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Systematic Review / Meta-analysis

Post COVID-19 neurological complications; a meta-analysis

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ABSTRACT

Introduction: Despite numerous studies regarding neurological manifestations and complications of COVID-19, only a few cases of neurological consequences following complete recovery from SARS-CoV-2 infection have been described.

Objectives: The current study aims to present a quantitative meta-analysis of published studies regarding the post-infectious neurological complications of COVID-19.

Data sources: The Web of Science, PubMed, MEDLINE on OVID, and Google scholar were searched for English-language researches published after January 1, 2020.

Result: The review of the literature revealed 60 cases - of which 40 (66.7%) cases were male, and 18 (30%) were female. The average age was 44.95 years. Overall, 17 (28.3%) patients had comorbid conditions. Twenty-four (40%) patients were hospitalized during an active COVID-19 infection. The average interval from the COVID-19 infection to the onset of neurological sequelae was 33.2 days. Guillain-Barre syndrome was the most commonly reported neurological condition (15, 25%).

Conclusion: Despite recovery from acute infection, the pandemic highlights the significance of ongoing, comprehensive follow-up of all COVID-19 patients - even those initially were believed to be asymptomatic.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the rapidly evolving coronavirus disease 2019 (COVID-19) pandemic [1]. SARS-CoV-2 is most commonly associated with pulmonary infection, resulting in pneumonia, but new studies have indicated that many other organ systems, including the cardiovascular, immunological, neurological, and gastrointestinal systems can be involved [2]. Although various neurological sequelae in COVID-19 individuals have been identified, the specific relationship between the infection and neurological disorders remains unknown. In a case series in Wuhan, China, 36.4% of the Covid-19 cases experienced central nervous system (CNS) symptoms, 8.9% peripheral nerve system (PNS) symptoms, and 10.7% reported skeletal muscle symptoms [3]. Neurological features do not always necessitate a direct infection of the PNS or CNS but can alternatively arise as a result of a severe systemic reaction to a viral illness outside the nervous system. However, reports of meningitis and encephalitis in the context of COVID-19 have been reported in recent months, suggesting that SARS-CoV-2 can directly infect the nervous system [4]. The reason for this involvement is that the SARS-COV-2 spike protein has a high affinity for binding to the angiotensin-converting enzyme 2 (ACE-2) receptor, which has recently been discovered on neurons and glial cells in several brain structures [5]. Other contributing factors include secondary hypoxia, cytokine-related damage, and retrograde transit via the olfactory nerve and bulb [6]. Studies on SARS-CoV-1 and MERS revealed that a minority of patients do not return to normal life quality after infection and may experience several neurological complications even for years after acute infection [7]. Despite numerous studies regarding neurological manifestations and complications of COVID-19, only a few cases of

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neurological consequences following complete recovery from SARS-CoV-2 infection have been described [8].

As a result, recognizing the neurological and musculoskeletal complications of COVID-19 would be valuable and might give more information to help understand the post-infectious complications of COVID-19. The current study aims to present a quantitative meta-analysis of published studies regarding the post-infectious neurological complications of COVID-19.

2. Method

2.1. Study design

This meta-analysis was carried out in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards [9].

2.2. Information sources

The Web of Science, PubMed, MEDLINE on OVID, and Google scholar were searched for English-language articles published after January 1, 2020. Post, after, following, COVID-19, SARS-CoV-2, nCOV-19 neurological, neurology, neurologic, complications, outcome, long, consequences, sequela, encephalitis, meningitis, meningoencephalitis, encephalopathy, seizure, status epilepticus, stroke, cerebrovascular disease, polyradiculopathy, neuropathy, myopathy, myelitis, Guillain-Barre barre syndrome, optic neuritis, vestibular neuritis, bell's palsy, Opsoclonus Myoclonus, and cerebral venous thrombosis were the search terms. References mentioned by included papers were used to complement data gathering.

