https://doi.org/10.31925/farmacia.2022.6.2 **REVIEW**

THE EVOLUTION AND TREATMENT OPTIONS OF PATIENTS WITH COVID-19 AND NEUROLOGICAL MANIFESTATIONS – A NARRATIVE REVIEW

IRINA ODAJIU [1], DRAGOȘ SANDU [1], EUGENIA IRENE DAVIDESCU [1,2]*, BOGDAN OVIDIU POPESCU [1,2,3]

[1]*Neurology Department, Colentina Clinical Hospital, Bucharest, Romania*
[2]*"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[3]*Laboratory of Cell Biology, Neurosciences and Experimental Myology, "Victor Babeș" National Institute of Pathology, Bucharest, Romania*
[4]*"Matei Balș" National Institute of Infectious Diseases, Bucharest, Romania*

**corresponding author: eugenia.davidescu@umfcd.ro*

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Abstract

COVID-19 is a multisystem disease with considerable heterogeneity of manifestations, including neurological. Neurological manifestations occur in up to 2/3 of patients in the acute phase and include non-specific, central nervous system and peripheral nervous system disorders. This is potentially explained because the SARS-CoV-2 virus has neuroinvasive properties, either directly by retrograde transport *via* nerve terminations or hematogenous dissemination, and induces neuroinflammation. The persistence of the SARS-CoV-2 in the nervous tissue for an extended period combined with secondary changes determined by neuroinflammation and hypoxia could be potential explanatory mechanisms for the long-COVID neurological manifestations, which occur even more often than those in the acute phase of COVID-19. Since available specialized therapies against neurological manifestations are still lacking, existing treatment options directed against viral invasiveness, the effects of immune dysregulation and hypercoagulable state, along with supportive measures to combat hypoxia, could serve as an efficient treatment for patients with COVID-19 and neurological manifestations. By preventing the SARS-CoV-2 from affecting the nervous tissue in the acute phase, it could also be possible to avoid long-COVID neurological impairment and probably the potential development of neurodegenerative diseases.

Rezumat

COVID-19 este o maladie multisistemică cu o heterogenitate considerabilă de manifestări, inclusiv neurologice. Manifestările neurologice se întâlnesc până la 2/3 dintre pacienți în faza acută și includ afecțiuni non-specifice și afecțiuni ale sistemului nervos central și periferic. Aceasta se explică potențial prin faptul că virusul SARS-CoV-2 are proprietăți neuroinvazive, fie direct prin transport retrograd de-a lungul germinațiunilor nervoase sau prin diseminare hematogenă și inducere de neuroinflamație. Persistența SARS-CoV-2 în țesutul nervos pentru o perioadă extinsă în combinație cu modificările secundare determinate de neuroinflamație și hipoxie pot servi drept mecanisme potențiale pentru manifestările neurologice din *long*-COVID, care apar chiar mai frecvent decât cele din faza acută a COVID-19. Din moment ce terapiile disponibile specializate pentru manifestările neurologice încă lipsesc, opțiunile de tratament existente direcționate împotriva invaziei virale, efectelor dereglării imune și statusului de hipercoagulabilitate, împreună cu măsurile suportive pentru a combate hipoxia, ar putea servi drept tratament eficient pentru pacienții cu COVID-19 și manifestări neurologice. Prin prevenirea ca SARS-CoV-2 să afecteze țesutul nervos în faza acută, ar putea fi posibilă și evitarea manifestărilor neurologice din *long*-COVID și posibil a potențialei evoluții a bolilor neurodegenerative.

Keywords: COVID-19, long-covid, neurologic manifestations, treatment

Introduction

The novel Coronavirus Disease 2019 (COVID-19) has a great heterogeneity of manifestations. This is possible due to the involvement of the Angiotensin Converting Enzyme 2 receptor (ACE2), which is expressed in almost all tissues and organs, but especially in the endothelium of blood vessels [48]. Therefore, COVID-19 is a multisystem disease that includes in the acute phase in up 2/3 of patients a diverse range of neurological manifestations [105].

