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REVIEW

Neurological manifestations of COVID-19: a systematic review and detailed comprehension

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ABSTRACT

The current pandemic caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is accompanied with a rapid increase of reports and papers detailing its neurological effects and symptoms. The virus infection causes respiratory illness named by the world health organization as corona virus 19 (COVID-19).This systematic review aims to study and summarize the different neurological manifestations of this virus. All articles published and indexed via Pubmed, Medline and Google Scholar databases between January 1st 2020 and February 28th 2021 that reported neurological symptoms of SARS-CoV-2 are reviewed following the Preferred Reporting Items for Systemic review and Meta-Analysis (PRISMA) guidelines.We included data from 113 articles: eight prospective studies, 25 retrospective studies and the rest were case reports/series. COVID-19 can present with central nervous system manifestations, such as headache, encephalitis and encephalopathy, peripheral nervous system manifestations, such as anosmia, ageusia and Guillian Barre syndrome, and skeletal muscle manifestations, such as myalgia and myasthenia gravis. Our systematic review showed that COVID-19 can be manifested by a wide spectrum of neurological symptoms reported either in the early stage or within the course of the disease. However, a detailed comprehension of these manifestations is required and more studies are needed in order to improve our scientific knowledge and to develop preventive and therapeutic measures to control this pandemic.

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1. Introduction

Corona viruses (CoV) are known to be the largest RNA viruses family whose genome sizes vary from 26 to 32 kb in length [1]. In December 2019, a new virus belonging to beta-corona virus subfamily called 'severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)' was reported to emerge in China causing a rapid and urgent outbreak and being the seventh known corona virus to infect humans; SARS-CoV-2 genome encodes for several structural proteins including spike protein (S), nucleocapsid protein (E), membrane protein (M) and envelope protein (N) [2]. The virus infection causes respiratory illness named by the world health organization as corona virus 19 (COVID-19). Due to its rapid and ease contagiousness, it spreads rapidly to the whole world causing a pandemic disease, becoming a global challenge with many social and economic devastating effects [3,4].

COVID-19 transmission can occur by either direct mode from covid-19 positive human to human transmission through respiratory droplets or indirect mode from contaminated surfaces and objects and airborne contagions to humans [5]. Disease presentation ranges from asymptomatic (in rare cases) to severe pneumonia and death [6]. The symptoms of this pandemic disease range from mild to moderate in most cases, and sometimes severe with high death risk especially in elderly people and those suffering from chronic diseases such as cancer, diabetes, hypertension, chronic obstructive pulmonary diseases and others. The most common symptoms identified include lower respiratory tract infection, pneumonia, dry cough, fever, shortness of breath and myalgia; other symptoms may occur but less frequently reported including confusion, sore throat, hemoptysis, runny nose, chills, chest pain, rhinorrhea, and diarrhea with nausea and vomiting [4].

Several vaccines and specific anti-viral medicines targeting various SARS-CoV-2 proteins have been recently developed and applied to prevent further disease progression and decrease mortality rate worldwide, while others are still under investigation. Nonetheless, hand washing, social distancing and personal hygiene remain the most effective measures to control the outbreak [6].

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SARS-CoV-2 invasion and infection are mediated primarily through the virus surface S proteins by interacting with angiotensin-converting enzyme 2 (ACE2) receptors expressed on the surfaces of a variety of our cells mediating thus viral cell entry [2]. ACE2 receptors are abundant in lungs, but they are also found in kidney, intestine, brain and capillary endothelium [7]. Therefore, it is evident why virologists reported that the lung is the main but not the only target of SARS-CoV-2 infection.

Despite the prominence of respiratory symptoms, there is emerging literature on diverse neurological manifestations reported more commonly by elderly COVID-19 patients and those with systemic diseases and medical comorbidities associated with higher disability and mortality rate [8]. SARS-CoV-2 entry to the brain is still a challenged question and many theories are hypothesized. For example, the virus can enter *via* retrograde axonal transport through the olfactory, respiratory, and enteric nervous system networks, or it can cross the blood brain barrier after damaging the endothelial lining [7]. Once in the brain tissue, the virus can interact with neurons as well as non-neuron cells (mainly astrocytes, oligodendrocytes and endothelial cells) expressing ACE2 receptors distributed in many brain regions such as the cerebral cortex, striatum, brain stem, choroid plexus, paraventricular nuclei of the thalamus, middle temporal gyrus and posterior cingulate gyrus [9]. This distribution can explain partially the different neurological complications resulting from COVID-19 infection that range from mild such as headache, dizziness and smell impairment to severe complications such as seizures, intracerebral hemorrhage and stroke [7,10].

Recently, the frequency of neurological symptoms reported by SARS-CoV-2- infected patients increased significantly. This systematic review aims to summarize the literature concerning the different neurological manifestations associated with COVID-19, including the central nervous system, the peripheral nervous system and the skeletal muscle involvement. We also aim to discuss the different hypotheses underlying the pathophysiology of such neurological manifestations in order to improve our knowledge about COVID-19 as well as to facilitate the decision-making by the clinicians treating COVID-19.

2. Materials and methods

2.1. Study design

This study is a systematic review that sums up all the primary search findings in order to produce a reliable summary of all identified neurological manifestations of COVID-19.

2.2. Literature search strategy

Our systematic review follows PRISMA guidelines for systematic reviews and meta-analyses. A deep electronic literature search was done for published studies assessing neurological symptoms of COVID-19 between January 1st 2020 to February 28th 2021 using Pubmed, Medline and google scholar databases. All reference lists were also checked in order to cover all relevant studies concerning the neurological complications associated with COVID-19. Keywords and search terms were linked using the Boolean search operators 'AND' and 'OR'. The following search strategies combining terms of interest were adopted: 'neurological symptoms' **OR '**neurological alterations' **OR** 'neurological manifestations' **OR** 'brain damage' **OR 'neuropathy' OR 'neuromuscular' AND** 'COVID-19' **OR** 'SARS-CoV-2' **OR** 'nCoV' **OR '**novel coronavirus'. All resulting studies were identified and saved separately on Mendeley software in order to remove duplicate records and to create our bibliography; the first round of screening based on titles and abstract was done in order to eliminate irrelevant studies, then the second round was conducted on full-text of all remaining articles that were assessed again for eligibility criteria.

