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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Review

Insights into neurological dysfunction of critically ill COVID-19 patients

Cristian Deana [a, *], Lorenzo Verriello [b], Giada Pauletto [b], Francesco Corradi [c, d], Francesco Forfori [d], Gianmaria Cammarota [e], Elena Bignami [f], Luigi Vetrugno [a, g], Tiziana Bove [a, g]

[a] Anesthesia and Intensive Care Department, Santa Maria della Misericordia Academic Hospital, ASUFC, Udine, Italy
[b] Neurology Unit, Department of Neurosciences, Santa Maria della Misericordia Academic Hospital, ASUFC, Udine, Italy
[c] Department of Anesthesiology, Ente Ospedaliero Ospedali Galliera, Genova, Italy
[d] Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine, University of Pisa, Pisa, Italy
[e] Department of Anesthesia and Intensive Care, Maggiore della Carità University Hospital, Novara, Italy
[f] Anesthesia, Intensive Care and Pain Therapy Service, University-Hospital of Parma, Parma, Italy
[g] Department of Medical Area, University of Udine, Udine, Italy

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ABSTRACT

Novel coronavirus spread rapidly around the world infecting millions of people. It was thus declared a pandemic. This new virus damages the lungs. In the most severe cases, it leads to acute respiratory failure that requires intensive care treatment. However, many clinical reports have listed different neurological symptoms, leading to increased interest in the neurological involvement of COVID-19.

Various pathophysiological mechanisms have been proposed to explain these neurological aspects. Direct viral invasion of the nervous system, systemic cytokine storm and severe hypoxemia are key factors in the development of symptoms.

Critically ill patients present several additional risk factors for nervous system damage. Reasons for these include deep sedation and extended muscular paralysis, bed rest for several days, and the inability to receive proper physical rehabilitation.

After ICU treatment, COVID-19 patients generally require an extensive rehabilitation program. However, distancing restrictions mean that in many cases physiotherapists are unable to enter ICUs, delaying the process of rehabilitation. The role of telemedicine should be considered as an adjunctive tool in the rehabilitation of critically ill COVID-19 patients.

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* Corresponding author. Anesthesia and Intensive Care 1, Anesthesia and Intensive Care Department, Santa Maria della Misericordia University Hospital, ASUFC, via Pozzuolo 330, 33100, Udine, Italy.
E-mail address: deana.cristian@gmail.com (C. Deana).

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1. Introduction

The first case of the novel coronavirus SARS-CoV2, responsible for Coronavirus Disease 19 (COVID-19), was reported in Wuhan, China, in December 2019. On March 11, 2020, it was declared a pandemic by World Health Organization [1].

The number of COVID-19 patients increased rapidly reaching more than 10 million in the world [2].

Hospitals faced a large number of admissions that often overwhelmed their routine capabilities.

The most severely affected patients were admitted to Intensive Care Units (ICU) [3]. The main reason for ICU admission was acute hypoxemic respiratory failure that required sedation, and muscular paralysis requiring extended mechanical ventilation. Of all patients admitted to the ICU in Lombardy, 99% required ventilatory support [4].

The majority of physicians focused mainly on respiratory failure. However, neurological symptoms, which were reported immediately, were frequently disregarded. We now know that these neurological manifestations can no longer to be overlooked. Indeed, several neurological complications have been reported [5]. A recent study of 214 COVID-19 patients by Mao et al. reported 33% of those hospitalized had manifestations involving the central nervous system (CNS) and the peripheral nervous system (PNS). Patients with severe infection were also more likely to develop neurological complications [6].

Neurological disorders related to COVID-19 have been addressed in large studies, case series and case reports. Some patients with COVID-19 present non-specific neurological symptoms, such as headache, myalgia, dizziness, excessive daytime sleepiness, and confusion [7]. A recent prospective study by Liguori et al. reported that of 103 hospitalized patients affected by COVID-19, 94 (91.3%) had early neurological symptoms that were expressed most frequently within the first two days of hospitalization [8]. Other studies have focused on more specific neurological manifestations, such as cerebrovascular disease, ataxia, seizures, cranial nerve involvement and Guillain-Barré syndrome [5,9–12]. The spectrum of acute neurological dysfunctions may implicate direct viral invasion, para-infectious complications, and neurological manifestations of systemic diseases or coincidental neurological diseases.