Neurological manifestations might be either secondary to the impairment of the respiratory, cardiovascular, gastrointestinal, or renal system or primary nervous system disorder due to SARS-CoV-2's a direct neuro-invasiness or as a result of neuroinflammation [42, 53]. Moreover, in the acute phase, COVID-19 patients can present almost all major described neurological disorders of the central and peripheral nervous system [42]. Additionally, because SARS-CoV-2 has neuro-invasive properties and the fact that it might persist

in the nervous tissue for a prolonged time [35, 124], it induces alterations either directly or mediated by the immune changes. Thus, it leads to manifestations that persist for long periods after the acute phase, included in the long-COVID entity [114]. Hypothetically, the pathological changes in the nervous tissue could even predispose to the development of neurodegenerative diseases [93].

Apart from supportive measures including supplemental oxygen to combat hypoxia, currently, available treatment options in COVID-19 are mainly directed against virus invasion into host cells, to halt the dysregulated immune response, and fight the immune-mediated hypercoagulability [101], which further leads to so-called disseminated immunothrombosis [57]. Specific therapies for neurological manifestations are still lacking, but there is a question whether existing therapies could make a difference in patients with COVID-19 and neurological manifestations.

In this narrative review, we intended to present the burden of the acute and long-COVID neurological manifestations along with their pathophysiological mechanisms and which current therapeutic options could be potentially helpful to reduce the impact of these manifestations in COVID-19 patients.

Materials and Methods

Relevant articles, mainly systematic reviews and meta-analyses available in English that included adult subjects, were included. The search was made in the PubMed Database, applying the following search items "neurological manifestations and COVID-19", "neurological manifestations and long-COVID" and "treatment and COVID-19".

Epidemiology of neurological manifestations in the acute phase COVID-19 patients

Since the publication of the first article describing the occurrence of neurological manifestations in patients infected with SARS-CoV-2 [82], many studies have tackled this aspect and presented a range of acute neurological manifestations in hospitalized patients between 13.5 - 66% [44, 75, 105]. Unfortunately, there is lacking data about the neurological involvement in patients with mild forms of COVID-19 that followed treatment at home. On the other hand, smell and taste disorders tend to occur more often in mild forms [20, 72], and according to a meta-analysis that involved healthcare workers who tested positive for SARS-CoV-2 infection, these are reported to occur in up to 70 - 85% of cases [119]. Therefore, we could assume that the actual incidence of neurological manifestations in all COVID-19 patients exceeds the one reported in hospitalized patients.

According to two large meta-analyses, the frequency of different neurological manifestations, one involving 168 articles with a total number of 292.693 subjects [50] and another including 240 studies with 190.785 subjects [121], is presented in Table I.

Apart from the manifestations recorded in both articles, other symptoms such as dizziness in 10% and vision impairment in 6% in the first meta-analysis [50], as well as fatigue in 33.6%, sleep disorders in 14.9%, movement disorders in 5.2% and neuralgia in 2.4% in the second meta-analysis [121], were also described.

Table I

Frequency of neurological manifestations in COVID-19 patients

Neurological manifestation	Yuanyuan He *et al.* [50]	Vitalakumar *et al.* [121]
Smell impairment	33%	26.4%
Taste dysfunction	33%	27.2%
Myalgia	33%	21.4%
Altered mental status	32%	17.1%
Headache	29%	14.6%
Encephalopathy	26%	23.5%
Confusion	13%	14.2%
Cerebrovascular diseases	12% - stroke 5% - intracerebral haemorrhage	9.9%
Dizziness	10%	6.7%
Seizure	4%	4.05%
Encephalitis	2%	0.6%
Guillain-Barré syndrome	1%	6.9%

Types of neurological manifestations in the acute phase of COVID-19

Types of neurological manifestations in the acute phase of COVID-19

In concordance with one of the first meta-analyses related to neurological manifestations involving 30,159 patients with COVID-19, these have been classified into three categories: (1) non-specific manifestations, including myalgia, headache, dizziness, vertigo and light-headedness; (2) central nervous system(CNS) manifestations – containing disturbances in consciousness, cerebrovascular diseases, seizures, encephalitis, encephalopathy, movement disorders, sleep disorders, neuropsychiatric symptoms, post-infectious myelitis, CNS vasculitis, demyelinating diseases and (3) peripheral

nervous system manifestations – including smell and taste disturbances, myositis, extraocular muscle abnormalities, cranial neuropathy, paraesthesia, Guillain-Barré syndrome, optic neuritis, neuralgia, dysautonomia and rhabdomyolysis [42].