2.3. Inclusion criteria

The study selection criteria focused on papers describing post-COVID neurological complications. The infection with SARS-CoV-2 must have been confirmed by real-time polymerase chain reaction (RT-PCR) and only English articles were involved. Only patients that acquired neurological disorders after fully recovering from COVID-19 disease were included. Recovery from COVID-19 was confirmed by a negative PCR or by being asymptomatic and discharged from the hospital.

2.4. Exclusion criteria

Studies describing neurological manifestations and complications during active COVID-19 infection were excluded.

2.5. Data extraction

Authors searched google scholars and databases such as Web of Science, PubMed, and MEDLINE on OVID. The duplicates were eliminated, and then the filtering was done according to the inclusion and exclusion criteria.

2.6. Data synthesis and statistical analysis

Extracted data was calculated and re-analyzed completely. They have been presented as percentages, mean values, and ranges of variance.

3. Result

Overall, 195 articles were discovered during the initial database searches. The data were gathered from three databases and google scholar. After deleting 35 duplicates, there were 160 non-duplicate studies. After reviewing the titles and abstracts, 75 non-relevant studies were eliminated from the evaluation. About 45 unrelated studies were also removed throughout the full-text screening process. Finally, 40 papers were selected for the final analysis. The majority of the studies (36) were case reports, with four being case series. The PRISMA chart is detailed in Fig. 1.

The findings indicate a total of 55 cases. There were 37 (67.3%) male cases and 16 (29.1%) female cases, and the remainders were inapplicable. The average age was 48.27 years, ranging from 7 months to 81 years. Overall, 17 (30.9%) patients had comorbid conditions such as diabetes, hypertension, dyslipidemia, IHD, and acute lymphoid leukemia (ALL), whereas 27 (49.1%) cases had no prior medical history and the remainder was not addressed. During COVID-19 illnesses, 24 (43.6%) patients were hospitalized with 3 (5.5%) of them being admitted to the intensive care unit (ICU), and the other 12 cases were not reported as to whether they were admitted to the hospital or not (20%). The average interval from the infection of COVID-19 to the onset of neurological symptoms was 33.2 days, ranging from 8 days to 130 days. Guillain-Barre syndrome (GBS) was the most commonly reported neurological condition (12, 21.8%), followed by stroke (9, 16.4%) and optic neuritis (7, 12.7%). Table 1 shows the characteristics of the studies that were involved. The occurrence of each reported neurological condition was disclosed in Table 2. Table 3 displays the characteristics of each condition (mean age, hospital, and ICU hospitalization).

4. Discussion

The COVID-19 outbreak has been a disaster worldwide, affecting many people's health and financial well-being across the world [49]. Even though the majority of SARS-CoV-2 infected individuals recover completely, for a significant number of patients, surviving COVID-19 may be the beginning of many struggles on the long journey to complete recovery, as they develop long-term morbidities ranging from moderate to severe sequelae [50]. Since the development of COVID-19, neurological symptoms, and consequences linked with this multi-organ viral infection have been recorded, and many aspects of neurological involvement are becoming more apparent [51]. COVID-19-related