2.3. Eligibility criteria

The included articles in this review have met the following inclusion criteria:

- Population: Patients tested positive for SARS-CoV-2.
- Outcome: Any aspects of neurological manifestations reported in SARS-Cov-2 positive patients.
- Study design: Randomized clinical trials, cross sectional, case reports and series, clinical trials and cohort studies.
- Language: All articles published in English and French.

We excluded all review articles and studies assessing neurological manifestations of other corona virus infection types.

2.4. Data collection

2.4.1. Data extraction

Data was extracted from eligible articles into a data extraction sheet based on the PRISMA guidelines; the following criteria were collected from each study: first author, study design, site of the study, time of publication, sample size if possible and reported neurological manifestations.

2.4.2. Data analysis

The results of selected articles were synthetized and classified into three categories: central nervous system, peripheral nervous system and skeletal muscle manifestations.

3. Results

A total of 651 articles were yielded in our literature. After removing duplicates, and after first and second rounds of screening, 113 articles meeting the inclusion criteria were included in our systematic review (Figure 1). The characteristics of these studies are summarized in Table 1; there were eight prospective studies [56,60–62,83–86], twenty five retrospective studies [55,57–59,63–82,87], and the rest were case reports/series.

3.1. CNS manifestations

3.1.1. Headache and dizziness

Headache is one of the most common neurologic manifestations associated with COVID-19. In addition to the increasing number of case reports/series of patients presenting headache after corona virus infection; three prospective and 10 retrospective studies reported COVID-19 patients presenting headache in different proportions ranging from 3.7% to 43%. New-onset headache was reported by a cross-sectional study in 22.6% out of 106 patients presenting first COVID-19 sign as neurological [68]. In addition, another cross-sectional study assessing the semiological characteristics of headache showed that 68.3% of COVID-19 patients reported headache most frequently presented as holocranial or bifrontal [63]. Further, a retrospective study showed that headache is associated with lower scores in memory and global cognitive functions [59].

Moreover, a single case aged 78 years was reported to present dizziness as the only neurologic symptom after COVID-19 infection [31]; two prospective studies showed that 10% out of 133 and 6.7% out of 239 COVID-19 cases developed dizziness in Italy and Turkey respectively [60,84]. Further, dizziness characterized sometimes as the initial registered neurologic symptom, was reported by three retrospective studies from 0.9% out of 1682 to 16.8% out of 214 COVID-19 patients [76,77,79].

3.1.2. Stroke/cerebrovascular complications

There is a growing body of evidence that cerebrovascular accidents including ischemic stroke, thrombosis and other hypercoagulable complications leading to variant degrees of vessels occlusion and damage to different tissues may occur after COVID-19 infection.

A retrospective observational study from Bergamo in Italy reported that 8.2% out of 1760 COVID-19 patients had neurologic complications of which 38.7% developed cerebrovascular diseases (CVD) including ischemic strokes, hemorrhagic strokes, transient ischemic attacks and cerebral venous thrombosis associated with elevated D-dimer values in all of them [71].

In Spain, a retrospective observational study of patients admitted to the ICU due to severe respiratory symptoms secondary to SARS-CoV-2 infection showed that 13.33% out of 30 patients (whose mean age ± SD was 57.41 ± 11.61) presented with CVD. All cases were negative to SARS-CoV-2 infection in the CSF [80]. A similar study design of MRI findings in COVID-19 patients in France showed abnormal MRI findings two to four weeks after symptoms onset including acute ischemic infarct (23.3%) and deep venous thrombosis (1.4%) from 73 patients aged 58.5 years ± 15.6 [82].

A retrospective analysis of stroke in USA showed that half of 16 patients developed large vessel occlusion (LVO) while the rest had non-LVO with median age 55 and 65.5 years, respectively. Even though D-dimer levels were similar in all of these patients, ferritin, C-reactive proteins (CRP), procalcitonin as well as the mortality rate were higher in the LVO compared to the non-LVO group [57].

A prospective study from Turkey found that 34.7% out of 239 patients aged 46.46 ± 15.41 years had neurological manifestations of which 3.8% had CVD including two patients evaluated as hemorrhagic CVD, three as transient ischemic attack and 4 as ischemic CVD. D-dimer levels were significantly higher in patients presented with neurologic manifestations than those without [84].

In addition, El Nahas *et al.* reported 10 cases with acute ischemic stroke secondary to COVID-19 infection within one to seven days after viremia symptoms onset (fever, dyspnea, fatigue, and/or myalgia). All patients had moderately elevated D-dimer levels and moderately to markedly increased CRP increasing the risk of thrombosis and platelet aggregation suggesting that stroke might be associated with severity of COVID-19 [46].

Moreover, five cases of ischemic stroke were also reported after COVID-19 infection including two cases of ischemic stroke, one with LVO and one with embolic infarct [51]. Sharifi-Razavi and his colleagues reported also three severe cases of ischemic stroke with left or right hemiplegia with the involvement of large cerebral