Table 1 shows the most reported neurological symptoms within the most populous studies.

The present narrative review analyzes the neurological alterations of COVID-19 critically ill patients admitted to ICU.

2. Pathophysiology of nervous system involvement

SARS-CoV-2 single-stranded RNA virus that is a member of the beta-coronoviridae family. Different mechanisms have been proposed to explain neurological damage produced by COVID-19. Direct CNS invasion, micro thrombosis, severe hypoxemia and systemic cytokine storm are the more likely causes [13].

However, it should be kept in mind that critically ill patients present additional factors related to the more severe illness that increase neurological damage risk (coloured Fig. 1). Examples of these factors include deep sedation, muscular paralysis, extended period of bed rest and multi-organ failure.

Several routes of direct CNS invasion can be used by neurotropic viruses, included both hematogenous and non-hematogenous routes (via the peripheral nerves or olfactory sensory neurons).

To date, no study has demonstrated that the novel coronavirus is able to pass the blood brain barrier (BBB). Case reports of COVID-19-related encephalitis suggest that this is possibly due to higher permeability of the BBB induced by systemic cytokines [7].

Increasing evidence shows that some coronaviruses may also enters the CNS through neuronal dissemination, whereby the viruses infect and migrate through the nerve endings. Viruses achieve this via the motor proteins dynein and kinesins, which are responsible for retrograde and anterograde neuronal transport [14].

Some coronaviruses have been shown to spread via a synapse-connected route to the medullary cardiorespiratory center from the mechanoreceptors and chemoreceptors present in the lung and lower respiratory airways. CNS infection by SARS-CoV with brainstem involvement has also been reported in patients and experimental animals. Given the high similarity between SARS-CoV and SARS-CoV2, it may be reasonable to assume that the potential invasion of CNS by SARS-CoV2 is partially responsible for the acute respiratory failure of patients with impaired ventilator response to severe hypoxemia (so-called 'silent hypoxemia') [15,16].

Viral neuroinvasion through the synapse-connected route can also occur via olfactory neurons [17]. The olfactory pathway begins with olfactory receptors in the epithelium of the mucous membrane. Each olfactory receptor cell sprouts two projections. One of these is a short peripheral dendrite, which reaches the surface of the epithelium. The other is a long and extremely thin axon (the olfactory nerve fiber), which reaches the cranial cavity by passing through the cribriform plate of the ethmoid bone, where it makes synapses with the cells present in the olfactory bulb.

Loss of smell alone or in combination with disorders of taste is frequently present in COVID-19 patients [18]. It is believed that SARS-CoV2 may enter the CNS using the olfactory pathway, as an altered sense of smell is a common manifestation of respiratory neurotropic viral invasion of the olfactory system. Like SARS-CoV, SARS-CoV2 infects cells by binding to the ACE2 receptor, which is expressed not only in nasal and oral mucosa but also in the nervous system. ACE2 receptor binding may hence be another gateway for the virus to invade the CNS [15].

Also antiviral medications may impact neurological manifestations in COVID-19 patients. The most frequently used antiviral drugs at the beginning of the pandemic (i.e. chloroquine and hydroxychloroquine) later demonstrated neurological side effects, such as seizures and peripheral neuropathy [19].

Likewise, other drugs used to limit COVID-19 (e.g., lopinavir/ritonavir, azithromycin, interferon, tocilizumab, etc.) are not free from neurological side effects [20,21].

Nutrition could play a role in neurological involvement. In a recent paper, Battaglini et al. describe the microbiota-gut-brain axis that is considered a regulator of the immune system after acute ischemic stroke [22].

There is a growing body of evidence about gut-brain crosstalk

Table 1
Available studies reporting neurological involvement in COVID-19 patients.

