reality (VR) can be used to improve upper limb function, gait and balance, global motor function, and cognitive function in patients with stroke (156-158). Also, serious exer-gamings have proven effective as an adjunct therapy to traditional treatment, especially in improving dynamic balance (158). However, for patients who are recommended to continue motor rehabilitation at home with adapted physical therapy, a supervision of self-managed home rehabilitation is necessary to avoid lacks compliance and abandonment daily exercise compromising a successful recovery (160). Home management of stroke patients is particularly important during pandemics, in order to avoid contagion.

The Italian Health system and the Lombardy region, in order to treat the overall COVID-19 complications established a unique *COVID-19 Disease Unit* at the San Raffaele Hospital, Milan, Italy (144,161). Three different types of rehabilitation were organised: 1) a high-complexity rehabilitation treating neurological disorders, such as post-stroke, traumatic brain

injury, or spinal cord injury; 2) a medium-complexity rehabilitation treating cardiological, orthopaedic and post-infectious patients; and 3) a low-complexity rehabilitation treating chronic conditions (162). Therefore, the organization of COVID-19 rehabilitation units as an integral part of the therapeutic process is fundamental to cope with specific needs of this new clinical entity, not previously provided (163). Consequently, as proportion of patients with COVID-19–related disability could be rapidly grow, a prompt response from physical medicine and rehabilitation specialists is crucial to reduce disability and help re-establish and optimize the function of the acute hospital setting (146). It has been suggested that Rehabilitation Units should constitute an intermediary stage between ICU and discharge and should be prepared to ensure a proper management for patients with COVID-19-related disabilities, including the Post Intensive Care Syndrome (169-174).

Finally, when general condition of post-Covid patients is favourable, advanced treatment, including robotics with or without VR, could be take into consideration, given the efficacy in different neurological diseases (169-174).

Conclusions

COVID-19 primarily affects the respiratory and cardiovascular system. However, neurological involvement is not uncommon and, in some cases, can even precede the respiratory symptoms or may be the only symptoms in COVID-19 patients. The pathogenesis of CNS infection is likely related to the direct effect of the virus on the endothelium and the inflammatory cascade activation after COVID-19 increasing the risk of stroke, but many indirect mechanisms should be taken into consideration. The rapid spread of the COVID-19 pandemic will probably modify the organization and functioning of the healthcare services, including the rehabilitation treatments. However, this kind of treatment represents one of the fundamental field to better recover from critical and long-term COVID-19 consequences. Nonetheless, as no specific conclusions in term of prognosis and treatment could be done, research and consensus paper are needed to provide NeuroCovid patients with the best treatment options, including neurorehabilitation.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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