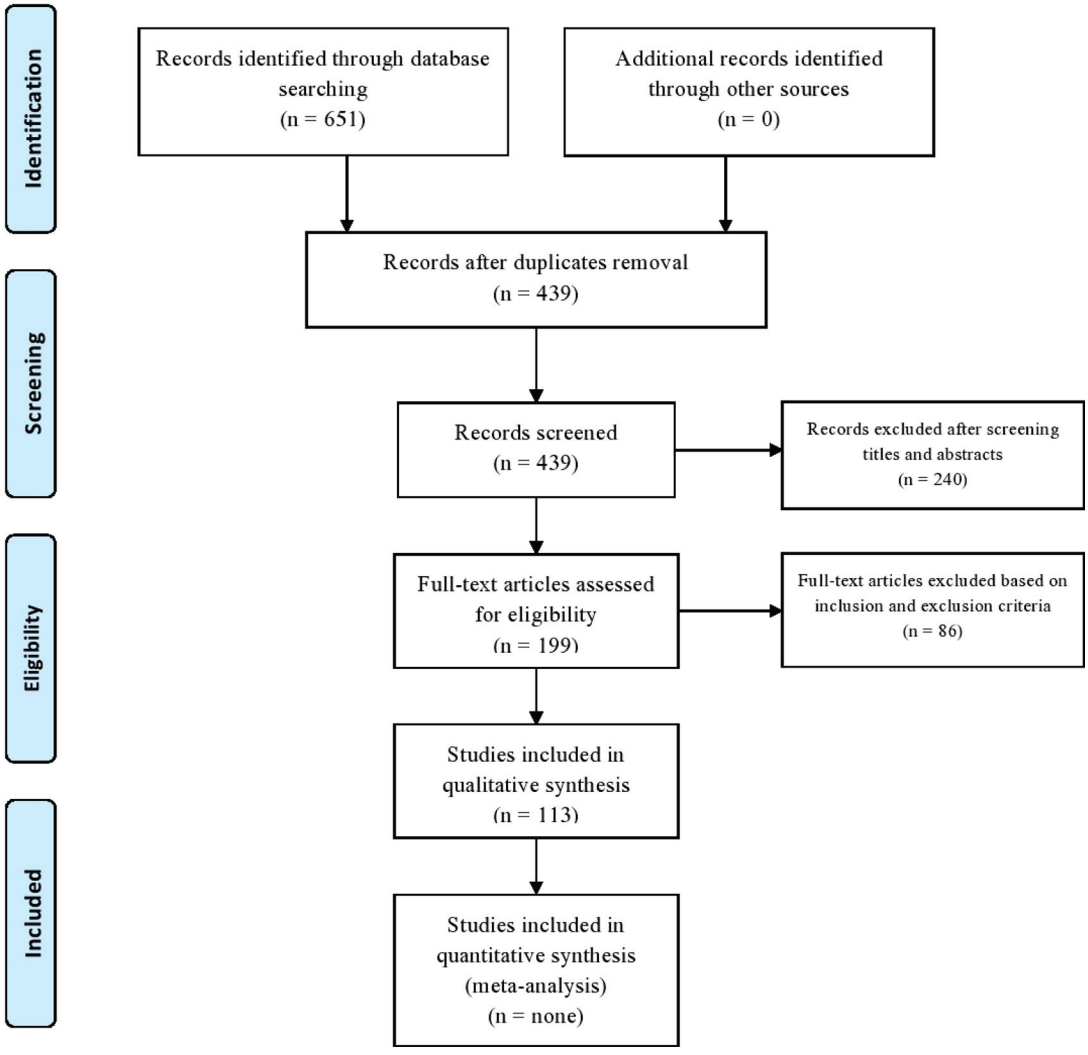

Figure 1. PRISMA flow chart for literature search results.

arteries characterized by lymphopenia and elevated levels of CRP. CT scan of patients revealed cerebral infarction in different brain regions [49].

Further, three case series reported cerebral venous sinus thrombosis (CVST) in two, three and 13 COVID-19 patients respectively all associated with poorer outcome and sometimes with deterioration of conscious level [42–44].

3.1.3. Intracerebral hemorrhage and microbleeds

Intracerebral hemorrhage (ICH) is a life-threatening type of stroke occurring when an artery inside the brain bursts which can result in a chronic aggregation of small blood products in different brain tissues called cerebral microbleeds. A COVID-19 critical case was reported to be associated with cerebral microbleeds identified by MRI that revealed expanded micro hemorrhages in the bilateral subcortical white matter, basal ganglia, corpus callosum, brainstem, and cerebellum [35]. A retrospective cohort study from USA showed that 68.75% out of 16 patients had microvascular lesions known to be associated with outcome severity and involving the corpus callosum, subcortical and deep gray matter. Brain autopsy of one patient who passed on revealed widespread microvascular damage including perivascular micro hemorrhages and microscopic ischemic lesions [74]. Furthermore, nine moderately to severely infected cases presented microbleeds in an unusual brain distribution with a tendency for the corpus callosum and the subcortical regions [54].

Three other patients were reported with severe COVID-19 and developed ICH; all of them had risk factors for ICH including hypertension and were characterized by elevated D-dimers and CRP levels, thus raising the risk of coagulable events and vascular damage [48]. In addition, a single COVID-19 case was reported to have non-traumatic ICH in the right

Table 1. Characteristics of studies included in our systematic review.