Author	N° of patients	Incidence of neurological involvement	Type of neurological symptom reported
Mao L. et al. [6]	214	36.4%	Dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, seizure, taste and smell impairment, vision disturbances, nerve pain
Helms J. et al. [90]	58	84.4%	Positive findings on CAM-ICU, agitation, corticospinal tract signs, dysexecutive syndrome, ischemic stroke
Gupta N. et al. [91]	21	13.6%	Headache
Vaira L.A. et al. [92]	320	19.4%	Chemosensory dysfunction
Lechien J.R. et al. [64]	417	88%	Olfactory and gustatory dysfunction
Varatharaj A. et al. [93]	153	74%	Cerebrovascular disease, altered mental status, peripheral nervous disease, vasculitis
Yan C.H. et al. [94]	59	71.2%	Ageusia, loss of smell, headache
Chen T. et al. [95]	274	11%	Headache, dizziness
Levinson R. et al. [96]	42	35.7%	Loss of smell, dysgeusia
Spinato G. et al. [97]	283	64.4%	Taste or smell disorder
Giacomelli A. et al. [98]	60	33.9%	Olfactory and taste disorders, headache,

The table below includes some of the available studies about neurological manifestations of COVID-19 infection. Incidence of these symptoms is various because of the different clinical manifestations. However the neurological symptoms in COVID-19 patients are not negligible.

and how gut dysbiosis negatively impacts CNS functioning and vice versa. This is well described in acute ischemic stroke. As in other critically ill patients, gut function in critically ill COVID-19 patients may be impaired, inducing delayed enteral feeding and its associated drawbacks. Similarly, acute CNS damage may impair gut function.

Nutrition as a whole could play an important role in maintaining a healthy gut. In addition, immunonutrition (containing ω-3, arginin, RNA) is an intriguing strategy for modulating immune response during the critically ill phase of COVID-19 patients. Unfortunately, however, there is little evidence in support of these claims [23].

3. Neurological disease manifestations

3.1. Cerebrovascular disease

In a study by Mao et al., 5.7% of patients with severe infection developed cerebrovascular disease, mainly ischemic stroke [6]. Acute ischemic stroke associated with COVID-19 can occur both early and later in the course of the disease [9,10].

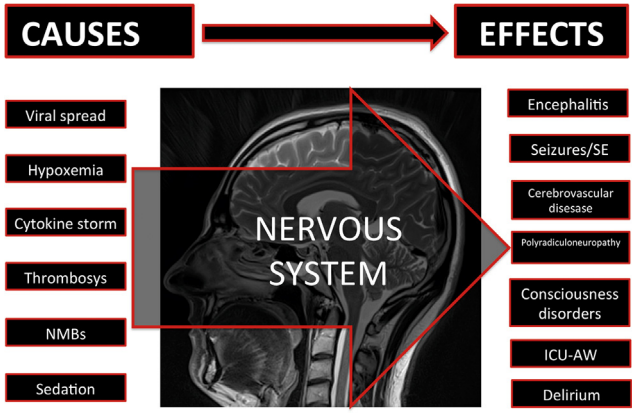

Fig. 1. Proposed causes to account for the neurological signs and symptoms reported in COVID-19 patients.

The pathophysiology and the optimal management of ischemic stroke associated with COVID-19 remain uncertain. Acute bacterial and viral infections, mainly respiratory infections, increase the risk of ischemic stroke. The association between acute infection and stroke results from the inflammatory response to infection, which induces a procoagulant state [24].

A recent study from the Netherlands reported that 31% of critically ill COVID-19 ICU patients developed thrombotic complications with autopsy findings suggesting thrombotic microangiopathy in multiple organs [25]. Moreover, COVID-19 patients frequently display coagulation dysfunction, such as thrombocytopenia and D-dimer increase. Based on this evidence, the likely mechanism of acute ischemic stroke in COVID-19 patients could be hypercoagulability, leading to macro- and micro-thrombi formation in the vessels [26]. This supports recommendations for immediate prophylactic anticoagulation with low molecular weight heparin (LMWH) [27].

However, while early therapeutic anticoagulation with LMWH reduces thromboembolism in patients with COVID-19, it must be balanced with the risk of hemorrhagic transformation in patients with acute ischemic stroke.

The same mechanism has been proposed to explain cerebral venous thrombosis in COVID-19 patients. However this neurological feature has only been described in a few case reports [28,29].