Subtypes

Regarding the subtypes of the neurological manifestations, the following are mentioned: disorders of consciousness, seizures, cerebrovascular diseases, encephalitis and movement disorders.

Among *disorders of consciousness* that occur relatively frequently in hospitalized patients – stupor, coma and somnolence, in addition to bradypsychia and acute confusional syndrome, need to be enumerated [104]. Moreover, almost all types of *seizures* were reported, such as febrile, focal, generalized tonic-clonic, convulsive, non-convulsive and myoclonic status epilepticus, as well as brainstem type of myoclonus [42]. Speaking about the *cerebrovascular diseases*, ischemic stroke caused by – small vessel disease, large vessel disease, cardioembolic, as well as stroke of undetermined origin [2], haemorrhagic stroke, cerebral vasculitis and cerebral venous thrombosis are described in COVID-19 patients [18, 80, 118]. Moreover, various types of *encephalitis* were reported in this category of patients, including limbic, radiological acute disseminated encephalomyelitis, radiological acute haemorrhagic necrotizing encephalopathy and cytotoxic lesions of the corpus callosum [68]. Among reported *movement disorders* in COVID-19 patients – tremor, myoclonus, non-specific psychomotor agitation and balance problems were enumerated [89, 113].

Neuropsychiatric manifestations

Post-traumatic stress disorder, acute stress disorder, depression, impulsivity and insomnia are the most frequent neuropsychiatric entities related to COVID-19 [25, 110]. Moreover, there was observed a bi-directional relationship between psychiatric disorders and COVID-19. It is presumed that pre-existing psychiatric disorders could facilitate the development of COVID-19, and at the same time, COVID-19 patients tend to have more severe anxiety/depression disorders compared to controls [114].

Imaging characteristics of the neurological manifestations

The neurological manifestations of COVID-19 can be documented using neuroimaging, on which the following changes could be observed: white matter changes, encephalitis, infarcts, posterior reversible encephalopathy syndrome, microbleeds, subarachnoid haemorrhage, cortical superficial siderosis, infarcts, encephalitis, demyelination, occlusions, stenosis, vasculitis, perfusion abnormalities, blood-brain-barrier disruption and leptomeningeal enhancement. Therefore a special MRI protocol was proposed for COVID-19 patients, which should include the following: sagittal 3D T2-weighted FLAIR, axial 3D SWI, axial 2D T2-weighted imaging, sagittal 3D T1-weighted GRE IR/TSE, arterial TOF, ASL perfusion, contrast-enhanced perfusion and sagittal 3D T1-weighted TSE [3].

Neurological manifestations – as prognostic factors in COVID-19

The significance of recognizing the presence of neurological symptoms and manifestations as early as possible is related to the fact that they can serve as prognostic factors of COVID-19's evolution. This is because, in some cases, neurological features could develop even before classical features of COVID-19, such as fever and cough [1], as in the case of Guillain-Barré syndrome, which was either the first or the only presentation of infection [46].

An association between major neurological manifestations and increased mortality *versus* patients without such manifestations during COVID-19 is established [65, 105], which seems to be up to 32.6 times higher in COVID-19 patients according to a study [109]. Moreover, the presence of any neurological sign, symptom, or disorder served as an important death predictor in patients with COVID-19 [65]. Increased mortality risk was mainly related to the need for intensive care unit (ICU) admission or to patients who developed neurological manifestations while in the ICU [123]. Additionally, the presence of any neurological complications was also related to the urgency for acute rehabilitation and transfer to nursing facilities [44].

Interestingly, prior cerebrovascular and neuro-immunological disorders in patients with COVID-19 are not related to adverse short-term outcomes, but previous neurodegenerative and excessive tiredness on presentation seems to be linked to higher risk [66].

