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REVIEW

Clinical manifestations and evidence of neurological involvement in 2019 novel coronavirus SARS-CoV-2: a systematic review and meta-analysis

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Abstract

Background Coronavirus disease 2019 (COVID-19) has become a global pandemic, affecting millions of people. However, clinical research on its neurological manifestations is thus far limited. In this study, we aimed to systematically collect and investigate the clinical manifestations and evidence of neurological involvement in COVID-19.

Methods Three medical (Medline, Embase, and Scopus) and two preprints (BioRxiv and MedRxiv) databases were systematically searched for all published articles on neurological involvement in COVID-19 since the outbreak. All included studies were systematically reviewed, and selected clinical data were collected for meta-analysis via random-effects.

Results A total of 41 articles were eligible and included in this review, showing a wide spectrum of neurological manifestations in COVID-19. The meta-analysis for unspecific neurological symptoms revealed that the most common manifestations were fatigue (33.2% [23.1–43.3]), anorexia (30.0% [23.2–36.9]), dyspnea/shortness of breath (26.9% [19.2–34.6]), and malaise (26.7% [13.3–40.1]). The common specific neurological symptoms included olfactory (35.7–85.6%) and gustatory (33.3–88.8%) disorders, especially in mild cases. Guillain–Barré syndrome and acute inflammation of the brain, spinal cord, and meninges were repeatedly reported after COVID-19. Laboratory, electrophysiological, radiological, and pathological evidence supported neurologic involvement of COVID-19.

Conclusions Neurological manifestations are various and prevalent in COVID-19. Emerging clinical evidence suggests neurological involvement is an important aspect of the disease. The underlying mechanisms can include both direct invasion and maladaptive inflammatory responses. More studies should be conducted to explore the role of neurological manifestations in COVID-19 progression and to verify their underlying mechanisms.

Keywords COVID-19 · SARS-CoV-2 · Neurological manifestations · Systematic review · Inflammation

Introduction

In December 2019, numerous patients had been diagnosed with unexplained pneumonia in Wuhan, China, which quickly spread to the other regions of the world. The disease, which was named as coronavirus disease

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2019 (COVID-19) by the World Health Organization (WHO), has now been confirmed to have originated from a severe acute respiratory syndrome (SARS)-like coronavirus (SARS-CoV-2). By May 3rd, 2020, the pandemic had affected more than 200 countries, with 3,349,786 cases having been confirmed as COVID-19, including 238,628 deaths (data from COVID-19 Situation Report-104 by the WHO). The disease in most patients is characterized by mild to medium fever, dry cough, chest distress or dyspnea, with interstitial pneumonia features on chest computed tomography (CT) scan [1, 2]. The main routes of transmission are respiratory droplets and close contact transmission. The average of the reproductive number of COVID-19 is 3.28, based on a summary of 12 related studies, which is much higher than SARS and Middle East respiratory syndrome (MERS) [3].

As knowledge of the SARS-CoV-2 virus has accumulated, most researchers have agreed that COVID-19 is not just a respiratory disease and that it could affect other systems in human. There have recently been increasing studies on the neurological involvement of COVID-19, which could be associated with more severe symptoms and higher mortality. However, there has been no comprehensive review regarding on this topic until now. Here in this systematic review with meta-analysis, we collected and analyzed the clinical manifestations and evidence of neurological involvement in this disease.

Methods

Search strategy and study selection

This study was approved by the Ethics Committee of the Tongji Medical College, Huazhong University of Science and Technology, and the written consent was exempted because it was a secondary analysis of the published studies. In this systematic review and meta-analysis, we searched the English literature that demonstrated clinical manifestations and that provided evidence of neurological manifestations in COVID-19, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA Checklist in Supplement materials). Given the novelty of the field, the search was conducted up to May 3rd, 2020, in two preprint databases (bioRxiv and medRxiv) and three popular medical databases (PubMed, Embase and Scopus). A combination of keywords related to COVID-19, neurological manifestations, neurological diseases and specific symptoms were used with Boolean operators for more efficient literature retrieval (search strategy in Supplement materials).

Eligibility criteria

The studies on clinical manifestations and evidence regarding neurological manifestations after COVID-19 were collected using Endnote X9 software (Clarivate Analytics), and the duplicates were removed accordingly. Case reports, case series, correspondence with relevant clinical data, and retrospective and cross-sectional studies were included for further analysis and review. The exclusion criteria included (1) clinical observation with no related neurological symptoms and a lack of related data; (2) the studies focused on a specific population (e.g., infants, children, patients with cancer, pregnant women); (3) repeated research on the same cohort of patients; and (4) other types of study (e.g., reviews, book chapters). All selected publications were comprehensively reviewed by two independent investigators to ensure their eligibility for inclusion in the review. If any disagreement occurred about eligibility of the literature, it was resolved by consensus after thoroughly discussing the publication with a third investigator.

Inclusion criteria, data extraction and quality evaluation for meta-analysis

Given that the articles reporting specific neurological symptoms (e.g., dysgeusia, agnosia) were limited, only articles that reported unspecific neurological symptoms (e.g., headache, weakness, respiratory failure) in patients with COVID-19 were selected for further meta-analysis. The quality assessment tool for case series studies designed by the National Institutes of Health (NIH) was applied to evaluate the included studies in the meta-analysis. For each item, we scored 1 point for "yes" and 0 points for "no," "not available," "not reported," and "cannot determine." The total score from all nine criteria (0–9) was generated accordingly to gauge the overall quality of the study.