Unfortunately CT scan and MRI do not reveal any specific cerebral finding in COVID-19 patients. In addition, these exams entail transporting patients across the hospital, with a risk of viral spreading outside the BLUE line (the isolated area dedicated to COVID-19 patients). However, MRIs have revealed ischemic-hypoxic damage and lacunar infarcts, venous thrombosis and strokes [30].

In addition to the findings regarding pulmonary embolism, these demonstrate that such patients require proper anticoagulation. Non-invasive bedside multimodal neuromonitoring to reduce the risk of cerebral damage for stroke or intracranial haemorrhage in sedated patients is also suggested [31,32].

Although thromboembolic prophylaxis with subcutaneous low molecular weight heparin is recommended for all patients

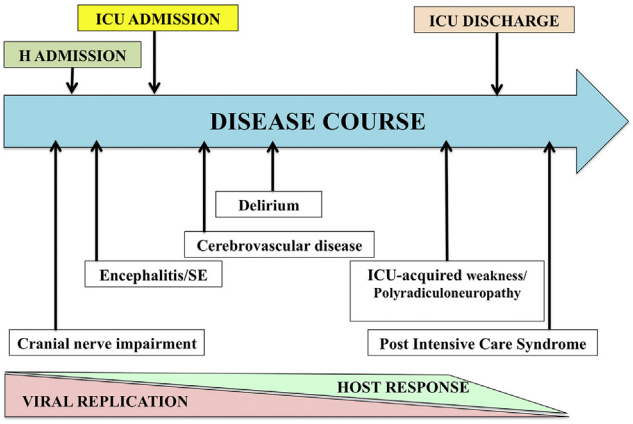

Fig. 2. Neurological manifestations during COVID-19 infection time course in critically ill patients.

hospitalized with COVID-19, studies to assess the best strategy to balance the risk of haemorrhage or thrombosis are ongoing [33].

3.2. Encephalitis, seizures, and status epilepticus

In February 2020, the first case of COVID-19 encephalitis was reported by Moriguchi et al. in Japan [34]. While the pathophysiology is not well understood, it seems that inflammation-related cerebral edema may explain the effects on consciousness and the need for ICU admission.

Acute necrotizing encephalitis has also been described in COVID-19 patients. However, this is an exceedingly rare and severe manifestation of the disease [35]. Seizures and status epilepticus (SE) are reported less frequently than expected in COVID-19 patients [36].

Direct invasion of the CNS, severe hypoxia, metabolic disarrangement, and systemic inflammatory response may cause acute symptomatic seizures or trigger seizures in subjects already suffering from epilepsy.

Historically, seizures have been described in SARS and MERS-related encephalitis, especially in children [37,38]. Other types of coronavirus infection have also been associated with febrile seizures in pediatric population [39].

Regarding COVID-19, one study specifically addressing neurological complications reported seizures in 0.5% of the studied population [6].

In February 2020, the first case of COVID-19 encephalitis was reported by Moriguchi et al. in Japan [34].

Case reports on acute infectious meningo-encephalitis due to direct invasion of the CNS by COVID-19 are limited. They are described mainly as meningo-encephalitis alone, with no respiratory symptoms and a positive test for COVID-19 [34,40].

Acute necrotizing encephalitis (ANE) has also been described in COVID-19 patients, as a rare and severe manifestation of the disease [35,41–43].

ANE is often rapidly progressive with reduced consciousness, seizure and vomiting. It usually occurs within 12–72 h of the onset of symptoms. Imaging includes symmetric multifocal lesions in the thalami, striatum, cerebral white matter and brain stem. Lesions appear as hypoattenuating on CT images, while MRI demonstrates T2-weighted hyperintense signal with internal haemorrhage. Cerebral Spinal Fluid (CSF) analysis frequently shows an elevated protein concentration, with normal white blood cell count. Testing for the presence of SARS-CoV2 in CSF is negative, except for one case in which the virus was detected after repeated CSF samplings [43]. ANE has been related to intracranial cytokine storms that cause focal damage of the blood-brain barrier, with edema and necrosis. Patients with ANE have a poor prognosis and there is no specific therapy indicated. However, immunotherapy with plasma exchange or intravenous immunoglobulin has been used, sometimes with encouraging results.