Stroke is a known neurological complication that substantially increases the disease severity and death risk in COVID-19 patients [87] and *vice versa*, patients with a more severe COVID-19 form are more predisposed to develop cerebrovascular diseases [71]. Although, in another systematic review, the authors state that there seems to be no association between COVID-19 severity and the risk of developing cerebrovascular disorders [6]. Apart from stroke, delirium was also linked to higher disease severity in COVID-19 patients as it leads to prolonged hospitalization, need for ICU admission, or in-hospital mortality [45, 85]. Furthermore, the presence of other disorders of consciousness also served as a mortality predictor [30]. In addition to stroke and consciousness disorders, myalgia, along with evidence of muscle injury and cardiovascular disease as well as encephalopathy, are also associated with severe forms of COVID-19 [132].

On the other hand, persistent olfactory dysfunction at 20 days of SARS-CoV-2 infection is also linked to disease severity [117]. Namely, chemosensory dysfunctions seem to be less likely associated with severe COVID-19 outcomes. Moreover, smell and

taste impairment could serve as diagnostic parameters for early isolation [20].

Potential pathophysiological mechanisms involved in the development of neurological manifestations in COVID-19

The main pathological processes responsible for neurological involvement in SARS-CoV-2 infection are presumed to be – the direct neural invasion *via* the hematogenous route or the retrograde pathway along peripheral nerve terminals, the inflammatory response and the immune dysregulation [42].

Neuroinvasiveness

Several nerves could be involved in the retrograde pathway along the nerve terminals. The most often described is the olfactory pathway [86]. It is presumed that by trans-synaptic invasion through the cribriform plate and olfactory bulb, the medulla could get invaded, and this could explain the central respiratory failure in critically ill infected patients [90].

Another potential route for SARS-CoV-2 neural invasion is *via* the trigeminal nerve by invading its sensory axon in the nasal cavity [86]. One post-mortem study remarked axonal degeneration and cell loss in the trigeminal nerve in COVID-19 patients [122]. Moreover, as the trigeminal nuclei act as a transportation hub between the terminal nerve endings and nucleus tractus solitarius in the brainstem, it could explain the development of micro-vascular clotting in some infected patients [106].

The vagus nerve is also listed as a potential entry route for SARS-CoV-2. Due to the increased expression of ACE2 on the gastrointestinal tract's epithelium, it is conceivable that the virus could invade the enteric plexus and move along the vagus nerve [106]. Or, according to other studies, SARS-CoV-2 could approach the vagus nerve *via* peripheral lung fibres as in influenza cases [74, 84]. In fact, in one study regarding brainstem neuropathology in SARS-CoV-2 infection, the virus was detected in vagus nerve fibres [22].

SARS-CoV-2 invasion *via* the hematogenous route is related to the fact that for the entry into host cells, the virus involves the ACE2, which is extensively expressed predominantly in the endothelial cells throughout most body parts [48], but also in the nervous system, including both neurons and glia cells in the cerebral cortex, striatum, substantia nigra and brainstem [70]. Other brain regions reported to have an increased expression of ACE2 are the posterior cingulum gyrus, middle temporal gyrus, olfactory bulb, contralateral medulla oblongata, nucleus solitarius, vagus nerve, astrocytes, microglia and oligodendroglia [35, 126]. Moreover, SARS-CoV-2 can penetrate the blood-brain-barrier (BBB) paracellularly due to its integrity alteration by systemic inflammation [53] and *via* S proteins of the SARS-CoV-2, which can substantially alter BBB properties [23]. In addition, it seems that macrophages and dendritic cells could serve as potential transportation means for viral entry into CNS [96].

Neuro-inflammation

Speaking about neuroinflammation, global inflammatory markers like interleukin (IL)-6, 12, 15, along with tumour necrosis factor α (TNF-α), can activate glial cells and lead to inflammatory reactions [125]. Moreover, it was established that reducing IL-6 levels is correlated with the amelioration of olfaction and taste dysfunction in COVID-19 [26]. Additionally, in stroke, as in other neurological manifestations, the neutrophil-lymphocyte ratio [116], C reactive protein [130] and serum ferritin are increased in a large proportion of patients with COVID-19 [8, 39]. Severe hypoxia, characteristic in many COVID-19 patients, can induce cerebrovascular dilation, oedema and ischemia [125]. Furthermore, in COVID-19 patients, there is an enhancement of the hypoxia-inducing genes in the brain disease-gene network, involving CUL2, TP53, UBC and MDM2 [98]. Associated brain hypoxia due to COVID-19 is also engaged in enhancing microglia transformation into a proinflammatory phenotype, leading to inflammatory cytokine production [43]. This favours the alteration of BBB integrity, which will further allow even more inflammatory cells to penetrate into CNS. The infiltrating T cells may afterwards induce axonal injury and demyelination [36]. Additionally, lymphocytes will also activate microglia, which release inflammatory cytokines, also favouring demyelination and neuronal death. Whereas infiltrating neutrophils lead to oligodendrocyte apoptosis [122]. All of these influences will eventually result in the neurological manifestations of COVID-19.