Authors	*Study design*	*Country*	*(n)*	*Neurological manifestations.*
Avula et al. [106]	Case report	USA	1	Locked in syndrome.
Colonna et al. [11]	Case report	Italy	1	GBS, cerebral vasculitis.
Agosti *et al.* [12]	Case report	Italy	1	GBS.
Lampe et al. [13]	Case report	Germany	1	GBS.
Ameer et al. [14]	Case report	UK	1	GBS.
Tiet and Alshaikh [15]	Case report	UK	1	GBS.
Hirayama et al. [16]	Case report	Japan	1	GBS.
Lowery et al. [17]	Case report	USA	1	Miller Fisher Syndrome/ GBS.
Scheidl et al. [18]	Case report	Germany	1	GBS (AIDP).
Khalifa et al. [107]	Case report	Saudi Arabia	1	Acute GBS
Naz et al. [19]	Case report	Pakistan	1	Meningitis, frontal headache.
Kamal *et al.* [20]	Case report	UAE	1	Severe confusion, drowsiness, encephalitis.
Pilotto et al. [21]	Case report	Italy	1	Akinetic mutism, encephalitis.
Sattar et al. [22]	Case report	USA	1	Encephalitis.
Afshar et al. [135]	Case report	Iran	1	Encephalitis.
Krett et al. [23]	Case report	Canada	1	Encephalopathy, cerebral hemorrhages.
Pensato et al. [108]	Case report	Italy	1	Aphasia, delirium, encephalitis.
Prasad et al. [24]	Case report	USA	1	Encephalopathy, multifocal ischemic stroke.
Al Mazrouei et al. [25]	Case report	UAE	1	Encephalopathy.
Princiotta Cariddi et al. [26]	Case report	Italy	1	PRES.
Al-Olama et al. [27]	Case report	UAE	1	Drowsiness, meningoencephalitis.
AlKetbi et al. [28]	Case report	UAE	1	Acute myelitis.
Chow et al. [29]	Case report	Australia	1	Acute transverse myelitis.
Águila-Gordo et al. [30]	Case report	Spain	1	Acute transverse myelitis.
Masuccio et al. [109]	Case report	Italy	1	AMAN.
Kimambo et al. [110]	Case report	Tanzania	1	Severe generalized headache.
Asif et al. [111]	Case report	UK	1	Headache associated with CVST.
de Oliveira et al. [136]	Case report	Brazil	1	Severe headache, aguesia and anosmia.
Yahalomi et al. [112]	Case report	Israel	1	Central retinal vein occlusion.
Zombori et al. [113]	Case report	UK	1	Cortical injury.
Klein et al. [114]	Case report	USA	1	Bilateral intention tremors.
Sia [31]	Case report	Canada	1	Dizziness.
Chia et al. [32]	Case report	UK	1	Occipital, thalamic and cerebellar infarcts.
Haroon et al. [115]	Case report	Qatar	1	Diffuse cerebral microhemorrhages and ischemic infarct.
Zoghi et al. [33]	Case report	Iran	1	Encephalomyelitis.
Moore et al. [116]	Case report	USA	1	Multiple sclerosis.
Ghosh et al. [117]	Case report	India	1	AMAN.
Chirakkal et al. [118]	Case report	Qatar	1	Hearing loss and tinnitus.
Selvaraj et al.	Case report	USA	1	Dysosmia and dysgeusia.
Dijkstra et al. [34]	Case report	Belgium	1	Severe myoclonic jerks, cerebellar ataxia and mild neurocognitive symptoms.
Bahouth et al. [119]	Case report	USA	1	Peripheral neuropathy.
Gupta et al. [35]	Case report	USA	1	Cerebral microbleeds.
Lim et al. 2021 [137]	Case report	UK	1	Delirium.
Wang et al. [36]	Case report	China	1	Deteriorated mental abnormalities.
Abdelhady et al. [37]	Case report	Qatar	1	Acute flaccid myelitis.
Thu et al. [38]	Case report	USA	1	Intracranial hemorrhage in the olfactory gyrus and persistent loss of smell.
Guennec et al. [120]	Case report	France	1	Anosmia, status epilepticus.
Kumar et al. [121]	Case report	India	1	Acute hemorrhagic necrotizing encephalopathy.
et al.	Case report	Italy	1	Myasthenia gravis.
Shitiz et al. [122]	Case report	USA	1	Myasthenia gravis.
Akilli et al. [123]	Case report	Turkey	1	Acute parkinosim.
Adriana et al. [124]	Case report	USA	1	Acute cerebellar ataxia.
Cohen et al. [39]	Case report	Israel	1	Parkinsonism.
Faber et al. [40]	Case report	Brazil	1	Parkinsonism**.**
Antonio M'Endez-Guerrero [41]	Case report	Spain	1	Parkinsonism (hypokinetic-rigid syndrome).
Foucard et al. [38]	Case series	France	2	**Acute cerebellar ataxia and myoclonus.**
Borroni et al. [18]	Case series	Italy	2	Diaphragmatic myoclonu
Rabano-Suarez et al. [86]	Case series	Spain	3	Generalized myoclonus.
Abouhashem et al. [42]	Case series	Egypt	2	CVST.
Nwajei et al. [43]	Case series	USA	3	CVST.
Mowla et al. [44]	Case series	USA	13	CVST.
Moghimi et al. [126]	Case series	Iran	9	Loss of consciousness.
Chen et al. [45]	Case series	USA	5	Encephalopathy.
El Nahas et al. [46]	Case series	Egypt	10	Cerebrovascular events.
Vargas-Gandica et al. [125]	Case series	Multinational.	10	Ageusia and anosmia.
Emamikhah et al. [127]	Case series	Iran	7	Opsoclonus-myoclonus-ataxia syndrome.
Mohammad et al. [128]	Case series	USA	2	Ischemic infarct.
Lima et al. [47]	Case series	Brazil	8	Peripheral facial palsy.
Pavlov et al. [48]	Case series	USA	3	Intracerebral hemorrage.
Sharifi-Razavi et al. [49]	Case series	Iran	3	Ischemic stroke.
Doo et al. 2020 [129]	Case series	USA	2	Carotid artery thrombosis.
Sabayan et al. [130]	Case series	Iran	15	Acute ischemic stroke.

(*Continued*)

Table 1. Continued.

Authors	*Study design*	*Country*	*(n)*	*Neurological manifestations.*
Parauda et al. [50]	Case series	USA	4	PRES.
Landa et al. [131]	Case series	Spain	2	Cerebrovascular events.
Agarwal et al. [51]	Case series	USA	5	Ischemic stroke, LVO and embolic infarcts.
Hepburn et al. [132]	Case series	USA	2	Acute encephalopathy.
Manganotti et al. [52]	Case series	Italy	5	Polyradiculoneuritis, cranial poly-neuritis.
Delorme et al. [53]	Case series	France	4	Cognitive impairment.
Fitsiori et al. [54]	Case series	Switzerland	9	Microbleeds.
Corrêa et al. [133]	Case series	Brazil	6	Cranial nerve abnormalities.
Koutroumanidis et al. [55]	Retrospective	UK	19	Encephalopathy
Helms et al. [56]	Prospective	France	140	Delirium and state of agitation.
Tiwari et al. [57]	Retrospective	USA	16	LVO and small vessel occlusion.
Pun et al. [134]	Retrospective	Multinational.	2088	Acute brain dysfunction and delirium.
Lersy et al. [58]	Retrospective	France	58	Encephalopathy, pyramidal dysfunction, seizures and headaches.
Almeria et al. [59]	Retrospective	Spain	35	Headache, anosmia, dysgeusia and diarrhea.
Vacchiano et al. [60]	Prospective	Italy	133	Headache, dizziness, smell disorders, taste disorders and muscle pain.
Perrin et al. [61]	Longitudinal	France	5	Confusion, tremor, cerebellarataxia, behavioral alterations and aphasia.
Kas et al. [62]	Longitudinal	France	7	Acute encephalopathy.
Membrilla et al. [63]	Cross sectional	Spain	145	Headache.
Iltaf et al. [64]	Cross sectional	Pakistan	350	Headache, paresthesia, altered level of consciousness, hyposmia/anosmia and encephalitis.
Campiglio and Priori [65]	Cross sectional	Italy	126	Headache, myalgia, taste and smell abnormalities.
Makda et al. [66]	Cross sectional	Pakistan	114	Dizziness, headache, stroke, taste and smell impairment.
Kushwaha et al. [67]	Cross sectional	India	14	Meningoencephalitis, stroke, GBS and anosmia.
Garg et al. [68]	Cross sectional	India	391	Altered taste, altered smell and headache.
Nalleballe et al. [69]	Retrospective	USA	40,469	Anxiety, mood disorders, suicidal ideation, sleep disorders and encephalopathy.
Petrescu et al. [70]	Retrospective	France	36	EEG alteration.
Rifino et al. [71]	Retrospective	Italy	1760	CVD, GBS and altered mental status.
Yuksel et al. [72]	Retrospective	Turkey	307	AMS and seizures.
Chachkhiani et al. [73]	Retrospective	USA	250	AMS, headache, seizures, ageusia, anosmia and encephalitis.
Conklin et al. [74]	Retrospective	USA	16	Microvascular lesions.
Luigetti et al. [75]	Retrospective	Italy	213	Headache, hyposmia, encephalopathy, skeletal muscle injury and ageusia.
Mao et al. [76]	Retrospective	China	214	Dizziness, headache, taste and smell impairment, CVD and skeletal muscle injury.
Ghaffari *et al.* [77]	Retrospective	Iran	361	Headache, anosmia/ageusia, dizziness and AMS.
Battaglini et al. [78]	Retrospective	Brazil	94	Delirium.
Yan et al. [79]	Retrospective	China	1682	Myalgia, headache, fatigue and dizziness.
Abenza-Abildúa *et al.* [80]	Retrospective	Spain	30	Acute confusional syndrome, neuromuscular disease, headache, CVD and encephalitis.
Kacem et al. [81]	Retrospective	Tunisia	646	Headache, smell and taste impairment, myalgia and sleep disturbances.
Chougar et al. [82]	Retrospective	France	73	Acute ischemic infarct, deep venous Thrombosis and multiple microhemorrhages.
Thakur et al. [83]	Prospective	India	250	Olfactory and gustatory dysfunction.
Karadaş et al. 84]	Prospective	Turkey	239	Headache, dizziness, impaired consciousness, smell and taste impairments, CVD, epileptic seizures and myalgia.
Liguori et al. [85]	Prospective	Italy	103	Sleep impairment, dysgeusia, headache, hyposmia and depression.