Statistical analysis

Stata (version 15.1) was used to perform a meta-analysis of single arm studies. The combined prevalence and 95% confidence interval were calculated using the random-effects model. Egger's test was performed to assess publication bias in all literature, and $P < 0.05$ was considered statistically significant. Subgroup analysis was done to discuss the heterogeneity of the meta-analysis.

Results

After a primary search, a total of 440 publications were retrieved, including 73 from Pubmed, 133 from Embase, 163 from Scopus, and 71 from medRxiv and bioRxiv. Among

these, 142 were duplicates and were removed accordingly. We evaluated the eligibility of the remaining 298 papers according to title, abstract, article type, and full-texts (Fig. 1). The 11 papers from other resource (e.g., references list of existing papers) were added. Ultimately, 41 studies were included for systematic review and meta-analysis, including 20 studies on unspecific neurological manifestations [1, 2, 4–21], 20 studies on the specific neurological symptoms [22–41], and 1 reporting both types of symptoms [42].

Unspecific neurological symptoms associated with COVID-19 and meta-analysis

From a clinical aspect and the reported symptoms, headache, myalgia, fatigue, nausea, vomiting, confusion, anorexia, dizziness, malaise, dyspnea/shortness of breath were regarded as unspecific symptoms and were included in the subsequent meta-analysis.

Twenty-one eligible papers that reported unspecific neurological symptoms are summarized in Table 1, among which 19 (90.5%) were retrospective case series with one retrospective cohort (4.8%) and 1 prospective case series (4.8%). Nineteen studies (90.5%) enrolled patients from China, with the other two from Korea and India, respectively. There were 7 (33.3%) multicenter studies and 12 (57.1%) reports from a single institute. The number of enrolled patients ranged from 13 to 1099, and the sex ratio varied from 0.69 to 3.33 (male/female). The quality assessment for the literature is detailed in Supplement Table S1.

We then meta-analyzed the prevalence of the nine unspecific neurologic COVID-19 manifestations in 3837 patients. For the common neurological manifestations (the number of the studies > 10 and total cases > 1500), fatigue (33.2% [23.1–43.3]) and dyspnea/shortness of breath (26.9% [19.2–34.6]) were the most prevalent symptoms, followed by myalgia (16.0% [12.3–19.8]), headache (9.2% [7.2–11.2]), and nausea/vomiting (5.1% [3.3–6.8]).