Neurological manifestations of long-COVID

Defining features

Lately, more evidence has emerged that neurological manifestations in patients with COVID-19 can occur in the acute period and weeks or even months after the infection – the so-called long COVID. Long COVID is defined as a set of symptoms or features that accompanies the patient for a prolonged time after hospital discharge [115]. The period when symptoms are related to long COVID was established to start three weeks after the acute phase of COVID-19, but it also includes symptoms appearing even after three months [10]. Long COVID, apart from neurological manifestations, encompasses also cardio-vascular, respiratory, gastrointestinal, musculoskeletal, inflammatory, generalized and non-specific [140].

Frequency

The frequency of long-term neurological symptoms after SARS-CoV-2 infection is estimated to be around 80%, according to a meta-analysis involving 47.910 patients, out of which fatigue (58%), headache (44%) and attention disorder (27%) were the most commonly

reported [76]. A detailed overall prevalence of long-COVID neurological manifestations is presented in Table II, data from a meta-analysis that encompassed 10.530 patients [99].

Table II

Frequency of long-COVID neurological manifestations

Manifestation	Percentage (range)
Fatigue	37% (25 - 48%)
Brain fog	32% (10 - 54%)
Memory issues	28% (22 - 35%)
Attention disorder	22% (7 - 36%)
Myalgia	17% (9 - 25%)
Headache	15% (4 - 26%)
Anosmia	12% (8 - 16%)
Dysgeusia	10% (6 - 14%)
Neuropsychiatric conditions:	
Sleep disturbances	31% (19 - 24%)
Anxiety	15% (14 - 32%)
Depression	17% (10 - 24%)

The duration of long-COVID neurological manifestations is not established. Data suggest that sleep disorders [54], double vision, hallucinations, disorientation, impaired attention, facial paralysis and hypogeusia persist even more than six months after initial infection [64]. Moreover, their persistence was higher in patients who had to be admitted to the ICU during the acute phase of COVID-19 [99]. On the other hand, it was observed that anosmia and dysgeusia are more characteristic of the acute phase and usually do not persist or develop after three months from the initial SARS-CoV-2 infection [114].

Pathophysiological mechanisms

Concerning the pathological mechanisms related to neurological manifestations in long-COVID, it is presumed that SARS-CoV-2 RNA could potentially remain in the brain tissue for prolonged periods, thus aggravating the neuronal loss over time [35, 124]. Neuroimaging alterations recorded after the acute phase of COVID-19 could prove SARS-CoV-2 RNA's prolonged stay in brain tissue. Most evident modifications appear on PET imaging, usually in the form of hypo-metabolism in different brain regions such as the right parahippocampal gyrus, thalamus [108], bilateral rectal/orbital gyrus including the olfactory gyrus, right temporal lobe including the amygdala and hippocampus, bilateral pons/medulla, bilateral cerebellum [47], cingulate and precuneus [40, 56].

Neuro-inflammation, which seems to be prolonged due to the entry of innate immune cells through altered BBB and oxidative stress, are documented pathological mechanisms responsible for hippocampal and hypoxic-ischemic changes, cortical atrophy and small vessel disease [11, 12, 35, 134]. Another hypothesis states that the neurological manifestations of long-COVID may derive from persistent brainstem dysfunction because there the regeneration rate of neurons is scarce, and in the brainstem reside the most important respiratory, cardiovascular, gastrointestinal and neurological centres. Moreover, the invasion of SARS-CoV-2 in the brainstem could disrupt neurotransmitter systems, leading to neurological symptoms [134]. Another important fact is that ACE2, involved in the SARS-CoV-2 cell invasion, is significantly expressed in the cerebral cortex, amygdala and brainstem [77].

