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REVIEW

Exploring the clinical association between neurological symptoms and COVID-19 pandemic outbreak: a systematic review of current literature

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Abstract

Object The novel severe acute respiratory syndrome (SARS)-CoV-2 outbreak has been declared a pandemic in March, 2020. An increasing body of evidence suggests that patients with the coronavirus disease (COVID-19) might have a heterogeneous spectrum of neurological symptoms

Methods A systematic search of two databases was performed for studies published up to May 29th, 2020. PRISMA guidelines were followed.

Results We included 19 studies evaluating 12,157 patients with laboratory-confirmed COVID-19 infections. The median age of patients was 50.3 (IQR 11.9), and the rate of male patients was 50.6% (95% CI 49.2–51.6%). The most common reported comorbidities were hypertension and diabetes (31.1%, 95% CI 30–32.3% and 13.5%, 95% CI 12.3–14.8%, respectively). Headache was reported in 7.5% of patients (95% CI 6.6–8.4%), and dizziness in 6.1% (95% CI 5.1–7.1%). Hypo/anosmia, and gustatory dysfunction were reported in 46.8 and 52.3%, of patients, respectively. Symptoms related to muscular injury ranged between 15 and 30%. Three studies reported radiological confirmed acute cerebrovascular disease in 2% of patients (95% CI 1.6–2.4%).

Conclusions These data support accumulating evidence that a significant proportion of patients with COVID-19 infection develop neurological manifestations, especially olfactory, and gustatory dysfunction. The pathophysiology of this association is under investigation and warrants additional studies, Physicians should be aware of this possible association because during the epidemic period of COVID-19, early recognition of neurologic manifestations otherwise not explained would raise the suspect of acute respiratory syndrome coronavirus 2 infection.

Keywords COVID-19 · SARS-CoV-2 · Coronavirus · β-coronavirus · Neurological symptoms

Introduction

In December 2019, several cases of atypical pneumonia occurred in the Wuhan province in China, and then spread to rest of the country, then to Europe, North America, and Asia. The outbreak was confirmed to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. This new coronavirus belongs to human β-coronaviruses, that also includes Middle East respiratory syndrome (MERS)-CoV, and SARS-CoV-1. These viruses are mainly associated with respiratory-related diseases, such as pneumonia, ARDS, and pulmonary edema [2–4]. In March 2020, the WHO declared the coronavirus disease 2019 (COVID-19) as an outbreak pandemic, and as of May 29th, more than 5 million people were confirmed positive, and there were more than 300,000

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deaths globally [5]. According to the clinical investigations from Asia, common clinical manifestations include fever, cough, dyspnea, diarrhea, and fatigue associated with typical laboratory findings and lung abnormalities on a computed tomography (CT) scan [6]. Additionally, some patients with COVID-19 presented neurologic manifestations, such as headache, loss of sense of smell, stroke and seizures, suggesting that SARS-CoV-2, like MERS-CoV and SARS-CoV-1, displays neurotropism and enters the central nervous system [7, 8]. The aim of this systematic review was to investigate the occurrence of different neurologic symptoms associated with COVID-19 and to assess their rate.

Methods

Literature search

A comprehensive literature search of two databases (PubMed and Ovid EMBASE) was conducted by an experienced librarian with input from the authors on May 29th, 2020 in accordance with PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [9]. The key words and the detailed search strategy are reported in Table 1. The inclusion criteria were the following: (1) series reporting patients with laboratory diagnosis of COVID-19 infection, and (2) cohort studies, case-controls studies, case series. Exclusion criteria were the following: (1) review articles, (2) studies published in languages other than English with no available English translations, (3) studies with overlapping patient population, (4) studies with no neurological evaluation, (5) case report or series with no epidemiological data. In cases of overlapping patient populations, only the series with the largest number of patients or most detailed data were included. Two independent readers (D.D.C. and G.P.) screened articles in their entirety to determine eligibility for inclusion. Senior author solved discrepancies (P.P.).