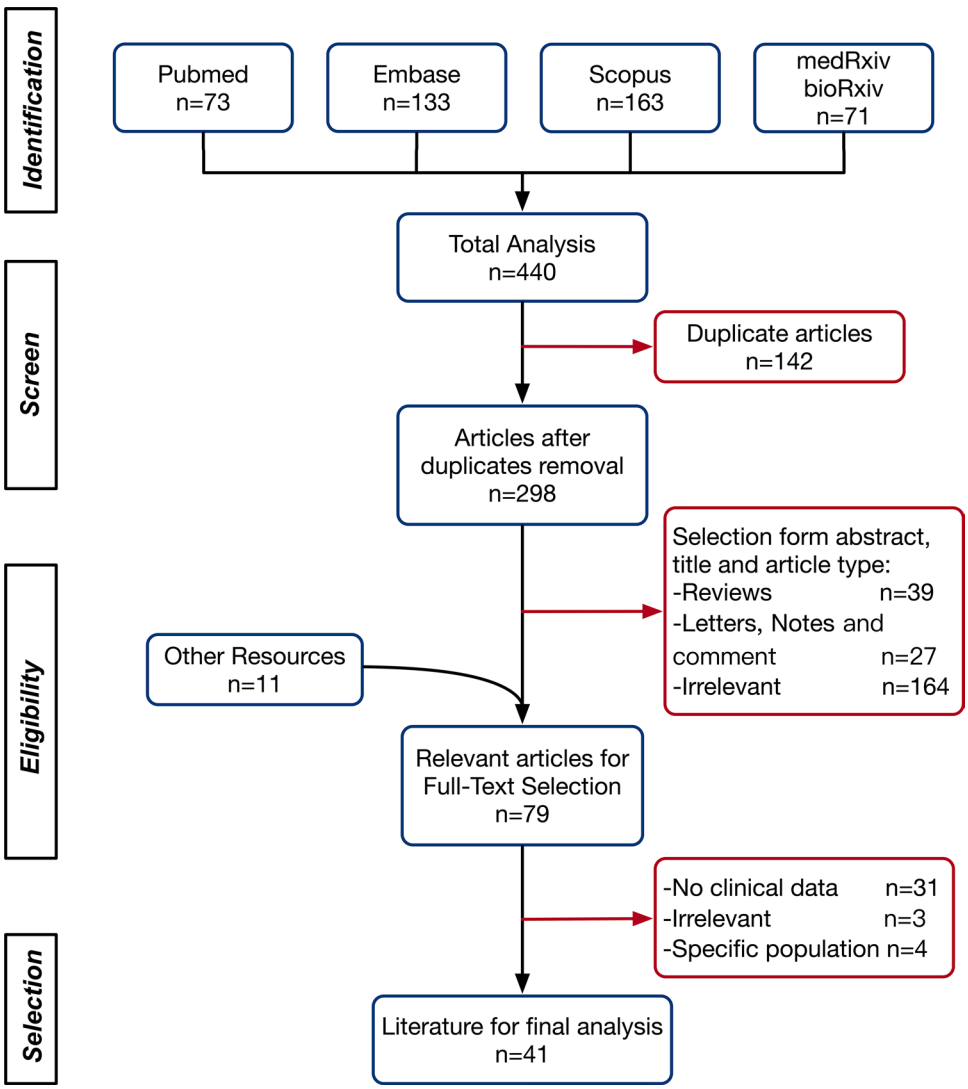

Fig. 1 Study selection and characteristics

Table 1 Summarization of selected literature for meta-analysis

Study	Date	Design	Location	Multi-center	Diag.	Case	M/F	Symptoms									Quality
								Headache	Myalgia	Fatigue	Nausea or vomiting	Confu-sion	Anorexia	Dizzi-ness	Malaise	Dyspnea/ shortness of breath	
Chang et al. [16]	Feb 7th, 2020	RCS	China-Beijing	Yes	PCR	13	10/3	3	3	–	–	–	–	–	–	–	2
Chen N et al. [17]	Feb 15th, 2020	RCS	China-Wuhan	No	PCR	99	67/32	8	11	–	1	9	–	–	–	31	7
Chen T et al. [7]	Mar 26th, 2020	RCS	China-Wuhan	No	PCR	274	171/103	31	60	137	24	–	66	21	–	120	7
Fan et al. [20]	Mar 17th, 2020	RCS	China-Wuhan	No	PCR or CT	101	64/37	3	9	–	7	–	–	7	21	75	7
Guan et al [8]	Apr 30th, 2020	RCS	China	Yes	PCR	1099	637/459	150	164	419	55	–	–	–	–	205	6
Gupta et al. [5]	April 6th, 2020	RCS	India	No	Clinical	21	14/7	3	–	–	–	–	–	–	–	1	2
Huang et al. [12]	Feb 15th, 2020	PCS	China	No	PCR	41	30/11	3	9*	9*	–	–	–	–	–	22	7
Korea CDC [14]	Feb 21th, 2020	RCS	South Korea	No	N.A	28	15/13	3	4	3	–	–	–	–	–	–	3
Leung et al. [21]	April 7th, 2020	RCS	China-Hong-kong	Yes	PCR	50	23/27	–	12	–	4	1	–	–	–	12	5
Liu K et al. [9]	May 5th, 2020	RCS	China-Hubei	No	PCR	137	61/76	13	22*	22*	–	–	–	–	–	26	6
Mao et al. [42]	Apr 10th 2020	RCS	China-Wuhan	Yes	PCR	214	87/127	28	–	–	–	–	68	36	–	–	6
Qian et al. [15]	Mar 17th, 2020	RCS	China-Zheji-ang	Yes	PCR or CT	91	37/54	7	5	40	11	–	23	–	–	17#	7
Tian et al. [4]	Apr 27th, 2020	RCS	China-Beijing	No	PCR	262	127/135	17	–	69	–	–	–	–	–	18	7
Wang et al. [2]	Feb 7th, 2020	RCS	China-Wuhan	No	PCR	138	75/63	9	48	96	14	–	55	13	–	43	7

Table 1 (continued)

Study	Date	Design	Location	Multi-center	Diag.	Case	M/F	Symptoms									Quality
								Headache	Myalgia	Fatigue	Nausea or vomiting	Confu-sion	Anorexia	Dizzi-ness	Malaise	Dyspnea/ shortness of breath	
Xu X et al. [19]	Feb 27th, 2020	RCS	China-Guang-zhou	No	PCR	90	39/51	4	25	19	5	–	–	–	–	–	5
Xu XW et al. [13]	Feb 19th, 2020	RCS	China-Zheji-ang	N.A	PCR	62	35/27	21	16*	16*	–	–	–	–	–	–	7
Xu YH et al. [1]	Feb 25th, 2020	RCS	China	N.A	PCR	50	29/21	5	8	8	–	–	–	–	–	4	6
Yang W et al. [6]	Feb 26th, 2020	RC	China-Zheji-ang	Yes	PCR	149	81/68	13	5	-	2	–	–	–	–	16	7
Yang X et al. [10]	Feb 24th, 2020	RCS	China	No	PCR	52	35/17	3	6	–	2	–	–	–	18	33	6
Zhang X et al. [18]	Mar 15th, 2020	RCS	China-Zheji-ang	Yes	PCR	645	328/317	67	71	118	22	–	–	–	–	26	6
Zhang G et al. [11]	Apr 5th 2020	RCS	China-Wuhan	No	PCR	221	108/113	17	–	156	–	–	80	–	–	64	6

Diag. diagnosis, *N.A.* not available, *RC* retrospective cohort, *RCS* retrospective case series, *PCS* prospective case series, *PCR* polymerase chain reaction

*Fatigue and myalgia were reported in the same symptom category in these studies and were equally attributed to each symptom for meta-analysis

#Dyspnea/shortness of breath were reported in separated symptom categories. To avoid overestimate, the maximum number of the two was selected to represent the case number of this symptom

Among the neurological manifestations that were reported sporadically (the number of the studies < 10 and total cases < 1500), the most common symptoms were anorexia (30.0% [23.2–36.9]), malaise (26.7% [13.3–40.1]), dizziness (10.0% [5.9–14.2]), and confusion (5.2% [− 1.7 to 12.2]), in descending order (Fig. 2). Significant publication bias was not observed in the common neurological manifestations including headache, myalgia, fatigue, nausea/vomiting, and dyspnea/shortness of breath (Fig. 2, all $p > 0.05$ by Egger's test).