List of abbreviations: GBS: Guillain-Barré syndrome. **PRES**: posterior reversible encephalopathy syndrome. **AMAN**: acute motor axonal neuropathy. **CVST**: cerebral venous sinus thrombosis. **AMS**: altered mental status. **EEG**: electroencephalogram. **CVD:** cerebrovascular diseases.

olfactory gyrus associated with status epilepticus (six seizures lasting each less than one minute). This case is consistent with neuro-tropism ability of corona virus for olfactory bulb through nasal mucosa leading to smell dysfunction, one of the most common symptoms of this virus [38].

3.1.4. Encephalopathy

Encephalopathy was reported as the most common neurological manifestation in many cohorts; it recorded 81% in a retrospective study done in France, including 58 COVID-19 patients with median age 62 years. Only four patients had a positive CSF SARS-CoV-2 RT-PCR decreasing the risk of direct infection of the nervous system [58]. Further, in Italy, another retrospective study including 213 COVID-19 patients possessing significantly elevated CRP levels when compared to control group found both encephalopathy related to fever or hypoxia as the most frequent CNS manifestations (35.2%) among patients expressing neurological symptoms [75].

Three other case reports of encephalopathy, documented in USA, Canada and United Arab Emirates, were aged 51, 69 and 43 respectively [23–25]. All cases were presented with fever and mild to severe cough, the Emirati case deceased due to septic shock and multi-organ failure, while the Canadian one that displayed deregulation of pro-inflammatory cytokines such as TNF-α and IL-6 due to a possible mechanism

of para-infectious inflammation recovered by supportive care and neuronal rehabilitations.

Electroencephalogram (EEG) analysis of 19 severely infected patients highlighted the role of severe encephalopathy occurring in 13 cases and causing a persistent state of comatose following sedation withdrawal [55]. In addition, a retrospective case series of five critically ill patients analyzed by EEG showed that all patients had variant degrees of non-specific markers of encephalopathy [45].

The cerebral network of COVID-19 - related encephalopathy remains moderately to severely altered six months after infection as confirmed by a longitudinal study including seven patients presented with various degrees of cognitive and behavioral frontal disorders and with a consistent state of hypometabolism affecting a widespread brain network such as the frontal cortex, anterior cingulate, insula and caudate nucleus [62]. Furthermore, four patients of COVID-19- related encephalopathy aged 60 years or older were reported to present various degrees of cognitive impairment with frontal hypometabolism and cerebellar hypermetabolism with onset of neurological symptoms between 0 and 12 days after first COVID-19 symptoms [53].

Four critically ill COVID-19 patients aged between 64 and 74 years admitted to the ICU were reported to have posterior reversible encephalopathy syndrome (PRES) following persistent confusion, lethargy, acute kidney injury and elevated blood pressure. These patients were improved by regulating blood pressure [50]. Further, in one female case aged 64 in Italy, PRES was found associated with altered mental status, blurred vision and drowsiness and it might be caused by alteration of blood brain barrier (BBB) by SARS-Cov-2 disrupting cerebrovascular endothelium [26].

3.1.5. Altered mental status and delirium

Several cohort studies found that altered mental status (AMS) is one of the most frequent neurological symptoms (68.1%, 29% and 35.8%) reported among 204 Turkish, 250 American and 1760 Italian COVID-19 cases and it is associated frequently with poorer outcome, prolonged hospital stay and higher mortality rate when compared to those without AMS [71–73]. Further, one COVID-19 case was reported to show aggressive neurologic damage and mental abnormalities lasting for months without severe respiratory symptoms [36].

Incidence of delirium/impaired consciousness was also common among COVID-19 patients recording 36.17% (among 94 critically ill patients), 14.8% (among 214 cases) and 84.3% (among 140 cases) in cohort studies and associated with longer hospital stay and sometimes with acute attention, awareness and cognitive disturbances [56,76,78]. Further, a multinational retrospective study including 2088 COVID-19 patients found that 54.9% had delirium [87]. Acute confusional syndrome was also reported as the most frequent neurological symptom recording 93.33% out of 30 critical cases in a Spanish retrospective study [80].

3.1.6. Encephalitis, meningoencephalitis and acute myelitis

Seven single case reports of encephalitis/meningitis/menigoencephalitis associated with corona virus were published. CSF analyses of three patients were positive to SARS-Cov-2 RT-PCR. One 31 year-old COVID-19 case-related encephalitis presented with severe confusion, drowsiness and abnormal brain MRI findings (alteration of bilateral temporal and parasagittal frontal lobe signal) [20]. The second case reporting encephalitis is a young patient also with no medical history who presented initially with fever and dry cough, then developed generalized tonic-clonic seizures and confusion. His cerebral MRI as well as CSF analysis revealed abnormalities in the bilateral medial cortical frontal region and pleocytosis respectively [22]. The last case with confirmed CSF SARS-Cov-2 RT-PCR is a 36 year-old case presented with menigoencephalitis confirmed by MRI analysis and was complicated by intracerebral and subdural hematoma [27]. In the remaining cases, corona virus was not detected in CSF. One young case reported meningitis as the initial symptom of COVID-19 and characterized by BBB alteration occurring due to the presence of red blood cells in the CSF [19]. Another 60 year-old COVID-19 case-related encephalitis showed generalized slowing by EEG and pleocytosis with increased levels of TNF-α and IL-8 by CSF analysis [21].