Data collection

From each study, we extracted the following: (1) demographic data, (2) patients' comorbidity, and (3) clinical symptoms at presentation. Symptoms including emesis, nausea, diarrhea, and abdominal pain were collected as "digestive symptoms". Neurological symptoms were categorized into three categories, as follows: central nervous system (CNS) manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizures), peripheral nervous system (PNS) manifestations (taste impairment and smell impairment), and muscular injury manifestations (myalgia, muscular pain, fatigue) [7]. Data were obtained for the whole population and subsequently we divided it into two groups: severe patients and non-severe patients, according to the American Thoracic Society guidelines for community-acquired pneumonia [10]

Outcomes

The primary objective of this systematic review was to analyze the overall rate of neurologic symptoms among COVID-19 patients. Secondary objective was to compare the results between patients with severe and non-severe infection.

Quality scoring

A modified version of the Newcastle–Ottawa Scale [11] was used for the quality assessment of the included studies. The quality assessment was performed by two authors independently, and the senior author solved discrepancies.

Statistical analysis

Inter-observer agreement was tested with Cohen's kappa coefficient (k). The Wald method was used to calculate confidence intervals for event rates. Fisher's exact test was used for categorical variables. Statistical analyses were performed with SPSS version 23 (SPSS Inc. SPSS® Chicago, IL, USA).

Results

Literature review

Studies included in our systematic review are summarized in Table 2. Intra-observer agreement was 0.82. The search flow diagram is shown in Fig. 1. Nineteen studies [4, 7, 8, 12–27] and 12,157 patients with laboratory-confirmed COVID-19 infection were included in our study.

Table 1 Search syntax

PubMed search accessed on May 29th, 2020	Embase search accessed on May 29th, 2020
((SARS-CoV-2[Title] OR 2019-nCov[Title] OR COVID-19[Title])) AND (neurological OR neurologic OR clinical characteristics)	('sars cov 2':ti OR '2019 ncov':ti OR 'covid 19':ti) AND (neurological OR neurologic OR 'clinical characteristics' OR (('clinical'/exp OR clinical) AND characteristics))

Table 2 Summary of the included studies

Study	Journal	Hospital	Location	Period of recruitment (2020)	N patients	Age (median)
Beltrán-Corbellini et al. [27]	Eur J Neurol	Multicentric	Madrid, Spain	NA	79	61.6[a]
Cai et al. [12]	Allergy	People's Hospital of Shenzhen	Shenzhen City, China	January 11–February 6	298	47,5
Chen et al. [4]	The Lancet	Jinyintan Hospital	Wuhan, China	January 1–January 20	99	55.5[a]
Duanmu et al. [22]	AEMJ	Stanford Health Care	California, USA	March 4–March 23	100	45
Feng et al. [13]	AJRCCM	Multicentric	China	February 1–February 15	476	53
Giacomelli et al. [14]	Clinic Infectious Disease	L. Sacco Hospital	Milan, Italy	NA	59	60
Helms et al. [8]	NEJM	Strasbourg University Hospital	Strasbourg, France	March 3–April 3	58	63
Jain et al. [24]	J Neurol Sci	New York City Department of Health and Mental Hygiene	New York, USA	March 1–April 13	3218	NA
Lechien et al. [15]	Rhinology	Multicentric	France-Italy	NA	417	36.9[a]
Li K et al. [16]	Invest Radiol	Chongqing Medical University	Chongqing, China	January NA–February NA	83	45.5[a]
Li R et al. [17]	Journal of Clinical Virology	Hanchuan City People's Hospital	Hanchuan, Cina	January 20–February 14,	225	50a
Mahammedi et al. [25]	Radiology	Multicentric	Italy	February 29–April 4	725	NA
Mao et al. [7]	JAMA neurolgy	Multicentric	Wuhan, China	January 16–February 19	214	52.7[a]
Qin et al. [23]	Stroke	Tonji Hospital	Wuhan, China	January 27–March 5	1875	63
Radmanesh et al. [26]	AJNR	New York University Langone Medical Center	New York, USA	March 1–March 31	3661	NA
Tian et al. [18]	Journal of Infection	Beijing Emergency Medical Service	Bejing, China	January 20–February 10	262	47.5
Wan et al. [19]	Journal of Medical Virology	Three Georges Central Hospital	Chongqing, China	January 23–February 8	135	47
Wang et al. [20]	JAMA	Zhongnan Hospital of Wuhan University	Wuhan, China	January 1–February 28	138	56
Xu et al. [21]	TheBMJ	Multicentric	Zhejiang, China	January 10–January 26	35	41