Serious concern was raised after it was established that following the onset of the inflammatory cascade in brain tissue, it could lead to α-synuclein and amyloid fibres aggregation [79], which is well-known to occur in neurodegenerative diseases. This could happen due to the implication of the following genes APP, TP53, MYC1, VCP and UBC, which are involved in protein misfolding and aggregation, ultimately leading to cell death [98]. Therefore, there is a potential risk that patients infected with SARS-CoV-2 could later develop neurodegenerative diseases such as Parkinson's disease or Alzheimer's [95].

Existing treatment options for COVID-19

General current available therapeutic options in COVID-19

The available therapeutic options for COVID-19 patients have to be repurposed through already existing drugs designed for other disorders due to the stringent need to handle the severe burden of the disease. They are mainly centred around three main domains: agents to prevent viral invasion and replication, including protease and RNA-dependent RNA-polymerase (RdRp) inhibitors [137], immunomodulators directed to reduce the dysregulated host immune response mainly in severe forms, and agents to oppose the effects of hypercoagulable state [101].

According to their directed action, all disposable drugs are presented in Table III.

Table III

Therapeutic options in COVID-19

Treatment	Established efficacy in COVID-19
Antiviral agents	
Viral entry and membrane fusion inhibitors:	
Umifenovir	- According to two meta-analyses, it proved no benefit compared to non-antivirals or other therapeutic agents [4]. However, in another one, the results showed that it might be superior to lopinavir/ritonavir, inducing a higher positive-to-negative conversion rate and higher amelioration of the chest computer tomography alterations [135].

Treatment	Established efficacy in COVID-19
Hydroxychloroquine and chloroquine	- although small initial studies [28] suggested that these drugs could be efficient against SARS-CoV-2, following studies: including small reports [37], more extensive randomized trials [5] and meta-analyses [32, 107, 131] found no benefit, on the contrary, a higher mortality risk due to adverse reactions, especially in combination with azithromycin [131].
ACE2 inhibitors and angiotensin II receptor blocker (ARB)	- according to one study, these agents might reduce the viral load due to the binding of the virus to the "false receptor" by using recombinant ACE2 intravenous infusion, and the patients usually show a less severe disease course [88]. Additionally, a meta-analysis proved that these drugs might have protective benefits, especially for hypertensive patients [13].
Protease inhibitors:	
Lopinavir/ritonavir	- although it proved beneficial against SARS-CoV-1 [34], the RECOVERY trial concluded that there was no benefit in hospitalized patients [142].
RdRp inhibitors	
Remdesivir	- early evidence from the adaptive COVID-19 treatment trial [17] was later supported by a meta-analysis that proved the significant improvement in the 28-day recovery, low flow oxygen support and invasive mechanical ventilation or extracorporeal membrane oxygenation as well as a lower risk of developing severe adverse drug reactions. Moreover, it suggested no difference between the 5-day regimen and the 10-day, the 5-day causing a reduced number of adverse events [103].
Favipiravir	- according to a meta-analysis and systematic review, it leads to viral clearance and clinical improvement within 14 days [81]. However, another meta-analysis showed no significant difference between treated patients and controls regarding mortality or mechanical ventilation need [95].
Inhibitors of nuclear transport proteins	
Ivermectin	- although with low certainty of evidence, several studies, including three meta-analyses [21, 67, 136], proved that this agent could reduce mortality, especially in severe forms [102].
Agents directed against the dysregulated immune response	
Corticosteroids	- in line with the RECOVERY trial, dexamethasone is beneficial for patients with moderate to severe COVID-19 who require oxygen supplementation [51]. In comparison, acute corticosteroid administration is also helpful in reducing mortality, according to two extensive systematic reviews [24, 111], though it did not influence the risk of admission to ICU, endotracheal tube placement and the need for mechanical ventilation [41].
Immunomodulators:	
Anti-IL-6 monoclonal antibody (Tocilizumab)	- starting with small reports that demonstrated the positive effect on COVID-19 patients [38], followed by results from randomized controlled trials like RECOVERY, that showed a reduced risk of impending intubation or death [52], supported by meta-analysis [69]. According to another one, Tocilizumab reduced superinfections and the need for ICU and mechanical ventilation [7].
IL-1 receptor antagonist (Anakinra)	- it also proved to reduce mortality and the need for mechanical ventilation, according to two meta-analyses [14, 97].
Neutralizing IgG1K monoclonal antibody (Bamlanivimab)	- this drug was interrupted early in the ACTIV-3 trial due to a lack of any clinical improvement on day 5 [78], but in BLAZE-I proved to induce an accelerated viral load decline by day 11 and reduced hospitalization rates [29] and also had positive results in another study [141].
JAK kinase inhibitors (Baracitinib)	- according to one study, it had a modest effect on the primary outcome of median recovery time and reduced the need for mechanical ventilation when added to remdesivir [62]. A systematic review and meta-analysis also showed reduced all-cause mortality, shorter clinical recovery rate and reduced need for mechanical ventilation when JAK inhibitors are administered [27].
Colchicine	- due to its diverse anti-inflammatory effects and alteration of the intracellular transport of viral particles, it reduces mortality but makes no difference in ICU admission risk [31, 49].
Azithromycin	- though it suppresses T-helper 1 and 2 lymphocyte-related cytokines(IL-1, IL-6, TNFα), an interferon-inducible protein 10, it did not influence mortality or the need for mechanical ventilation and thus is not justified in COVID-19 treatment according to a meta-analysis [63].
Intravenous immunoglobulins	- in concordance with the meta-analysis results, this treatment did not reduce mortality, and there was no difference between the severe and non-severe groups [127].