A retrospective study from Spain including 30 COVID-19 critical cases expressing neurological complications reported that 13.33% had encephalitis/encephalopathy with 66.6% and 26.66% showing alterations in brain MRI (intraparenchymal hemorrhage, venous thrombosis, encephalopathy, cavernoma, and chronic lacunar lesions) and EEG (mild slowing without epileptiform activity) respectively [80].

Furthermore, among 14 confirmed SARS-Cov-2 patients, four developed meningoencephalitis in which the virus is not detected in the CSF. Pleocytosis was a significant observation and all patients were characterized by irritability, altered sensorium and headache. Memory impairment was also seen in some of these patients [67].

Acute myelitis was also described in four case reports whose CSF were negative for COVID-19 and

presented all with urinary retention and lower limb weakness. Their CSF analysis showed increased CRP concentrations but all except one had normal white blood cells count [28–30,37].

A 21 year-old case of demyelinating event in the CNS associated with encephalomyelitis following COVID-19 infection was reported and characterized by MRI abnormalities (bilateral posterior internal capsule lesions extending to the ventral portion of the pons) and mononuclear pleocytosis in the CSF [33]. In addition, a retrospective study including 58 COVID-19 cases reported two patients presenting acute inflammatory demyelinating lesions close to what can be seen in acute disseminated encephalomyelitis or acute hemorrhagic leukoencephalitis [58].

3.1.7. Seizures

In addition to COVID-19 patients described above who developed seizures as a consequence of many neurological complications (encephalitis, encephalomyelitis, ICH, etc.), a retrospective study including 58 COVID-19 cases reported six patients presenting with seizures. Five of those patients performed brain MRI and showed CVST, extensive and confluent supratentorial white matter hyperintensities. One patient showed abnormalities related to status epilepticus involving the mesial temporal lobe [58]. In addition, seizure was reported also in only a single patient out of 350 infected cases in Pakistan [64].

3.1.8. Neuropsychiatric symptoms

A 39 year-old COVID-19 case with brain MRI showing bilateral, occipital, thalamic and cerebellar infarcts was reported to develop a florid neuropsychiatric syndrome, including paranoia, irritability, aggression and disinhibition after resolution of respiratory symptoms. The recovery was done by neurorehabilitation and antipsychotic drugs including citalopram and olanzapine [32].

Several neuropsychiatric manifestations were reported in a retrospective study in 22.5% out of 40,469 COVID-19 patients including anxiety which is the most common (4.6%), mood disorder (3.8%), emotional state symptoms and suicidal ideation in less than 1% [69]. Further, a prospective study including 103 patients from Italy reported that 37.86% and 49.51% of cases presented with depression and sleep impairment respectively; the latter being the most frequent symptom occurring in those that were hospitalized for more than seven days and having higher white blood cells [85].

3.1.9. Parkinsonism

Acute Parkinsonism due to COVID-19 infection was reported in few cases. In fact, several single case reports presenting Parkinsonism were published. The first case is a 72 year Turkish male patient having diabetes mellitus, hypertension and peripheral artery disease. He developed Parkinsonism on the third day of COVID-19 diagnosis and characterized by tremors, impaired walking and rigidity [88]. In addition, three other cases of relatively young COVID-19 patients presenting Parkinsonism with no family history for Parkinson disease aged respectively 35, 45 and 58 years have been reported [39–41]. Moreover, all three required hospitalization due to severe respiratory symptoms and they showed signs of Parkinson disease by brain MRI.

3.1.10. Cerebellar ataxia and myoclonus

Cerebellar ataxia, myoclonus and opsoclonus-myoclonus-ataxia (OMA) syndrome were reported among COVID-19 population in several case reports/series. In fact, acute cerebellar ataxia was reported in a 30 year- COVID-19 patient that was diagnosed with cerebellitis and characterized by incoordination, imbalance and trouble reaching for objects [89]. Acute cerebellar ataxia and myoclonus (ACAM) were also reported in a single 44 year-COVID-19 patient without opsoclonus and presented with prominent limb ataxia, severe myoclonic jerks, speech impairment and neuropsychiatric symptoms [34]. In addition, ACAM was also reported in two patients between 10 days and six weeks after the first symptoms of viral infection [90]. The first case had confusion with myoclonic jerks, ataxic dysarthria and opsoclonus. The second case was characterized by progressive cerebellar syndrome with stimulus-sensitive action myoclonus. Their cerebral MRI and CSF analyses were normal.

Diaphragmatic myoclonus was reported among two Italian COVID-19 patients with different pathophysiological origins. The first 54 year-COVID-19 case did not have probably a cortical origin since its EEG did not reveal any cortical correlates whereas in the second 80 year-COVID-19 case, the cortical origin of myoclonus was confirmed [91]. In addition, a case series, including three COVID-19 patients aged 63-88 years presenting generalized myoclonus with both positive and negative jerks and having good outcomes, was published [92].

3.2. PNS manifestations

3.2.1. Guillain-Barre syndrome and its variants

Five COVID-19 cases of Guillain-Barre syndrome (GBS) were reported in Italy [52]. All were affected by

bilateral pneumonia, fever, cough, taste and smell impairment. The interval between the onset of respiratory symptoms and neurological involvement ranged from 14 to 30 days. Under neurological examination, four patients revealed a flaccid paresis with variable lower/upper limbs predominance accompanied with unilateral mild facial nerve involvement limited to the lower face muscles. The fifth patient had bilateral ophthalmoplegia, hypoesthesia in the territory of maxillary and mandibular trigeminal branches, mild right lower facial nerve palsy and limb ataxia. Nerve conduction studies showed a conduction block in lower limbs in three patients while the remaining cases had conduction block in the upper limbs. CSF analysis showed a significant increase in inflammatory mediators (mainly Il-6 and Il-8) among three patients. The patients were treated successfully with intravenous immunoglobulin (IVIg).