AEMJ Academic Emergency Medicine, *AJNR* American Journal of Neuroradiology,*AJRCCM* American Journal of Respiratory and Critical Care Medicine, *JAMA* The Journal of the American Medical Association, *NA* not available, *NEJM* New England Journal of Medicine

[a]Value expressed as mean

Quality of studies

There was complete agreement between the two reviewers for the examined articles. Twelve studies were retrospective single-center designed, whereas five studies were multicentric investigations. All 17 papers were rated as "high quality" (Table 3). Two publications were letters to the editor. Accordingly, they were rated as "low quality" evidence, due to the type of the publication.

Demographic data and clinical characteristics

Overall, the median age of patients was 50.3 (IQR 11.9), and the proportion of male patients was 50.6% (95% CI 49.2–51.6%). Hypertension was the most common comorbidity (31.1%, 95% CI 30–32.3%) among our population, whereas fever was the most common clinical presentation 80.6%, 95% CI 79.3–81.8%). Detailed data and CI are reported in Table 4. When considering the severity of the

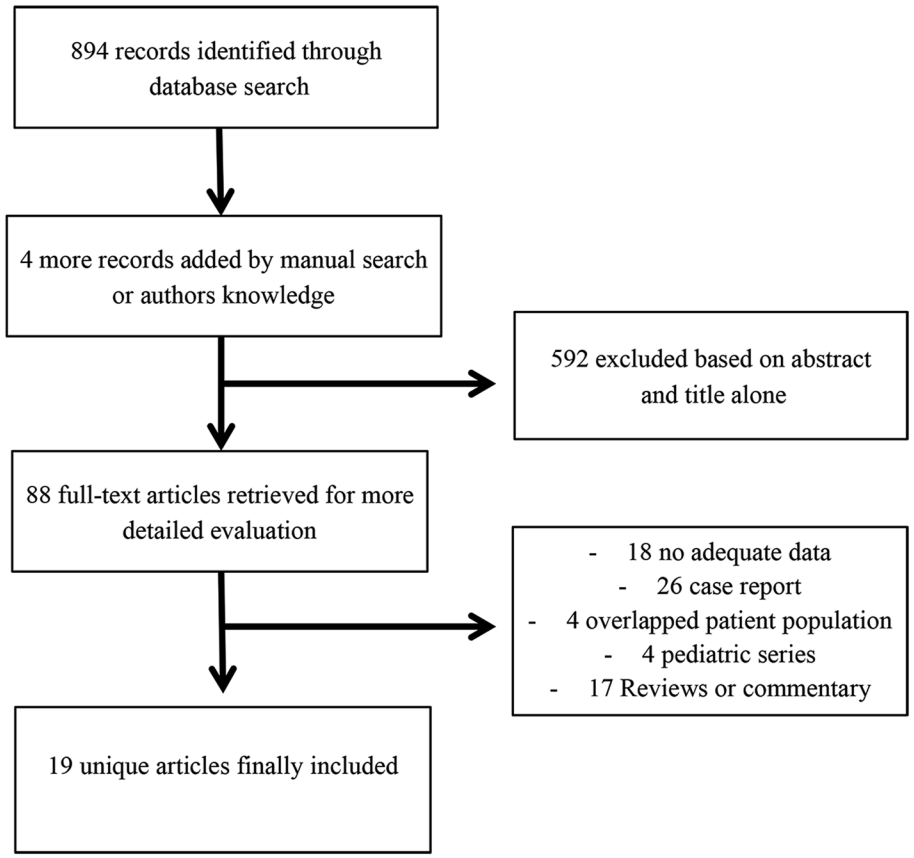

Fig. 1 PRISMA diagram detailing the specifics of the systematic literature review