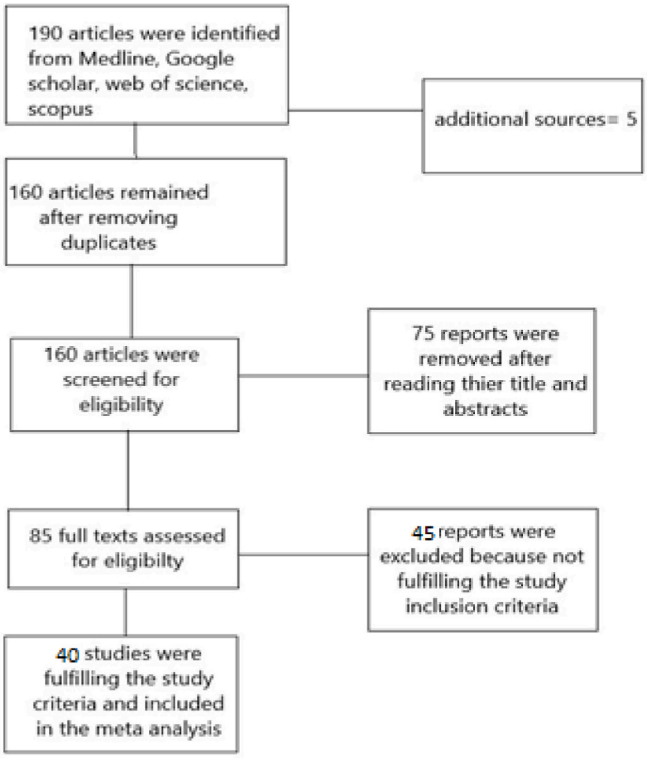

Fig. 1. PRISMA chart.

Table 1
The characteristics of involved studies.

Studies	Type of study	Published date	Total number of COVID-19 cases	Number of post-COVID-19 neurological disorder	Mean age	Sex (n)		Interval between COVID-19 infection and neurological presentations (days)
						Male (n)	N/A (n)	
Ortelli et al. [10]	Case series	December 14, 2020	12	12	67	10	0	81
Sud et al. [11]	Case series	January 1, 2021	3	3	52.6	2	0	26
Goel et al. [12]	Case series	September 21, 2021	2	2	3	2	0	15
Khalid et al. [13]	Case report	July 24, 2021	1	1	41	1	0	30
Maramattom et al. [14]	Case report	April 16, 2021	1	1	60	1	0	60
Mezzeoui et al. [15]	Case report	June 20, 2021	1	1	3	0	0	15
Gupta et al. [16]	Case report	August 11, 2021	1	1	35	1	0	15
Gracia manzanedo et al. [17]	Case report	August 2020	1	1	77	1	0	15
Ahmad et al. [8]	Case report	August 23, 2021	1	1	34	0	0	15
Kara et al. [18]	Case report	October 27, 2021	1	1	39	0	0	90
Munz et al. [19]	Case report	May 26, 2021	1	1	60	1	0	8
Bagnato et al. [20]	Case report	July 21, 2020	1	1	62	0	0	20
Ahmad et al. [21]	Case report	November 11, 2021	1	1	58	0	0	30
Ivan et al. [22]	Case report	October 8, 2021	1	1	48	0	0	60
Priftis et al. [23]	Case report	March 25, 2021	1	1	72	1	0	26
Rodriquez et al. [24]	Case report	September 6, 2021	1	1	70	1	0	16
Rose et al. [25]	Case report	July 9, 2021	1	1	66	1	0	15
Sartoretti et al. [26]	Case report	September 9, 2020	1	1	60	1	0	14
Shala et al. [27]	Case report	June 18, 2021	1	1	14	1	0	N/A
Dono et al. [28]	Case report	November 3, 2020	1	1	81	1	0	14
Faber et al. [29]	Case report	August 17, 2021	1	1	35	0	0	11
Baltaziak et al. [30]	Case report	November 5, 2021	1	1	46	0	0	130
Farouk et al. [31]	Case series	October 8, 2021	2	2	N/A	0	2	33
Kivanany et al. [32]	Case report	September 30, 2021	1	1	35	0	0	45
Rojas corea [33]	Case report	May 24, 2021	1	1	69	1	0	45
Singh et al. [34]	Case report	September 22, 2021	1	1	37	1	0	14
Sinha et al. [35]	Case report	August 11, 2021	1	1	13	1	0	N/A
Zoric et al. [36]	Case report	May 25, 2021	1	1	63	1	0	N/A
Carroll et al. [37]	Case report	August 14, 2021	1	1	69	0	0	44
Kashyap et al. [38]	Case report	April 21, 2021	1	1	7 m	1	0	20
Appleberry et al. [39]	Case report	June 7, 2021	1	1	1	1	0	30
Llorente Ayuso et al. [40]	Case report	September 3, 2021	1	1	72	0	0	10
Fukushima et al. [41]	Case report	March 15, 2021	1	1	20	1	0	50
Siripurapu et al. [42]	Case report	July 19, 2021	1	1	32	1	0	43
Toricco et al. [43]	Case report	November 6, 2021	1	1	56	1	0	60
Ruwanpathirana et al. [44]	Case report	October 8, 2021	1	1	27	0	0	21