Substantial heterogeneity was observed in most symptoms within subgroups (Fig. 2 and Supplement Tables S2–5). In the subgroup analysis, dyspnea/shortness of breath was more prevalent in the studies performed in Wuhan, on elder patients (median or mean age > 47 years), with higher M/F ratio (M/F ratio > 1.38), and higher percentage of severe cases (> 15%) ($p < 0.05$). In addition, fatigue was more frequent in the severe cases and studies in Wuhan ($p < 0.05$), and younger patients tended to experience more headaches. No other potential sources of heterogeneity of these five unspecific neurological manifestations were identified.

Specific neurological symptoms associated with COVID-19

We retrieved 21 studies regarding the specific neurological symptoms and diseases after COVID-19 (summarized in Table 2), among which 6 (28.6%) studies were case series and the rest (71.4%) were cases reports. In the six cases series, two studies focused on a relatively wide spectrum of neurological manifestations (e.g., central nervous system [CNS], peripheral nervous system [PNS], neuromuscular disorders) [36, 42], with the other four focused on olfactory and gustatory dysfunction [23, 24, 29, 37]. In the 15 case reports, 5 were associated with Guillain–Barré syndrome [31–35], 5 focused on neurological inflammation (e.g., myelitis, encephalitis, meningitis) [22, 26, 28, 30, 39, 41], 2 on cerebrovascular diseases [27, 38], and the rest on specific neurological symptoms [25, 40].

Laboratory, electrophysiological, radiological, and pathological evidence of neurological manifestations after COVID-19

Eleven papers that demonstrated laboratory, electrophysiological, radiological, and pathological changes after COVID-19 were distilled from the summarized literature, including seven on the examination of cerebrospinal fluid [30, 32, 34–36, 39, 41], three on electroencephalogram [36, 39, 41], two on nerve conduction [32, 34], six on magnetic resonance imaging (MRI) scans [26, 27, 30, 32, 36, 40], two on CT images [27, 40], and one post-mortem examination [25] (summarized in Table 3).

Discussion

To our knowledge, this is the first systematic review with meta-analysis of more than 41 studies involving approximately 4700 patients that provides a comprehensive view of neurological manifestations in COVID-19. In comparison with previous review and proposal on the topic, both clinical manifestations and related evidence were demonstrated to investigate multifaceted mechanisms underlying neurological involvement in COVID-19.

After the primary exploration, the neurological manifestations in COVID-19 were found to mainly fall into three categories: (1) neurological diseases comorbid with COVID-19, in which neurological symptoms occur prior to the infection that also make patients themselves

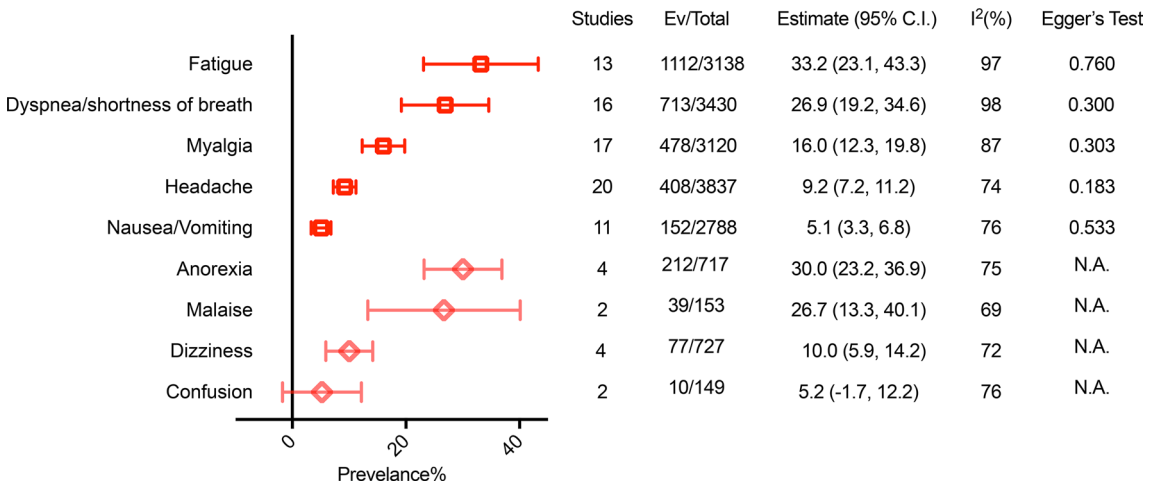

Fig. 2 Meta-analysis of the prevalence of unspecific neurologic manifestations in COVID-19