Table 3 Quality measure of included studies by the Newcastle–Ottawa quality assessment scale

Cohort retrospective studies (12/15)										
Study	Selection				Comparability		Outcome			Tot
	1)	2)	3)	4)	a)	b)	1)	2)	3)	
Beltran-Corbellini et al. [27]	*	*	*		*	*	*	*		77
Cai et al. [12]	*	*	*		*	*	*	*		7
Chuan Qin et al. [4]	*	*	*		*	*	*	*		7
Duanmu et al. [22]	*	*	*	* *			* *	*		88
Feng et al. [13]	*	*	*		*	*	*	*		7
Jain et al. [24]	*	*	*		*	*	*	*		77
Lechien et al. [15]	*	*	*		*	*	*	*		7
Li K et al. [16]	*	*	*		*	*	*	*		7
Li R et al. [17]	*	*	*		*	*	*	*		7
Mahammedi et al. [25]	*	*	*		*	*	*	*		77
Mao et al. [7]	*	*	*		*	*	*	*		7
Qin et al. [23]	*	*	*		*	*	*	*		7
Radmanesh et al. [26]	*	*	*		*	*	*	*		77
Tian et al. [18]	*	*	*		*	*	*	*		7
Wan et al. [19]	*	*	*		*	*	*	*		7
Wang et al. [20]	*	*	*		*	*	*	*		7
Xu et al. [21]	*	*	*		*	*	*	*		7

Table 4 Systematic review main data

	Raw data	Rate (95% CI)	N of articles
Demographic data			
N patients included in the analysis	12157		19
Male patients	2261/4460	50.6% (49.2–51.6%)	14
Age (median, IQR)	50.3 (11.9)	-	9
Comorbidity			
Hypertension	1969/6321	31.1% (30–32.3%)	10
Diabetes	384/6321	13.5% (12.3–14.8%)	8
Cardiovascular disease	297/2842	10.5% (9.3–11.6%)	7
Malignancy	85/2561	3.3% (2.6–4%)	6
Smoking	277/3082	9% (8–10%)	6
Neurological symptoms			
CNS			
Dizziness	136/2227	6.1% (5.1–7.1%)	3
Headache	237/3163	7.5% (6.6-8.4%)	10
PNS			
Hypo/anosmia	407/869	46.8% (43.5–50.2%)	5
Gustatory disorders	402/769	52.3% (48.7–55.8%)	4
Muscular injury manifestation			
Myalgia	441/2806	15.7% (14.4–17.1%)	7
Fatigue	667/2732	24.8% (23.2–26.4%)	6
Fatigue or myalgia	117/384	30.5% (25.9–35.1%)	3
Other symptoms			
Fever	3222/3999	80.6% (79.3–81.8%)	13
Cough	1908/3964	48.1% (46.6–49.7%)	12
Dyspnea	1009/2976	33.9% (32.2–35.6%)	98
Pharyngodynia	124/1502	8.3% (7–9.8%)	7
Digestive symptoms	357/1320	27.1% (24.7–29.5%)	10

CNS central nervous system, *IQR* inter-quartile range, *PNS* peripheral nervous system

disease, the two sub-groups were not homogeneous in terms of comorbidity in our analysis. Indeed, patients with a history of hypertension, cardiovascular disease, diabetes, and concurrent malignancy were significantly more common in the "severe" subgroup ($p < 0.01$) (Table 5).