Seizures and/or SE are observed mainly in the context of COVID-19- related meningo-encephalitis [34]. In a few anecdotical cases, these are the clinical presentation of the disease [44,45].

In the ICU, seizures, or more frequently SE, may present with sub-clinical features such as subtle myoclonia or unexpected unresponsiveness leading to a delay in awakening from sedation. Non-convulsive epileptic manifestations may thus be underestimated in critically ill patients in the absence of continuous EEG monitoring. For this reason, it is recommended to start EEG monitoring if SE is suspected in COVID-19 patients. However, given the infectious risk, it is not easy to perform EEG in ICU for neurophysiology technicians. To overcome this problem, easy to use headset with EEG telemetry amplifier could be a valid option. This technology has recently been placed on the market. In this way ICU personnel would apply the EEG headset with disposable electrodes attached beforehand to a patients head and neurologist outside COVID-area could easily read and understand EEG pattern.

The clinical management of sustained seizures or SE in COVID-19 patients does not differ from the common management of SE [46]. However, it is necessary to choose appropriate anti-seizure medications (ASMs), taking into consideration drug interactions, age, respiratory, renal, hepatic, and cardiac functions [5]. ASMs with cardiac and respiratory adverse effects such as sodium blockers and barbiturates should be avoided. Even the new-generation sodium blocker, Lacosamide, should be cautiously prescribed in the presence of severe AV block, heart failure or concomitant medication that prolong PR and QT interval, such as chloroquine [47,48].

Levetiracetam and its new analogue Brivaracetam are safer, given their metabolism, poor drug interactions and lack of adverse cardio-respiratory events [49,50].

Likewise, Brivaracetam presents a favorable pharmacokinetic profile that is linear and predictable, with low inter-subjective variability and almost 100% bioavailability. Brivaracetam is a highly lipid soluble and rapidly crosses the BBB. It reaches the CNS within 10 min after intravenous administration, making it of use to critically ill patients experiencing recurrent seizures or SE [51–53].

Treatment with ASMs should be continued for about six weeks in case of acute symptomatic SE or seizures, than tapered under neurological overview and EEG controls. For COVID-19 patients already suffering from epilepsy, the subsequent management of recurrent seizures of SE may require a longer and more complicated neurological follow up due to possible consequences of severe hypoxia, fever, organ failure and systemic inflammation of epileptogenic foci (especially in epilepsy due to known causes), or epileptic encephalopathy [50].

The International League Against Epilepsy (ILAE) recommends attention to seizure control in epileptic patients during the pandemic period, as fever and respiratory difficulties may trigger seizures. Moreover, people under medication with uncontrolled seizures may descend into SE if not properly managed.

For this reason, telemedicine should be promoted in the context of a pandemic [54].

3.3. Delirium

Delirium is defined as: “an acute disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention” [55]. It generally fluctuates during the course of the day. The condition is very frequent

among critically ill patients, with rates reported up to 75% [56,57]. However, the use of screening tools remains low, resulting in many delirium episodes being undetected.

In their retrospective report, Mao and co-workers describe that only 7.5% of COVID-19 patients were documented as having "impaired consciousness" [6]. These data do not properly address the question of delirium within the COVID-19 population, and they are likely underestimated [58]. Indeed, delirium is a central issue in critically ill COVID-19 patients, as in addition to the classical risk factors for delirium (i.e. prolonged hospitalization, pain, sedation with benzodiazepines and antipsychotics, physical restraints, metabolic derangement, immobility, noise, etc.), they are exposed to other risks, in particular prolonged severe hypoxemia with the need for deep sedation and prolonged mechanical ventilation, severe cytokines storm, and direct CNS invasion.

Epidemiological aspects are also important. A large percentage of COVID-19 patients are elderly, for whom delirium is a common complication of respiratory disease. Environmental considerations must be added to all these factors, including isolation precautions, distancing from family, reduced and short physical contact with hospital staff, and protective equipment [59]. Likewise, sleep deprivation and circadian rhythm disarrangement due to the ICU setting, as well as direct pharmacological effects, may prolong and worsen delirium in critically ill patients. This is especially the case for elderly patients with pre-existing cognitive impairment.