Table 2 Summarization of studies on specific neurological manifestations

Study	Date	Diag.	Case	M. Age	M/F	Symptoms
Case series						
Mao et al. [42]	Apr 10th	PCR	214	53	87/127	CNS manifestations (53 cases, 24.8%): dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure), peripheral nervous system PNS manifestations (19 cases, 8.9%): taste impairment, smell impairment, vision impairment, and nerve pain Skeletal muscular injury manifestation (23 cases, 10.7%)
Helms et al. [36]	Apr 15th	PCR	58	63	N.A	Agitation (40 cases, 69.0%); Corticospinal tract signs (39 cases, 67.2%); Dysexecutive syndrome (14 cases, 35.9%)
Klopfenstein et al. [29]	Apr 17th	PCR	114	47	N.A	Olfactory dysfunction (54 cases, 47.4%); Gustatory disorders (46 cases, 40.3%)
Lechien et al. [37]	Apr 2nd	PCR	417	37	154/263	Olfactory dysfunction (357 cases, 85.6%); Gustatory disorders (342 cases, 88.8%): salty, sweet, bitter, and sour
Levinson et al. [23]	Apr 14th	PCR	45	34	23/18	Olfactory dysfunction (15 cases, 35.7%); Gustatory disorders (14 cases, 33.3%)
Yan et al. [24]	Apr 12th	PCR	59	N.A	29/29	Olfactory dysfunction (40 cases, 67.8%) Gustatory disorders (42 cases, 71.2%)
Case reports						
Eliezer et al. [40]	Apr 8th	PCR	1	> 40	F	Acute loss of the olfactory function
Toscano et al. [32]	Apr 17th	PCR	5	58	4/1	Guillain–Barré syndrome The primary symptoms Lower limb weakness and paresthesia in four cases (80%) Facial diplegia followed by ataxia and paresthesia in one case (20%) The progression of disease Generalized, flaccid tetraparesis or tetraplegia (4 cases, 80%)
Sedaghat et al. [31]	Apr 15th	PCR	1	65	M	Guillain–Barré syndrome The primary symptoms: weakness of distal lower extremities The progression of disease: quadriplegia and bilateral facial paresis
Virani et al. [33]	Apr 18th	PCR	1	54	M	Guillain–Barré syndrome: numbness and weakness of the lower extremities
Zhao et al. [34]	Apr 1st	PCR	1	61	F	Guillain–Barré syndrome Symmetric weakness, areflexia and paresthesia in lower limbs
Gutiérrez et al. [35]	Apr 17th	PCR	2	45	M	Miller Fisher syndrome and polyneuritis cranialis
Zhao et al. [22]	Mar 16th	PCR	1	66	M	Acute myelitis: flaccid paralysis of the bilateral lower limbs, urinary and bowel incontinence
Pilotto et al. [39]	Apr 12th	PCR	1	60	M	Encephalitis: conscious and cognitive fluctuations
Bernard et al. [41]	Apr 17th	PCR	2	66	F	Meningitis/encephalitis: tonico-clonic seizure and psychotic symptoms
Moriguchi et al. [30]	Apr 3rd	PCR	1	24	M	Meningitis/encephalitis: consciousness disturbance
Ye et al. [28]	Apr 10th	PCR	1	N.A	M	Encephalitis: meningeal irritation signs and extensor plantar response
Zhang et al. [26]	Apr 16th	PCR	1	N.A	F	Encephalitis and myelitis: dysphagia, dysarthria, and bulbar impairment
Poyiadji et al. [27]	Mar 31th	PCR	1	> 50	F	Acute necrotizing hemorrhagic encephalopathy: altered mental status
Al Saiegh et al. [38]	Apr 30th	PCR	2	47	M	Cerebrovascular disorders: subarachnoid hemorrhage (1 case) and ischaemic stroke with massive hemorrhagic conversion (1 case)
Paniz et al. [25]	Apr 21st	PCR	1	74	M	Agitation and confusion

Diag. diagnosis, *F* female, *M.* media or mean, *M* male, *N.A.* not available, *PCR* polymerase chain reaction

susceptible to COVID-19 due to frequent exposure in medical facilities and suboptimal health status (e.g., cerebrovascular diseases, neural trauma); (2) unspecific neurological manifestations, which can be caused by systematic responses and partially by the neuroinvasive behavior of the infection (e.g., headache, myalgia, fatigue); (3) specific neurological symptoms and diseases that were due to neurological involvement in COVID-19 (e.g., encephalitis, myelitis, seizures). This review mainly focused on the last two categories of COVID-19 neurological manifestations.

Table 3 Laboratory, electrophysiological, radiological, and pathological evidence of neurological manifestations after COVID-19

Study	Date	Case (%)	Exam.	Features
Pathological evidence				
Paniz et al. [25]	Apr 21st	1/1 (100%)	TEM	The presence of Viral particles in brain and endothelium cells in post-mortem examination
Cerebrospinal fluid				
Moriguchi et al. [30]	Apr 3rd	1/1(100%)	PCR	Detection of SARS-CoV-2 RNA;
				High intracranial pressure and slightly increasing of cell counts
Helms et al. [36]	Apr 15th	2/7 (29%)	ECF	Oligoclonal bands
		1/7 (14%)	ECF	Elevated IgG and protein levels
Gutiérrez et al. [35]	Apr 17th	2/2(100%)	ECF	Increase of protein (62–80 mg/dL)
Pilotto et al. [39]	Apr 12th	1/1(100%)	ECF	Lymphocytic pleocytosis (18/uL) and increase of protein (696 mg/dL)
Toscano et al. [32]	Apr 17th	4/5(80%)	ECF	Increase of protein (40–193 mg/dL)
Bernard et al. [41]	Apr 17th	2/2 (100%)	ECF	Increase of protein (~46 mg/dL) and lymphocytic pleocytosis (21–26/uL)
Zhao et al. [34]	Apr 1st	1/1(100%)	ECF	Increase of protein (124 mg/dL)
Electrophysiological examinations				
Helms et al. [36]	Apr 15th	2/7(29%)	EEG	Diffuse bifrontal slowing
Pilotto et al. [39]	Apr 12th	1/1(100%)	EEG	Theta waves on the anterior brain regions
Bernard et al. [41]	Apr 17th	1/2 (50%)	EEG	Focal status epilepticus
Toscano et al. [32]	Apr 17th	5/5(100%)	NC	Low compound muscle action potential amplitudes and prolonged motor distal latencies
Zhao et al. [34]	Apr 1st	1/1(100%)	NC	Delayed distal latencies and absent F waves in early course
Radiological scans				
Eliezer et al. [40]	Apr 8th	1/1(100%)	CT/MRI	Inflammatory obstruction of the olfactory clefts
Poyiadji et al. [27]	Mar 31th	1/1(100%)	CT	Symmetric hypoattenuation within the bilateral medial thalami
		1/1(100%)	MRI	Hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions
Moriguchi et al. [30]	Apr 3rd	1/1(100%)	MRI	Hyperintensity along the wall of the lateral ventricle and hyperintensity in the temporal lobe and hippocampus
Zhang et al. [26]	Apr 16th	1/1(100%)	MRI	Extensive patchy areas of abnormal signal involving bilateral frontoparietal white matter, anterior temporal lobes, basal ganglia, external capsules and thalami
Toscano et al. [32]	Apr 17th	2/5 (40%)	MRI	Enhancement of the caudal nerve
		1/5 (20%)	MRI	Enhancement of the facial nerve
Helms et al. [36]	Apr 15th	8/13 (62%)	MRI	Leptomeningeal enhancement
		11/11 (100%)	MRI	Perfusion abnormalities
		3/13 (23%)	MRI	Cerebral ischemic stroke