Neurological symptoms

Among CNS symptoms, headache was reported in ten studies and in 7.5% of patients (95% CI 6.6–8.4%). Dizziness was observed in 6.1% of patients in two different series (95% CI 5.1–7.1%). Myalgia was reported in 441 of 2806 patients (15.7%, 95% 14.4–17.1%) in seven studies, and fatigue occurred in 667 of 2732 patients (24.8%, 95% CI 23.2–26.4%) in six series. Three studies reported the overall rate of fatigue/myalgia as a single data, obtaining an overall rate of 30.5% (95% CI 25.9–35.1%) of patients complaining these symptoms at clinical admission. The most common neurological symptom was the impairment of olfactory and gustatory functions (46.8%, 95% CI 43.5–50.2% and 52.3%, 95% CI 48.7–55.8%, respectively). Interestingly, both CNS symptoms and muscular injury manifestations were more common among severe patients (dizziness: 20.1% vs 10.5%, $p = 0.02$; headache: 13% vs 8%, $p = 0.01$; skeletal muscle injury: 29.4% vs 11.8%, $p < 0.01$). The rate of PNS were compared between severe and non-severe populations only in one study, and no significant difference arose from the analysis (Table 5). Furthermore, three studies showed an overall rate of radiological confirmed acute cerebrovascular disease of 2% (95% CI 1.6–2.4%).

Discussion

Limited reports described neurologic complications of SARS-CoV-1 and MERS-CoV, mainly restricted to axonal peripheral neuropathy, acute disseminated encephalomyelitis, and stroke [28, 29]. Our systematic review of 2499 patients reported the occurrence of a wide spectrum of neurologic complications in hospitalized patients with laboratory-confirmed COVID-19 infection, supporting the possible neuroinvasive potential of SARS-CoV-2.

Table 5 Comparison of neurological symptoms among subgroups (nonsevere vs severe infection)

	Nonsevere	95% CI	Severe	95% CI	*P*-value	N. studies
Comorbidity						
Hypertension	151/973	15.5% (13.4–17.9%)	121/371	32.6% (28–37.6%)	< 0.01	6
Cardiovascular disease	41/1127	3.6% (2.7–4.9%)	40/465	8.6% (3.4–11.5%)	< 0.01	5
Diabetes	66/973	6.8% (5.4–8.6%)	64/371	17.3% (13.7–21.4%)	< 0.01	6
Malignancy	19/915	2% (1.3–3.2%)	24/346	6.9% (4.7–10.2%)	< 0.01	5
Smoking	35/447	7.8% (5.7–10.7%)	18/164	11% (7–16.8%)	0.26	2
Neurological symptoms						
CNS						
Dizziness	24/228	10.5% (7.2–15.2%)	25/124	20.1% (14–28.1%)	0.02	2
Headache	67/837	8% (6.3–10%)	40/308	13% (9.7–17.2%)	0.01	6
PNS						
Hypo/anosmia	8/126	6.4% (3.1–11%)	3/88	3.4% (0.7–9%)	0.5	1
Gustatory disorders	9/126	7.1% (36.4–13.2%)	3/88	3.4% (0.7–9%)	0.7	1
Muscular injury manifestation						
Myalgia or fatigue	140/1189	11.8% (10.1–13.7%)	127/432	29.4% (25.3–33.9%)	< 0.01	7