Managing delirium in COVID-19 patients may be particularly difficult due to the overwhelming workload and the limited resources. However, regular pain assessment and delirium screening using tools such as CAM-ICU or ICDSC are recommended in COVID-19 patients [58].

The overuse of sedative and psychoactive drugs should be avoided whenever possible. The administration of melatonin (10 mg) or melatonin receptor agonists may improve the sleep-wake rhythm and consciousness disturbances in ICU patients, minimizing the need for antipsychotics [60–62]. Visual and vocal contact with family and loved ones via technological devices should be regularly provided to re-orientate patients, reduce their sense of loneliness and isolation, and facilitate recovery from delirium [58]. Patient waking up should interact with ICU personnel to provide mental stimulation, with a view to early mobilization [63]. Novel communication tools such as videocalls, tablets or headphones may be an important aid in reducing delirium and keep the patients in touch with relatives.

3.4. Cranial nerve impairment

Reduced or loss of smell have been reported the early stages of COVID-19. A recent prospective study of 417 patients in 12 European hospitals with mild to moderate laboratory-confirmed COVID-19 reported olfactory and gustatory dysfunctions in 85.6% and 88% of patients, respectively, with a significant association between the disorders. Olfactory dysfunction appeared before (11.8%), after (65.4%) or at the same time (22.8%) as the other symptoms, and significantly more often in women [64]. Two patients with Miller-Fisher syndrome and cranial polyneuritis linked to COVID-19 have been reported in Spain [11]. Two American COVID-19 patients with ophthalmoparesis have also been reported [65].

3.5. Neuromuscular complications

In subjects with COVID-19, it is mandatory to be vigilant for neuromuscular complications, which may be directly or indirectly related to the coronavirus infection [66]. Patients with COVID-19 infection may develop Guillain-Barrè syndrome (GBS), critical illness myopathy and/or polyneuropathy [7].

GBS is an acute inflammatory immune-mediated polyradiculoneuropathy. The initial symptoms are typically changes in sensation or pain along with muscle weakness, starting in the feet and hands, often spreading proximally [67]. In the most severe cases, respiratory function compromise requires ICU admission for ventilatory support. GBS is caused by an aberrant autoimmune response induced by various immunological triggers, most of which are antecedent infections caused by Campylobacter jejuni, Haemophilus influenzae, Mycoplasma pneumoniae or Cytomegalovirus. Recently, Zika virus has been associated with GBS [68]. It is likely that molecular mimicry between specific viral proteins and proteins on peripheral nerves cause an attack against the myelin or the axon of peripheral nerves.

Several cases of GBS have been associated with COVID-19 [69–74]. Most of these patients had fever and respiratory symptoms 5–10 days before the onset of the neurological manifestations. However, a few cases had no preceding fever or respiratory symptoms [12].

Regarding the electro-diagnostic features, classical demyelinating subtype and axonal variant have been described. In all cases, a real-time polymerase-chain reaction assay was negative for SARS-CoV2 in cerebrospinal fluid (CFS).

Given that SARS-CoV2 may be a trigger for GBS, we suggest testing for COVID-19 infection all new-diagnosed cases of GBS, even in subjects not complaining of previous or concomitant respiratory symptoms.

Two types of treatment can speed recovery and reduce the severity of the illness: plasma exchange (plasmapheresis) and immunoglobulin therapy. While both of these are equally effective, intravenous immunoglobulin is easier to administer. Mixing the treatments or administering them one after the other is no more effective than using either method alone. Supportive care, including careful monitoring of breathing and swallowing; use of a ventilator, if necessary; prevention or treatment of complications like pneumonia, blood clots in the veins of the legs, and bed sores; and pain control, are also important for patients with Guillain-Barrè syndrome.

Critically ill patients may develop acute and severe muscle weakness due to axonal sensorimotor polyneuropathy, termed critical illness polyneuropathy (CIP), acute primary myopathy, and the overlap critical illness, polyneuromyopathy (CIPNM). Unsurprisingly, patients with very severe COVID-19 develop critical illness neuropathy and myopathy. CIP and CIM are the most common causes of neuromuscular weakness in ICU, and a common cause of failure to wean from ventilation [61]. The real incidence of CIP and CIM is unknown due to wide variations in diagnostic criteria. Available data indicate very high percentages for both disorders: up to 58% of patients with prolonged ICU stay (>1 week) and 70–80% of patients with severe sepsis or multi-organ failure may develop CIP, while CIM presents an incidence ranging from 48 to 96% in critically ill patients [75–78].