CT computed tomography, *EEG* electroencephalogram, *EMG* electromyogram, *ECF* examinations of cerebrospinal fluid, *Exam.* examinations, *MRI* magnetic resonance imaging, *NC* nerve conduction, *TEM* transmission electron microscopy

Unspecific neurological manifestations in COVID-19

Unspecific neurological manifestations are various and insidious in COVID-19. It has been reported that unspecific neurological manifestations occurred in the early onset of the infection and could serve as the primary and only symptom when COVID-19 patients were admitted to the hospital [32]. Neurologic manifestations were also more prevalent in the patients with severe disease, which increased the risk of transmission and could lead to death if not handled properly and effectively [42]. However, there is a wide symptomatic spectrum of neurological manifestations in COVID-19, and it is easy to misdiagnose them during the epidemic due to the respiratory nature of the virus. After a systematic exploration of the literature, we found that the headache, myalgia, fatigue, nausea/vomiting, confusion, anorexia, dizziness, malaise, and dyspnea/shortness of breath were reported as unspecific neurological symptoms. Among them, the dominant clinical manifestations were fatigue, dyspnea/shortness of breath, anorexia, and malaise, which affected approximately one-third of patients with COVID-19.

Whether dyspnea/shortness of breath is a neurological symptom is still a matter of debate. Recently, several patients with dyspnea in an intense care unit (ICU) subjectively described that active and conscious breath was needed to maintain a normal breathing rhythm [43]. As we know,

angiotensin-converting enzyme 2 (ACE2), an important SARS-CoV-2 receptor, is found to be expressed in the cardiorespiratory center of the medulla together with other brain regions [44, 45]. Given the high similarity among coronaviruses and the fact that other coronaviruses (e.g., SARS-CoV, MERS-CoV) could invade the nervous system [46], it is reasonable to speculate that SARS-CoV-2 virus might play a role in the dyspnea/shortness of breath via affecting the respiratory center of the medulla, especially in those patients with rapid disease progression but without severe respiratory symptoms. Thus, dyspnea/shortness of breath was included as one of the neurological manifestations in this review, and we observed that it was one of most prevalent neurological symptoms in COVID-19 infection. However, further clinical and experimental studies should be performed to differentiate the exact cause of dyspnea and to explore its potential association with neurological involvement.

Specific neurological manifestations and diseases associated with COVID-19

In this review, we found six case series focused on the specific neurological manifestations, including CNS-related symptoms (e.g., impaired consciousness, acute cerebrovascular disease, corticospinal tract signs, ataxia, and seizure), PNS-related symptoms (e.g., taste impairment, smell impairment, vision impairment, and nerve pain), and musculoskeletal injury [23, 24, 29, 36, 37, 42]. Interestingly, olfactory dysfunction and gustatory disorders were observed 30–80% in patients with mild COVID-19. Recently, Fodoulian et al. and Brann et al. had reported that ACE2 and SARS-CoV-2 entry genes were expressed by sustentacular cells in the human olfactory neuroepithelium [47, 48]. In addition, bilateral inflammatory response in the olfactory clefts was observed in a patient with COVID-19 with sudden olfactory loss but without nasal obstruction by MRI and CT scans, which suggests the virus might affect olfactory function via direct invasion of the olfactory neuroepithelium [40]. However, we lack definitive evidence regarding the potential association between the PNS symptoms and the risk of CNS infection.

Regarding the neurological diseases, we found that aseptic neuroinflammation appeared to be related to COVID-19, including Guillain–Barré syndrome, Miller Fisher syndrome, myelitis, meningitis, and encephalitis [22, 30, 32, 34, 35, 39]. Notably the polymerase chain reaction (PCR) tests of cerebrospinal fluid (CSF) were negative in all cases. The mechanism for the neuroinflammation in the patients with COVID-19 is unclear. However, in a recent report on a rare condition (hemorrhagic necrotizing encephalopathy) in COVID-19, the author inferred that the breakdown of the blood–brain barrier (BBB) by cytokine storm could be the primary cause of disseminated brain necrosis and hemorrhage in this case [27]. Together with the increase in protein levels and immunoglobulin in CSF, we suspect that both the cytokine storm secondary to the systematic infection and the overactivation of the immune system might play a role in this process.