CNS central nervous system, *PNS* peripheral nervous system

The potential neurotropism of SARS-CoV-2

A growing body of evidence suggests that SARS-CoV-2, similarly to SARS-CoV-1, has neuroinvasive potential, possibly through the retrograde neuronal route [30, 31]. Recent studies reported that the expression level of angiotensin converting enzyme 2 (ACE2) is critical for the susceptibility of SARS-CoV-1 and SARS-CoV-2 infection [32]. The cellular receptor ACE2 is expressed in different tissues and organs including the nervous system and skeletal muscles [33]. Autopsy samples from patients with SARS clearly demonstrated the presence of SARS-CoV-1 in brain samples [34, 35]. Interestingly, laboratory investigations on transgenic mice for the SARS-CoV receptor (ACE2) demonstrated that the virus enters the brain via the olfactory bulb with resultant rapid transneuronal spread to different brain regions including cortical areas (piriform and infralimbic cortices), basal ganglia (ventral pallidum and lateral preoptic regions), and midbrain (dorsal raphe). In these regions, a significant neuronal death occurs [36]. A recent report confirmed the presence of SARS-CoV-2 in cerebrospinal fluid by genome sequencing in a patient with viral encephalitis, confirming the neurotropism of SARS-CoV2 [37, 38]. They proposed that the respiratory failure in patients with COVID-19 is related to the neuronal loss at the level of the cardiorespiratory center in the brainstem. However, type 1 respiratory failure with low CO2 levels and raised respiratory rate observed in patients with COVD-19 is more likely related to pneumonia instead of brainstem dysfunction that leads to failure of breathing associated with reduced respiratory rate and high C02 levels (type 2 respiratory failure) [39].

Symptoms related to skeletal muscle injury are generally associated with elevated creatine kinase and lactate dehydrogenase levels. It was initially suspected that this injury was related to the presence of ACE-2 in skeletal muscle [40]. However, immunohistochemistry and in situ hybridization failed to detect SARS-CoV in the skeletal muscle of patients who died of SARS, suggesting a putative role of a systemic inflammatory response syndrome (SIRS) in the pathogenesis of muscular damage [34]. It is supposed that SIRS can occur in pneumonia caused by COVID-19 infection and promotes multiple organ failures in patients with severe infection. Further clinical and laboratory investigations are required to clarify the neurotropism of SARS-COV-2 and its neuroinvasive potential. Nonetheless, some reports detected SARS-CoV-2 in the CSF of patients presenting with meningoencephalitis and unremarkable medical history, strengthening the idea of a direct neuroinvasive potential of this novel coronavirus [41, 42].

Neurologic manifestations of SARS-CoV-2 Infection

Neurologic manifestations in patients with COVID-19 are common. In a recent retrospective study, Mao et al. reported nervous system-related clinical findings in 78 of 214 hospitalized patients (36.4%) and categorized neurological disturbances into three groups: CNS manifestations, PNS manifestations, and skeletal muscular injury manifestations. Interestingly, their report suggested that patients with severe infection were more likely to develop CNS and muscular injury symptoms [7]. The results of our analysis are consistent with their findings, demonstrating a significant difference among severe and non-severe patients. Nonetheless,

the two groups were not homogeneous in terms of clinical comorbidity, and severe patients were characterized by a significant higher rate of concomitant hypertension, cardiovascular disease, malignancy, and diabetes. Accordingly, as previously discussed, a direct link between the occurrence of neurological symptoms and the clinical condition cannot be drawn at the current state of knowledge. However, the occurrence of multiorgan damage in patients with muscle injury suggests that infection-mediated immune response probably plays a role as a causative factor of skeletal muscle damage. In fact, these patients present not only significantly higher levels of creatine kinase but also higher neutrophil counts, lower lymphocyte counts, higher C-reactive protein levels, and higher D-dimer levels indicating increased inflammatory response and coagulation activation [7, 30]. Similar findings were reported in patients with MERS and SARS-CoV-1 infection [43, 44]. Our study demonstrated that olfactory and gustatory function impairment were the most common neurologic manifestations in patients with COVD-19 and were detected in approximately 50% of patients. Lechien et al. extensively examined this topic in a multicentric investigation and reported an overall rate of olfactory and gustatory dysfunctions of roughly 85 and 88%, respectively [15]. In this study, olfactory and gustatory dysfunction were both prevalent in patients with mild-to-moderate COVID-19 infection and hyposmia was generally observed in patients without nasal obstruction or rhinorrhea before, during or after the general symptoms. It is worth noting that the prevalence of olfactory and gustatory dysfunction was substantially higher in European cohorts compared with the Asian cohorts [4, 15]. This difference is poorly understood and requires further investigation.