There were also six other case reports of GBS among COVID-19 patients, one in Italy [11], one in Germany [13], two in UK [14,93], one in Japan [16] and one in USA [17]. All the six cases aged between 30 s and 60 s were characterized by various degrees of weakness in lower and/or upper limbs associated sometimes with numbness in their extremities. They developed some peripheral neuromuscular disorders such as flaccid tetraplegia, paresis of the right arm, paraparesis and paraesthesia of the lower limbs, ataxia or areflexia after experiencing respiratory symptoms. Recovery that is prolonged sometimes due to the disease severity was done with variable response by IVIg.

Two cases of acute demyelinating inflammatory polyneuropathy (AIDP) which is the most common variant of GBS were also reported among two COVID-19 patients in Italy [12] and Germany [18]. They are respectively a 68 year-old man presenting with ascending flaccid tetraparesis and distal muscular weakness of lower limbs and a 54 year-old female presenting with paraparesis, areflexia and sensory loss of all extremities. Both cases showed delayed distal latencies and absent F waves under electrophysiological studies and an albumninocytologic dissociation under CSF analysis. Although most cases developed GBS and its variants after respiratory symptoms, the latter case draws attention to the occurrence of GBS in COVID-19 patients who did not experience respiratory or general symptoms suggesting an inflammatory process activated directly by SARS-CoV-2.

3.2.2. Smell and taste dysfunctions

Anosmia 'Smell loss' and ageusia 'taste loss' are common COVID-19 symptoms reported by several case reports/series and cohort studies. An Indian prospective study including 250 COVID-19 patients showed that 68.5% were diagnosed with anosmia and 66.4% had both olfactory and gustatory dysfunctions from which 18 patients were totally asymptomatic suggesting a direct nervous system infection; the sense of smell was recovered in most patients within one to two weeks from the first day of anosmia onset [83]. Another prospective study in Italy reporting symptoms of 133 COVID-19 patients showed that 37% and 61% had smell and taste disorders respectively. Smell impairment was not associated with rhinorrheas, IL-6 and CRP levels [60]. Furthermore, anosmia and ageusia were found to be associated with favorable outcome occurring in 19.1% out of 361 COVID-19 patients in an Iranian retrospective study [77].

3.2.3. Peripheral nerve palsy

Peripheral nerve palsy should be added to the spectrum of neurological symptoms as it becomes increasingly reported by COVID-19 patients. In fact, eight cases of corona virus infections were reported to develop peripheral nerve palsy. This nerve damage resulted in mild to moderate dysfunctions in five and three patients respectively with complete recovery after few weeks of supportive care and steroids treatment [47].

3.3. Skeletal muscle manifestations

3.3.1. Myalgia and skeletal muscle injury

Myalgia and associated fatigue is commonly reported by COVID-19 patients. A prospective study showed that 36 out of 239 COVID-19 patients had muscle pain that is associated with significantly higher levels of creatinine kinase (CK) compared to patients without muscle pain [84]. However, this association was not found to be significant in another prospective study reporting 37 out of 133 COVID-19 patients having myalgia [60]. Further, skeletal muscle injury was reported also in two retrospective studies in 4.7% and 19.43% out of 213 and 214 COVID-19 patients respectively [75,76]. In the latter study, muscle involvement was associated with higher CK, CRP and D-dimer levels suggesting an active immune reaction, and some of those patients showed serious liver and renal dysfunctions.

3.3.2. Myasthenia gravis

Some cases of myasthenia gravis (MG) were reported among COVID-19 patients. In fact, the first case of ocular MG was reported in USA affecting a 65 year-COVID-19 woman case. She showed a decremented response on repetitive orbicularis oculi nerve

stimulation after experiencing respiratory symptoms [94]. Further, another 77 year- COVID-19 case in Italy was reported to develop bulbar MG after eight weeks of SARS-CoV-2 infection. Improvement of MG symptoms was encountered after two months of pyridostigmine medication followed by immunosuppressive therapy [95].

4. Discussion

The aim of the present systematic review is to summarize the relevant findings on neurological symptoms of COVID-19 and to assess the different mechanisms underlying the virus neuro-tropism.

Our review included 113 articles reporting many neurological manifestations that are classified into three categories: central nervous system, peripheral nervous system, and skeletal muscle manifestations. The central nervous system complications included headache, dizziness, stroke, ICH, encephalitis, acute myelitis, encephalopathy that can result in AMS and delirium, seizures and neuropsychiatric symptoms. In the peripheral nervous system, GBS was most frequently reported, followed by anosmia/ageusia and peripheral nerve palsy. Other uncommon manifestations include: hearing loss and tinnitus, akinetic mutism, tremors and multiple sclerosis. All of these symptoms can occur prior to any other respiratory symptoms and many were associated with higher degrees of disease severity, disability and mortality risk. This confirms the importance of considering these symptoms during the diagnosis of disease and to manage patients to prevent disease progression and development of unpredictable outcomes.

The high risk of developing neurological manifestations in COVID-19 patients is confirmed by previous studies of other corona viruses such as the Middle East respiratory syndrome coronavirus (MERS-CoV) and the severe acute respiratory syndrome coronavirus (SARS-CoV). In fact, both viruses induced many nervous system complications including anosmia, acute ischemic strokes, viral meningoencephalitis, acute necrotizing encephalopathy and acute flaccid paralysis [96].

4.1. What are the possible mechanisms of SARS-Cov-2 neuro-tropism?

The way SARS-Cov-2 does enter the central nervous system is a current debate and many theories are proposed and divided into direct and indirect pathways (Figure 2). First, the virus can invade the brain directly *via* the olfactory route where it could be internalized in nerve terminals, then transported retrogradely to different brain regions where it can spread by trans-synaptic transport [97]. Moreover, the presence of ACE2 receptors in the nasal mucosa can suggest another way for reaching the brain through olfactory route what can explain partially the origin of smell impairment, one of the most common reported symptom of COVID-19 [98].

Furthermore, SARS-CoV-2 can enter the brain directly through the blood circulation where it can interact *via* its S protein with endothelial cells expressing ACE2 receptors, infecting and damaging the endothelial lining of capillaries, thereby facilitating the virus entry to the various regions of CNS [97].