Evidence for neurological involvement of COVID-19

Currently, our knowledge regarding on neurological involvement of COVID-19 is still limited. The definitive evidence for the invasive behavior of COVID-19 in CNS is mainly from two neuropathological reports. Paniz-Mondolfi et al. had reported the presence of SARS-CoV-2 in brain tissue from post-mortem examination of a COVID-19 patient by employing a transmission electron microscope. Viral particles of approximately 80–110 nm, which were pleomorphic and spherical with distinct stalk-like projections and perfectly matched the structural features of SARS-CoV-2, were spotted in the frontal lobe section of the brain [25]. Notably, these viral particles were found to be located not only in the cytoplasmic vacuoles of neuronal cells but also in the small vesicles of endothelium cells, which suggested this direct neuroinvasive behavior via hematogenous pathways might be a leading cause for rapid progression of neurological symptoms [25]. In consistence with this finding, SARS-CoV-2 was also detected in CSF via PCR examinations in a male patient suffering from consciousness disturbance and transient generalized seizures, with typical meningitis and encephalitis characteristics shown on the MRI [30]. Interestingly, this case presented negative PCR result in nasopharyngeal swab at the time point, which indicated that CNS invasion might happen in the early phase of COVID-19 [30]. However, several similar studies had reported negative findings in the CSF examination, which suggests that direct neuroinvasion of SARS-CoV-2 is not a universal phenomenon for COVID-19 [32, 34]. But the interpretation of these negative results should be cautious due to the limitation of PCR examinations, which is currently the most prevalent test for viral detection. Its low sensitivity in CSF specimen may lead to repeated negative findings. Thus, more investigations are needed to further confirm this direct invasive behavior.

The adjuvant evidence for neurological involvement in COVID-19 includes CSF examination, electrophysiology, and radiological findings. The characteristic change in CSF after COVID-19 is the slight increase in cell counts and protein levels, especially immunoglobulins, which suggests its inflammatory or infective status [30, 32, 34–36, 39]. For electrophysiology, two cases presented unspecific alterations, another patient exhibited focal seizure in electroencephalogram [36, 39], and the rest showed delayed nerve conduction, attenuation of action potential amplitude, and absent F-Waves, which are associated with the damage to myelin and axons in Guillain–Barré Syndrome [32, 34]. In

the radiological examination, MRI and CT scans had been commonly adopted to search for clues for neurological disorders after COVID-19, such as inflammation and cerebrovascular dysfunction, which suggest the direct invasion of SARS-CoV-2. In the patients diagnosed with encephalitis, myelitis, meningitis, and Guillain–Barré Syndrome, enhancement of lesion sites in meninges, brain, spinal cord, and nerve roots was detectable in MRI and correlated with individual clinical manifestations [30, 32, 36]. Poyiadji et al. reported a unique case of acute hemorrhagic necrotizing encephalopathy associated with COVID-19 and the patient presented bilaterally hemorrhagic lesions within multiple brain regions, which implied that the breakdown of the BBB might serve as an explanation of COVID-19-associated cerebrovascular diseases [27]. In addition, perfusion abnormalities appeared to be prevalent (100%) in the patients with COVID-19 with severe neurological symptoms and were not only found in the patients with cerebrovascular disorders [36].

Potential mechanism underlying the neurological manifestation in COVID-19

From the limited studies on the neurological involvement of COVID-19, SARS-CoV-2 could impair the nervous system via two potential pathways: (1) direct invasion of neural tissue and (2) maladaptive inflammatory responses (Fig. 3).

In terms of direct invasion, SARS-CoV-2 could affect the CNS mainly through the hematogenous and the neuronal retrograde routes. First, ACE2 was found to be enriched in the endothelium cells of the CNS. Thus, viruses might invade nervous systems by infecting the endothelial cells of the BBB and the blood–CSF barrier in the choroid plexus. This hypothesis was strongly supported by the study conducted by Paniz-Mondolfi et al. [25]. The authors captured the viral particles using a cytoplasmic vacuole at the endothelial neural cell interface in a transmission electron microscope, which suggests that SARS-CoV-2 could bind to vascular endothelium, penetrate the BBB, and invade nervous tissues through hematogenous pathways. However, some researchers believe that the hematogenous route is not the only pathway, and that the neuronal retrograde transmission serves as another potential mechanism. In this route, SARS-CoV-2 might first invade peripheral nerve terminals and infect the CNS retrogradely. Previous animal studies on SARS-CoV and OC43-CoV had suggested the virus could enter the brain by disruption of the nasal epithelium and lead to subsequent neuronal dissemination when administered intranasally [46] [49]. Due to the high similarity among SARS-CoV, SARS-CoV-2, and OC43-CoV, it is likely that this same route also works in COVID-19. Notably, anosmia and dysgeusia were reported recently to be prevalent among patients with COVID-19 despite a lack of upper respiratory symptoms [23, 37]. In addition, ACE2 and other entry genes of SARS-CoV-2 are found to be highly expressed by sustentacular and non-neuronal cells in the human olfactory neuroepithelium [47, 48]. However, definitive evidence for this transmission route is lacking, and more solid pathological