Accumulating evidence suggests that SARS-CoV-2 infection is associated with a prothrombotic state, with elevated D-dimer [45] that can eventually lead to acute cerebrovascular disease, especially in severe patients [7]. In the series of Helms et al., MRI was performed in 13 patients because of encephalopathic features and demonstrated one subacute and two acute ischemic strokes [8]. Recently, several case reports described the occurrence of ischemic and hemorrhagic stroke (see supplementary material 1), confirming the association of cerebrovascular complications with severe COVID-19 infection, older age, and the presence of multiple comorbidity [46, 47]. On the other hand, our study showed an overall rate of acute cerebrovascular disease (ischemic or hemorrhagic) of 2% that is similar to the rate of stroke in the US [48]. It is noteworthy that these data could be underestimated due to the number of critical patients with neurological signs that did not undergo any neuroradiological investigation during the pandemic outbreak [46]. Furthermore, it has been reported that hospitalization for infection is associated with a short-term increased risk of stroke [49]. Accordingly, even though a causal relationship between COVID-19 infection and acute cerebrovascular disease cannot be drawn at the current state of knowledge, it is conceivable that ischemic stroke can occur in the context of a systemic highly prothrombotic state in severe patients.

No definitive epidemiologic data support the link between SARS-CoV-2 infection and polyradiculopathy. Nonetheless, an increasing number of studies are reporting the occurrence of Guillain-Barré syndrome or polyneuritis cranialis (Supplementary Material 1) in COVID-19 patients. Although scanty information is available on this topic, two different clinical presentations are described: (1) an interval of 5–10 days between the onset of viral illness and the first symptoms of Guillain-Barré [50] (2) and an unusual concomitant progression of both the infection and the neurological syndrome [51]. Guillain-Barré syndrome is caused by an aberrant autoimmune response evocated by a cross-reaction against ganglioside components of the peripheral nerves, ensuing different viral or bacterial infections [50]. As previously discussed, SARS-CoV-2 can cause an excessive immune reaction that lead to extensive tissue damage. Clinical and laboratory data are not definitive: antiganglioside antibodies were often absent, albuminocytologic dissociation in CSF was not constant [50–53], and PCR for coronavirus was negative in CSF.

Seizure are infrequently reported in patients with COVID-19, and only few cases are described in the literature. Viral encephalitis or a blood–brain barrier breakdown ensuing the excessive release of pro-inflammatory cytokine have been hypothesized as the cause of cortical irritation that precipitates seizures related to COVID-19 infection [41, 54]. Nonetheless, data are insufficient, and no definitive conclusions can be currently drawn.

Limitations of the study

Our study has limitations. The series are often small, retrospective, and single-institution experiences. Furthermore, due to the contemporaneity of the outbreak, the follow-up is short, and the occurrence of late onset neurological deficits cannot be analyzed. Furthermore, only two studies [7, 8] have analyzed, as primary outcome, the neurological characteristics of their patients. In addition, advanced neuroimaging (MRI) and diagnostic procedures (lumbar puncture, electromyography/nerve conduction velocity) were rarely reported in the studies included. However, our review is the largest study to date that provides a representation of data concerning neurological symptoms among laboratory-confirmed COVID-19 population.

Conclusions

Accumulating evidence suggests that a significant proportion of patients with COVID-19 infection develops neurological manifestations, especially olfactory and gustatory dysfunction. The pathophysiology of this association is under investigation and warrants additional studies. Physicians should be aware of this possible association because during the epidemic period of COVID-19, early recognition of neurologic manifestations otherwise not explained should raise the suspect of acute respiratory syndrome coronavirus 2 infection.

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Compliance with ethical standards

Conflicts of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Research involving Human Participants and/or Animals This article does not contain any studies with human participants or animals performed by any of the authors.

Ethical approval For this type of study formal consent is not required.

Informed consent The nature of this article did not require informed consent.

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