The exact pathogenesis of these disorders is not completely understood. However, it is known that an increased production of cytokine linked to a systemic inflammatory response induces: 1) microvascular alteration (vasodilation, increased permeability, extravasation of leucocytes); 2) metabolic alteration (reactive oxygen species production, catabolic pathway activation, mitochondrial failure); 3) electrical alteration (sodium channel dysfunction and altered calcium homeostasis) [79].

There is no specific pharmacological treatment for CIP and myopathy acquired in ICU. However, recognizing these disorders often improves the management of these patients. Physical therapy and rehabilitation play an important role, and should be instituted as soon as possible.

Systemic inflammatory response syndrome (SIRS) is the major risk factor for CIP, and it plays an important role in critical illness myopathy. The aggressive treatment of underlying medical disorders and infections is likely reduce the incidence and the severity of these disorders.

Hyperglycemia has been associated with an increased risk of critical illness neuropathy and myopathy. When strict glycaemia control is achieved by means of intensive insulin therapy, the mortality rate of critically ill patients reduces significantly, as does the frequency of critical illness neuropathy and myopathy [80].

Patients with CIP may recover from neuropathy within weeks or months. Neurological recovery from CIP is variable and depends on the degree of axonal degeneration. Patients with severe forms of CIP and significant axonal degeneration may not recover completely, and distal sensory and motor impairment may persist indefinitely. In the case of critical illness myopathy, recovery is generally excellent in all patients within 1–3 months.

Infection with COVID-19 may exacerbate known neuromuscular disorders, such us autoimmune diseases (for example chronic inflammatory demyelinating polyneuropathy and myasthenia gravis) and degenerative illnesses. A retrospective study has shown infections to be the leading cause in the exacerbation of myasthenia gravis [81]. It is thus likely that we will see increased rates of disease worsening during the COVID-19 pandemic.

Patients with motor neuron disease, hereditary neuropathy, various muscular dystrophies, and metabolic myopathies, and who have ventilator muscle weakness present an increased risk for severe COVID-19 infection. Patients with neuromuscular disorders who use immunosuppressive therapies are at an increased risk of contracting COVID-19 or undergoing a more severe course of the disease.

Taking into consideration the number of neurological complications induced by SARS-CoV-2 and by prolonged ICU stay, we strongly believe that the neurologist should be part of the multidisciplinary team caring for ICU COVID-19 patients, in line with claims made by other authors [82].

ICU COVID-19 patients should undergo MRI and eventually lumbar puncture for cerebrospinal fluid investigation in the presence of symptoms suggesting CNS involvement, such as seizures, status epilepticus, altered consciousness and awareness, multiple cranial nerve impairment, vegetative disarrangement, delirium, and other behavioural disturbances. Moreover, cerebrospinal fluid investigations are mandatory in cases of suspected Guillain-Barrè Syndrome.

4. What care for COVID-19 patients after ICU? Suggestions for rehabilitation

After the critically ill acute phase COVID-19 is over, patients will require an extensive and prolonged rehabilitation program. Respiratory, neurocognitive, and physical, rehabilitation must be considered as standard. Rehabilitation clinical pathways should include a dedicated multidisciplinary team made up of pulmonologists, neurologists, cardiologists, nutritionists, physiotherapists, and neuropsychologists [83].

COVID-19 not only damages multiple organs such as the heart, lungs, brain, and kidneys, but also impairs functional activities and self-management. There are no reports about the requirements for post-COVID-19 rehabilitation. However, it is estimated that at least 40% of COVID-19 survivors will present fatigue or weakness after hospital discharge [84]. It is reasonable to assume that about 30% of ICU survivors will need facility-based care, while another 20% will require home care [85].

ICU survivors often experience physical and mental effects that persist for months or even years and that lead to reduced quality of life, inability to return to work, and disabilities in daily living [86,87].