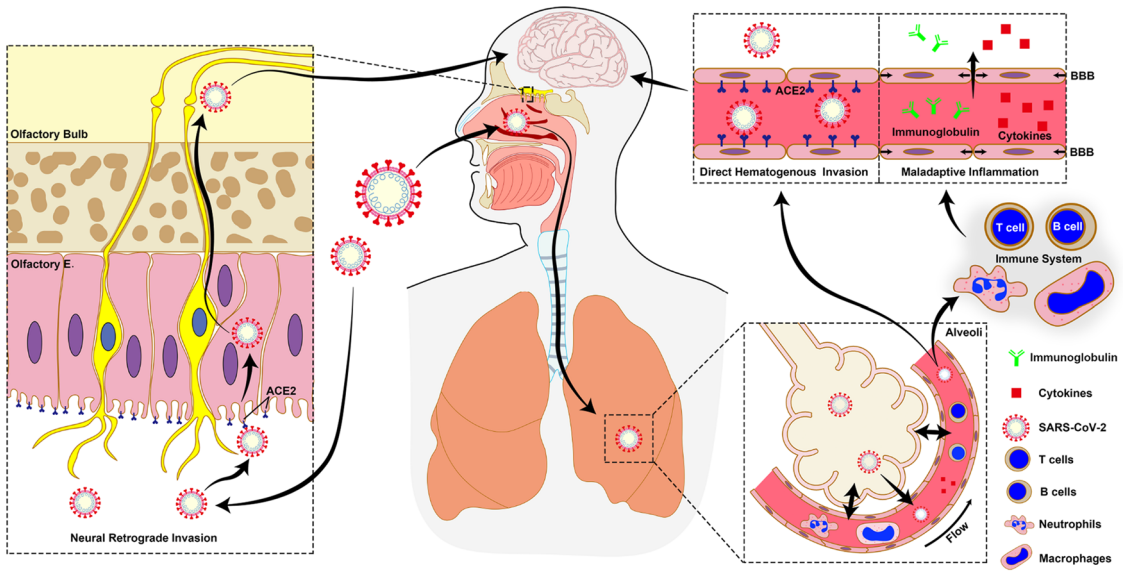

Fig. 3 The potential mechanism underlying the neurological manifestation in COVID-19. Based on the current evidence, there are two routes for the neurological involvement of COVID-19. (1) SARS-CoV-2 could direct infect nervous system via hematogenous and neural retrograde pathways; (2) SARS-CoV-2 overactivates the immune system, and secondary cytokines storm and immunoglobins impair the nervous system

and experimental investigations should be conducted to validate this pathway.

Maladaptive inflammatory responses can also contribute to the neurological manifestations of COVID-19, especially in those patients in whom no virus RNA is detected in CSF. In the early phase of COVID-19, the increased secretion of inflammatory cytokines (e.g., IL-1β, IFN-γ, TNF-α, IL-4, IL-10) was a signature feature caused by rapid viral replication and secondary cellular injury. In addition, higher plasma levels of these inflammatory cytokines were observed in the ICU patients, which suggests that a cytokine storm presented in the severe patients [12]. This cytokine storm could induce various neurological symptoms and was previously reported to be able to disrupt the BBB and induce neuroinflammation in the sepsis [27, 50, 51]. In addition, the neutralizing antibodies (anti-S protein lgG), which are assumed to clear the virus and promote the recovery, can also cause severe secondary injury by altering inflammatory responses. In a previous study on SARS-CoV, anti-S protein lgG was found to facilitate severe tissue injury in other organs, such as the lung [52, 53]. In a recent case series of neurologic features in severe SARS-CoV-2 infection, oligoclonal bands and elevated IgG were detected in the CSF, which suggests that the activation of the immune system might be a double-edged sword [36].

Limitations

This systematic review with meta-analysis has several limitations. First, in the meta-analysis of the unspecific manifestations we included all the related symptoms, some of which were not classical neurological presentations. Neurological involvement could contribute partially to these symptoms, and an overall analysis may exaggerate its role in COVID-19. Second, in the systematic review, most of the included papers on clinical characteristics were of retrospective design and were performed in China, which could introduce potential bias. Third, the studies on specific neurological symptoms and diseases were mostly case reports and were limited. Fourth, during the outbreak of COVID-19, the influx of numerous COVID-19 patients made advanced neuroimaging, CSF tests, electrophysiological tests, and pathological examinations impractical due to high risk of cross-infection, which limited the evidence of neurological involvement. Fifth, this study was conducted during an ongoing outbreak. Many related studies have not yet been published, which could influence the results. The potential mechanism underlying the neurological manifestation in COVID-19 will be updated along with emerging evidence.

Conclusions

The neurological manifestations are various and prevalent in COVID-19, but are usually underestimated. Emerging clinical evidence suggests that neurological involvement is an important aspect of the disease. The multifaceted mechanisms are involved in its neurological impact, which includes both direct invasion and maladaptive inflammatory response. Nevertheless, more clinical and experimental research should be conducted to further explore the role of neurological manifestations on the disease progression and its underlying mechanism.

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Author contributions HW supervised and conceived the study, analyzed and interpreted data, and wrote and revised the manuscript. LW and YS performed the study, searched the literature, collected and analyzed data, and wrote the first draft of manuscript. ML, HC, YY, and HZ conceived the study and contributed to data interpretation and substantial revision of the manuscript.

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Availability of data and material Most of analyzed data were included in this manuscript and supplemental materials. The relevant data can also be obtained with the request from any qualified investigator for purposes of replicating procedures and results.

Compliance with ethical standards

Conflicts of interest All authors declare no conflicts of interest.

Ethics approval This study was approved by the Ethics Committee of the Tongji Medical College, Huazhong University of Science and Technology.

Informed consent The informed consent was exempted because it was a secondary analysis of the published studies.

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