(*continued on next page*)

Table 1 (*continued*)

Studies	Type of study	Published date	Total number of COVID-19 cases	Number of post-COVID-19 neurological disorder	Mean age	Sex (n)		Interval between COVID-19 infection and neurological presentations (days)
						Male (n)	N/A (n)	
Al-mashadli et al. [45]	Case report	August 25, 2021	1	1	21	1	0	14
Inui et al. [46]	Case report	November 6, 2021	1	1	43	1	0	30
Aasfara et al. [47]	Case report	January 13, 2021	1	1	36	0	0	40
Ishaq et al. [48]	Case report	June 7, 2021	1	1	63	1	0	24

neurological consequences pose a danger to patients' functional capacity and life. Suspicion of these illnesses, careful management of metabolic changes, cardiovascular risk factors, and effective and safe treatment of these individuals are all ongoing challenges throughout the outbreak [52]. The published studies regarding post-infectious neurological complications of COVID-19 were evaluated in the current study, which is the first meta-analysis on this subject. The result of this study showed a total of 55 cases who developed various neurological sequelae after recovering from an acute infection of SARS-CoV-2.

COVID-19 has been classified into four stages: acute respiratory distress syndrome, cytokine storm, acute hypercoagulable condition, and autonomic dysfunction [51]. Increased IL-6 drives B-cell differentiation and has an anti-inflammatory effect. However, it has the potential to produce acute phase cytokine overproduction and cytokine release syndrome (cytokine storm), which is characterized by fever and multi-organ failure [53]. It has been proposed that in cured patients, SARS-CoV-2 stays latent in the central nervous system for an extended period, making it capable of reactivating and causing neurological problems [52]. The "post-covid neurological syndrome" provides a diagnostic dilemma for the clinical neurologists due to various manifestations: central and peripheral nervous systems, musculoskeletal, and neuropsychiatric manifestations [54]. Age over 65, chronic lung illness, cardiovascular disease, hypertension, diabetes, and obesity are all risk factors for complications related to SARS-CoV-2 infection [55]. In the present analysis, 17 individuals had at least one comorbidity and 27 patients had no prior medical history. The average age of the patients was 48.27 years.

COVID-19 neurologic symptoms range from anosmia, ageusia, encephalopathy, encephalitis, myelitis, and post-infectious sequelae such as GBS, plexopathies, and cranial neuropathies [56]. In a prospective cohort study, Rass et al. discovered neurological disorders unknown before COVID-19 in every sixth patient at the 3-month follow-up, with a predominance in ICU patients, including polyneuro/myopathy, mild encephalopathy, parkinsonism, orthostatic hypotension associated with vasovagal syncope, and stroke [57]. Similarly, Taquet et al. showed that neurological disorders were substantially more prevalent among hospitalized COVID-19 patients, particularly those admitted to the ICU [58]. According to Rass et al. seriously affected individuals had a greater prevalence of persisting neurological symptoms 3 months after the disease onset than patients with milder disease courses [57]. This analysis includes the following post-infectious neurological complications: GBS, Transverse myelitis, stroke, critical illness neuromyopathy (CIN), encephalopathy, optic neuritis, myopathy, Bell's palsy, status epilepticus, vestibular neuritis, Opsoclonus Myoclonus Syndrome (OMS), and parkinsonism. Only 24 of them were hospitalized.

Table 2
The frequency of each neurological disorder.