A recent paper reported that up to 80% of patients discharged from the ICU and admitted to rehabilitation facilities present abnormal mini mental status examination (MMSE) or Montreal Cognitive Assessment (MoCA) [83]. This is significant, as these changes have a great impact on their daily lives. As a general principle, rehabilitation should aim at allowing the patients to acquire sufficient autonomy to be discharged into their homes. Pulmonary rehabilitation is required, especially for the non-negligible group of patients undergoing tracheostomy. However, as some patients still test positive for SARS-CoV2 after ICU discharge, the rehabilitation process requires dedicated wards, personnel, and equipment. It is also important to mention that rehabilitation for COVID-19 positive patients should be carried in location isolated from COVID-19 negative patients. However, limited resources mean this is unfortunately not always the case.

Again, telemedicine could represent a valid alternative, either in ICU or post-ICU. For instance, since physiotherapists must also continue their work with non-COVID-19 patients, it is important to avoid cross contacts to limit viral spread. Early rehabilitation starting in the ICU under the guidance of physiotherapist who can guide nurses by teleconference or videocalls may hence be an option. There are a number of reports regarding the use of telemedicine during pandemics, although this is not so widespread in ICUs. The acute phase of the COVID-19 pandemic has doubtless been extremely challenging. However, there will also be a post-acute phase, which will have to support survivors in providing an optimal functional recovery. Only via early rehabilitation programs will we be able to transform ICUs from “delirium factories” to places of proactive recovery and telemedicine may help us to achieve this goal [88,89].

5. Conclusions

The COVID-19 pandemic has spread rapidly. In the most severely affected patients, it is a multiorgan disease that mainly involves lungs. However, multiple neurological involvement along time course of the disease has been described frequently (coloured Fig. 2). While the pathophysiology is not completely understood, and requires further studies, it seems that COVID-19 could directly invade the CNS. Secondary causes such as hypoxemia and cytokine storm may also explain the neurological involvement. Different neurological symptoms have been reported, from mild to high severity. These include loss of smell, disorder of taste, consciousness alterations, encephalitis, and stroke. Critically ill COVID-19 patients admitted to ICU present additional risk factors for CNS damage, including severe prolonged hypoxemia requiring deep sedation and mechanical ventilation for long periods, the inability to move from bed due to rapid muscular atrophy, social isolation, and the impossibility of seeing loved ones with the consequent development of delirium. All of these present further challenges for the post acute phase of the pandemic.

Rehabilitating critically ill COVID-19 patients will require multiple resources and involve a range of different professionals such as nutritionists, physiotherapists and psychologists. Telemedicine could probably help in this regard, beginning inside the ICU environment and continuing throughout the rehabilitation process.

Legend: NMBs = neuromuscular blockers, SE = status epilepticus, ICU-AW = intensive care acquired weakness.

Neurological manifestations result from the interaction of viral spread, that represents the direct COVID-19 CNS invasion, and the host response. At the beginning of the ill direct viral effect probably represents the main cause of neurological symptoms. Over time, secondary effects of COVID-19 such as severe hypoxemia and

cytokine storm, play a pre-eminent role in causing neurological damage. Many of critically COVID-19 patients will present post intensive care syndrome after being discharged from the ICU.

Legend: H admission = hospital admission, ICU = intensive care unit, SE = status epilepticus.

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Author statement

Cristian Deana and Lorenzo Verriello equally contributed to this work: conceptualization, writing-original draft preparation, writing-review&editing, visualization and supervision.

Giada Pauletto: writing-original draft preparation, writing-review&editing, visualization. **Francesco Corradi:** writing-review&editing, visualization.

Francesco Forfori: writing-review&editing, visualization.

Gianmaria Cammarota: writing-review&editing, visualization.

Elena Bignami: writing-review&editing, visualization.

Luigi Vetrugno: conceptualization, writing-original draft preparation, writing-review&editing, visualization and supervision.

Tiziana Bove: writing-original draft preparation, writing-review&editing, visualization and supervision.

Luigi Vetrugno and Tiziana Bove share the senior authorship.

Declaration of competing interest

All authors declare no conflict of interest. Prof. Luigi Vetrugno received travel support for Congress lecture by Cook Medical.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tacc.2020.09.005.

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