Treatment	Established efficacy in COVID-19
Anticoagulants	- prophylactic enoxaparin dose proved to be beneficial for improvement in gas exchange and release from mechanical ventilation in concordance with the HESACOVID trial [73], in contrast to the interim results of another trial, indicating that therapeutic anticoagulation was associated with decreased need for mechanical support and mortality [138]. This was not supported by a meta-analysis, according to which higher-dose anticoagulation was not associated with a reduced mortality rate but increased the risk of major bleeding [60].

If to summarize the efficacy of the available therapies, it was concluded that in comparison to the standard of care, the risk of mortality was reduced by tocilizumab, bamlanivimab and intravenous immunoglobulins. Baricitinib + remdesivir, colchicine and dexamethasone diminished the need for mechanical ventilation, whereas shorter hospitalization was linked with the use of remdesivir, tocilizumab and baricitinib + remdesivir. In contrast, the viral clearance rate was augmented by ivermectin and ivermectin + doxycycline. Generally speaking, tocilizumab achieved the best results in COVID-19 patients compared to standard of care in terms of reduced mortality, mechanical ventilation rates and increased hospital discharge rate [137].

Among other studied treatment options, antiplatelet therapy was also reported to be independently associated with the reduced need for mechanical ventilation and in-hospital mortality due to its anti-inflammatory effects, antiplatelet aggregation and potential antiviral properties [33]. Another helpful treatment is high-dose vitamin C, which was described to ameliorate the pro-inflammatory response, enhance the barrier function of the epithelium and might also prevent coagulation abnormalities related to sepsis in patients with acute respiratory distress syndrome [19]. Therefore, according to a meta-analysis, it could be an efficient treatment in COVID-19 patients, but randomized trials need to be performed [55]. On the other hand, although initially, in a correlational study, convalescent plasma seemed to induce lower mortality [61], later on, confirmed to have no positive influence on COVID-19 patients, according to the results of a systematic review and meta-analysis [59].

Treatment options with a potential impact on neurological manifestations in COVID-19

Managing neurological manifestations is of utmost importance due to their usual negative influence on COVID-19's evolution in infected patients, except for chemosensory alterations [126]. However, there have not been yet elaborated specialized treatment options for neurological manifestations of COVID-19, apart from established standard therapies, most of which address symptomatology, such as, for example, antiseizure drugs for seizures; immunoglobulins, or plasmapheresis for Guillain-Barré. Considering the pathophysiology of neurological alterations in COVID-19 patients, the available therapeutic options could help prevent neuroinvasion and neuro-inflammation. For example, umifenovir [135], remdesivir [103], favipiravir [95], ACE2 inhibitors and ARB [88] and ivermectin [136], with established results to increase the viral clearance rate, might also prevent neuroinvasion if they are instituted as early as possible in SARS-CoV-2 infection. Regarding neuro-inflammation, such drugs as anti-IL-6 monoclonal antibodies [69], IL-1 receptor antagonists [14], JAK kinase inhibitors [62], neutralizing IgG1K monoclonal antibodies [141] and probably also colchicine [49] could help to reduce the amount of neuronal and glial cells alteration. It is also essential to timely administer immunomodulators in patients with a dysregulated immune response, ideally before the onset of neurological symptoms. Since in COVID-19 patients, there is a hypercoagulable state that can potentially induce disseminated micro-thrombosis and venous thromboembolism [92], anti-coagulants are mandatory in all COVID-19 patients, especially in those with neurological manifestations either to prevent or to treat cerebrovascular diseases.