On the other hand, damaging the brain does not require necessarily the presence of the virus as the CSF of many COVID-19 patients presented with neurological symptoms was negative for SARS-CoV-2. In fact, the virus can trigger an active and systemic immune response leading to uncontrolled and continuous inflammation. The release of pro-inflammatory markers, such as CRP, TNF-α and the increased number of leucocytes confirm the presence of cytokine storm syndrome known to be responsible for many brain complications after COVID-19 infection. This can lead to BBB disruption increasing thus the availability of inflammatory markers and oxidative reactive species (ROS) in the brain which is associated with neuronal dysfunction and damage. Therefore, the negative impact of the virus on the brain can be explained partially by the immune-mediated systemic inflammation implicated in COVID-19-related CVD, encephalopathy, encephalitis and myoclonus as described in our present systematic review [92,99]. Further, the release of IL-6 and the high levels of D-dimer were also known to increase vascular permeability and to promote complement and coagulation cascades leading to many acute cerebrovascular events such as stroke and ICH [93].

Chronic neuro-inflammation and cytokine storm syndrome are associated with disease severity and can have long-term devastating effects on the brain function and structure. Although the exact cellular and molecular mechanisms are poorly understood, they can underlie the pathogenesis mechanisms and the clinical features of different demyelinating and neurodegenerative disorders such as Parkinson disease, Alzheimer disease and multiple sclerosis [100]. Furthermore, Parkinsonism is strongly associated with neurotropic viruses. This association originated from the Spanish flu in 1918 that evoked an increase in the number of Parkinsonian cases in the long term [88].

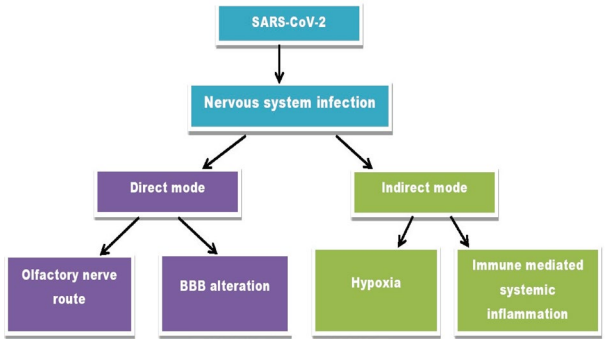

Figure 2. Possible pathways of SARS-CoV-2 neuro-invasion. SARS-CoV-2 can invade the nervous system by both direct mode through olfactory nerve pathway or disrupting the BBB and indirect mode through an active immune response leading to systemic inflammation or hypoxia.

This had drawn the attention to the possibility of occurrence of a Parkinsonism wave in the near future suggesting that SARS-CoV-2 could affect neuronal brain populations including the brainstem, the diencephalon and other brain regions.

GBS and its variants were also shown to be associated in some cases with increased inflammatory markers. However, the exact mechanism underlying these auto-immune conditions in which the organism's own antibodies attack and damage the nerves is still unknown. One possible hypothesis is the resemblance between some virus and nerve antigens resulting in the development of these disorders.

Moreover, many cases of COVID-19-related skeletal muscle injury are characterized by elevated levels of pro-inflammatory markers. In fact, skeletal muscle cells were shown to be negatively affected by such markers that contribute to diverse pathology implicated in skeletal muscle dysfunction leading to muscle weakness, shrinkage and atrophy [101].

It is important to note that the increased release of inflammatory markers secondary to COVID-19 infection can lead to immune-mediated damage such as that seen in MG which is caused by auto-antibodies against the neuromuscular junction. Furthermore, the resulting muscle weakness can cause high risk of severe respiratory symptoms when affecting respiratory muscles that might lead to high disease severity and hence death risk.

Another mode of indirect invasion of the virus can be mediated by systemic hypoxia caused by pneumonia which is a clinical feature of SARS-CoV-2 infection. Hypoxia can damage the brain cells by obstructing cerebral blood flow, inducing cerebral vasodilation and causing edema and ischemia [93].

In addition to ACE2 receptors, neuropilin-1 trans-membrane receptor (NRP1) expressed in both the respiratory and olfactory epithelia was also suggested to be implicated in SARS-CoV-2 entry to the brain after confirming its expression in some CNS regions including the olfactory tubercles and the para-olfactory gyri [102]. This association originates from previous studies demonstrating that S proteins of SARS-CoV-2 can bind to NRP1 *in vitro* in addition to the infection of NRP1-positive cells by COVID-19 in the olfactory bulb and epithelium [103,104].

Additionally, the trans-membrane protease serine 2 (TMPRSS2) appears to play a crucial role in the virus entry to the brain. This proteinase is involved in priming and activation of S proteins of SARS-CoV-2 and was found to be expressed with ACE2 receptors in the enteric nervous system neurons and glia cells, as well as in the endothelial cells lining the choroid plexus of the lateral ventricles which are key regions for viral entry to the CNS [105]. Despite the identification of many molecular targets for SARS-CoV-2 route into the brain, further studies are needed to search in greater details for the underlying mechanisms of the virus neuro-invasion *via* NRP1, TMPRSS2 and other key mediators implicated in viral infection.

To sum up, our systematic review had some limitations. First, due to the heterogeneity of the included articles, we cannot do a meta-analysis lacking thus the possibility to obtain the frequency of each neurological symptom. Second, most of articles included in this systematic review are case reports/series and retrospective cohort studies which might include data with inappropriate quality. Finally, as COVID-19 pandemic continues to disrupt the whole word at the economic, social and health public levels, similar most recent published studies assessing COVID-19 neurological symptoms need to be continuously analyzed and compared with previous papers in order to find a strong correlation between the virus and its neurological complications.

5. Conclusion

Our systematic review showed that SARS-CoV-2 can be manifested by a wide spectrum of neurological symptoms reported either in the early stage or within the course of the disease. These manifestations can be recovered rapidly within days or weeks while others can persist for a longer period after viral infection resolution. Some of these complications such as CVD, encephalopathy, encephalitis and GBS are associated with disease severity and longer hospital stay highlighting the importance of early monitoring of neurological symptoms in COVID-19 patients. Despite the increasing number of papers assessing SARS-CoV-2-related

neurological manifestations, more investigations are needed in many countries in order to identify the targets and to fully understand the impact of the virus on the nervous system. Finally, experimental studies are also required in order to determine the exact cellular and molecular mechanisms and the different mediators involved in the neuro-tropism pathways of SARS-CoV-2, facilitating thereby the development of therapeutic approaches to control this pandemic.

Data availability statement

All data mentioned in this study have been extracted from cited articles.

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