Disorder	No. of cases	References
Guillain-Barré syndrome	12	[10–17]
Transverse myelitis	3	[8,18,19]
Critical illness neuromyopathy/neuropathy	3	[10]
Encephalopathy	3	[10]
Stroke	9	[10,21–27,30]
Parkinsonism	1	[29]
Optic neuritis	7	[31–36]
Status epilepticus	3	[37–39]
Encephalitis	5	[28,40,41]
Bell's palsy	3	[44–46]
Vestibulocochlear neuritis	1	[47]
Opsoclonus Myoclonus Syndrome	1	[48]
Myopathy	4	[10,20]

The frequency of GBS has grown since the pandemic's outbreak. There have been several publications describing the relationship between SARS-CoV-2 infection and GBS [16]. The incubation period of SARS-CoV-2 is variable, making it difficult to predict the interval between infection and the emergence of GBS [11]. Whittaker et al. conducted a comprehensive evaluation of 2504 COVID-19 patients, = 11 cases of GBS were reported. Despite their lower proportion, these individuals suffer long-term chronic neurological impairments or even fatal consequences [12]. In this regard, there is a growing interest in the relationship between COVID-19 and the development of GBS, which nearly always occurs during the acute phase of the infection [59]. In a systematic review of 73 cases, Abu Rumeileh et al. observed that classic GBS was the most common variant identified, with sensory presentation and acute inflammatory demyelinating polyneuropathy. Rarely, variants such as Miller-Fischer syndrome or BFP have been described [60]. Several pathways have been postulated to explain the etiology of GBS after COVID-19. The most widely accepted mechanism is the development of antibodies against pathogen surface glycoproteins, which may cause peripheral nerve injury owing to similar native protein structures [16]. The vast majority of GBS with COVID 19 cases have been para infectious while post-infectious GBS is uncommon [14]. The total number of GBS cases reported after recovering from COVID-19 was 12, with a mean age of 51.4. Ten of them were males. In four of the cases, at least one comorbid condition was present. Six of them were admitted to the hospital during an active infection without being admitted to the ICU.

In addition to GBS, post-infectious transverse myelitis has been reported. The pathogenesis of postinfectious myelitis is most likely similar to that of other postinfectious acute disseminated encephalomyelitis (ADEM). It involves both adaptive and innate immunity [18]. Three cases of transverse myelitis were described in the study, with a mean age of 36 years. Two of them were female. Two patients were hospitalized during an active infection but they were not admitted to the ICU. In terms of enhancing recovery and selecting a better prognosis, individuals with GBS and myelitis related to COVID-19, as with other acute neurological disorders, may benefit from a neurorehabilitation intervention initiated in the early stages following the onset of neurological symptoms [61]. In a study of severe COVID-19 patients admitted to the hospital due to severe infection, encephalopathy and frontal

Table 3
The characteristics of each neurological disorder.

Disease	Age	Sex			Hospital admission during COVID-19 illness			ICU admission during COVID-19 illness			PMH (HTN, DM, IHD)		
		M	F	N/A	Yes	No	N/A	Yes	No	N/A	Yes	No	N/A
Guillain-Barré syndrome	51.4	10	1	1	6	4	2	0	9	3	4	6	2
Transverse myelitis	36	1	2	0	1	2	0	0	3	0	1	2	0
Critical illness neuromyopathy/neuropathy	62.3	3	0	0	0	0	3	0	0	3	0	0	3
Encephalopathy	68.5	2	1	0	0	0	3	0	0	3	0	0	3
Stroke	56.5	5	4	0	5	3	0	0	8	1	3	5	1
Parkinsonism	35	0	1	0	0	1	0	0	1	0	0	1	0
Optic neuritis	43.4	4	1	2	3	4	0	0	7	0	2	5	0
Status epilepticus	23.5	2	1	0	1	2	0	1	2	0	1	2	0
Encephalitis	52.2	3	2	0	4	1	0	0	5	0	3	2	0
Bell's palsy	30.3	2	1	0	3	0	0	1	2	0	1	2	0
Vestibulocochlear neuritis	36	0	1	0	0	1	0	0	1	0	0	1	0
Opsoclonus Myoclonus Syndrome	63	1	0	0	0	1	0	0	1	0	1	0	0
Myopathy	48.6	3	1	0	1	0	3	1	0	3	1	0	3