Moreover, it is compulsory to manage hypoxia by using supplemental oxygen either through nasal cannulas, facial masks, or even mechanical ventilation for severe forms because of the deleterious effects of hypoxia on nervous tissue, leading to severe sequelae [35]. Apart from these measures, timely neuro-rehabilitation [15] should be instituted as early as possible for patients with acute manifestations to prevent the onset of long-COVID symptoms and for those with long-COVID to ameliorate the evolution. Another effective option against COVID-19 complications, including neurological, is the available vaccines, especially mRNA-based ones, which help prevent the development of severe COVID-19 forms [9, 94]. In combination with other prevention methods, such as social distance and wearing protective masks, vaccines could help prevent SARS-CoV-2 infection [139].

By reducing or even preventing the neuroinvasion and neuro-inflammation in the initial phase of COVID-19, it would be possible to prevent the establishment of acute neurological manifestations and the long-COVID ones. As it is not yet known how long the manifestations of long-COVID persist, and taking into consideration the possibility that SARS-CoV-2 infection might, later on, induce neurodegenerative diseases [93], by preventing their onset, it would be possible to significantly ameliorate the quality of life of these patients and the burden on the healthcare system.

Future directions

Regarding future directions for COVID-19 treatment options in general and its neurological manifestations in particular, more specialized therapies are needed that could have a more decisive action against the invasiveness of the virus and immunomodulation.

Among novel advanced potential therapies in COVID-19 patients is selinexor – a selective inhibitor of nuclear export (SINE) compound that blocks the cellular protein XPO1, which enables viral proteins' transport from nucleus to cytoplasm, which has already been enrolled in randomized clinical trials for COVID-19 patients [143]. Moreover, stem-cell-based therapies, designed as a tool for personalized medicine, could also be used due to their immunomodulatory and regenerative properties. Due to data lacking regarding their safety, tumorigenicity and potential profibrogenicity, no clear conclusion has been established so far [16].

Another interesting developing therapy option are nanobodies – a novel class of recombinant antibodies, originating from heavy-chain antibodies from sharks and camels [83]. Among their advantages are – their small size, perfect water solubility, stability, suitability for large scale production and inhalation and low immunogenicity [91]. Regarding SARS-CoV-2, these molecules could either block the interaction between spike and receptor-binding domain to ACE2 or have an inhibitory effect against spike receptor-binding domain of SARS-CoV-2 [128].

Additionally, more than seven trials are ongoing on testing molnupiravir – a new antiviral treatment, which acts by inhibiting the RdRp enzyme of SARS-CoV-2, and thus inducing several errors in the RNA virus replication [116, 100]. In this line another antiviral tested in clinical trials is Camostat Mesilate, a potent inhibitor of SARS-CoV-2's entry ability by reducing the expression the TMPRSS2 protease [112]. Dasabuvir is another antiviral, which is being investigated in clinical trials and acts by inhibiting the activity of PL^{PRO} and $3CL^{PRO}$, 2 SARS-CoV-2 proteases that manage the virus' life cycle [58]. These are only a few of the many more other molecules investigated for their potential use against SARS-CoV-2, but more qualitative studies need to be performed in order to prove their real efficacy in patients with COVID-19.

Conclusions

COVID-19 might induce various acute and long-lasting neurological manifestations, some of which might severely impact the patients. Moreover, SARS-CoV-2 could potentially lead to the development of neurodegenerative diseases. Therefore, it is of utmost importance to either prevent the infection or halt it as early as possible by instituting effective treatment options at the earliest signs of infection, thus preventing neuronal injuries.

Conflict of interest

The authors declare no conflict of interest.

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