symptoms were quite common [62]. Another study found encephalopathy in one-third of ICU patients during acute illness, with just one of those patients having residual symptoms three months later. At follow-up, 15% of the patients had positive frontal release signs, which are unspecific but prevalent in individuals with encephalopathy [57]. In the current meta-analysis, three cases of encephalopathy with a mean age of 68 years were described. It was not mentioned whether they were admitted to the ICU or not.

Consistent with the earlier studies, the risk of cerebrovascular events increased following COVID-19, with the incidence of ischemic stroke increasing to nearly one in ten (or three in 100 for a first stroke) in individuals with encephalopathy [58]. Recent studies have found that the incidence of stroke in people infected with COVID-19 varies between 0.9 and 2.7% [63]. SARS-CoV-2 can induce stroke by a variety of mechanisms, including invasion of the vascular endothelium, which causes coagulopathy owing to endothelial inflammation, cardiac injury, which causes clot formation, or instability of a preexisting atheroma plaque [64]. Although stroke has been reported in several studies in the context of active COVID-19, stroke after COVID-19 with no active infection has only been reported in a few case reports in the literature [21]. In this analysis, there were nine cases of post-infectious stroke, with a mean age of 56.5 years. Five of the patients were male, and five of them were admitted to the hospital during active infection without ICU hospitalization.

Electrolyte and metabolic abnormalities, hypoxia, and inflammatory processes all lead to the development of seizures or abnormal electroencephalogram (EEG) patterns in individuals with severe COVID-19 [65]. Panda et al. reported 12 cases of seizure secondary to COVID-19 out of 3707 cases [66]. Seizures are becoming more common in COVID-19 patients worldwide, indicating a viral invasion of the central nervous system. Seizure is a symptom of acute brain damage induced by hypoxemia as a result of severe pneumonia. Metabolic abnormalities and septic encephalopathy are also prominent in this group of individuals. Those who have a history of status epilepticus have a worse prognosis since the severity and frequency of seizures may increase due to a lower threshold [52]. In the current study, three cases of post-infectious status epilepticus were described, one of which had a history of ICU hospitalization during the active illness. Several studies have recently revealed COVID-19-associated OMS. Interestingly, the majority of these COVID-19 patients who developed OMS had mild-to-moderate respiratory symptoms [48]. Emamikhah et al. reported seven COVID-19 patients with OMS who had normal brain MRI scans [48]. OMS post-COVID-19 was reported in only 1 case with no history of hospital admission.

COVID-19 neuro-ophthalmology problems have been documented rarely [30]. Several neuro-ophthalmological consequences of COVID-19 have been described, either as separate events or as part of a larger neurological disorder [33]. COVID-19-related neuro-ophthalmic symptoms include optic neuritis, cranial nerve palsies, vision disturbances, and visual field abnormalities [32]. In the current meta-analysis, three cases of post-infectious optic neuritis were described. Three of them were male. Two of the patients had pre-existing medical conditions. None of them were admitted to the intensive care unit.

It is also a possibility that the virus acts as an initiating agent of some neurodegenerative diseases like Parkinson's disease in the long term [6]. Although the incidence was low, concerns have been raised about post-COVID-19 parkinsonian syndromes. It might be a delayed outcome [58]. In the current analysis, one case of post-COVID-19 parkinsonism was found.

In conclusion, this study showed that despite recovery from acute infection, the pandemic highlights the significance of ongoing, comprehensive follow-up of all COVID-19 patients, even those initially believed to be asymptomatic, with routine screening for possible long-term persistent neurological involvement.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103440.

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