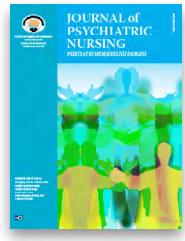
JOURNAL OF
PSYCHIATRIC NURSING

DOI: 10.14744/phd.2021.71324
J Psychiatric Nurs 2022;13(1):92-99



Systematic Review

A systematic review of detailed neurological and psychiatric manifestations in patients with COVID-19

Semra Bülbüloğlu,[1] Nermin Gürhan[2]

[1]Division of Surgical Nursing, Department of Nursing, İstanbul Aydın University Health Sciences Faculty, İstanbul, Turkey
[2]Division of Psychiatry Nursing, Department of Nursing, Tokat Gaziosmanpaşa University Faculty of Health Sciences, Tokat, Turkey

Abstract

Objectives: The aim of this research was to conduct a systematic review of studies examining neurological and psychiatric disorders in patients diagnosed with coronavirus 2019 (COVID-19).

Methods: This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. Related studies and case reports published in the ScienceDirect, PubMed, EMBASE, EBSCO, and Scopus databases between December 1, 2019 and September 1, 2020 were examined, and 21 studies that met the inclusion criteria were included in the review. The data gathered were summarized and analyzed.

Results: All of the studies included were descriptive in nature. The most common findings were headache, central nervous system problems, cerebrovascular events, and polyneuropathy. Dizziness, Guillain-Barré syndrome, ischemic problems, and encephalopathy were among the other neuropsychiatric findings.

Conclusion: Important psychiatric and neurological problems may begin with onset of COVID-19 and continue to have post-recovery effects. The results of this study indicated that neuropsychiatric signs and symptoms were common in COVID-19 patients and can prolong the recovery period. These data may raise awareness among clinicians and help them develop a care plan for neuropsychiatric problems in COVID-19 patients.

Keywords: Brain; central nervous system; coronavirus; COVID-19; neurological disorders; psychiatric disorders.

Coronavirus 2019 (COVID-19), a potentially fatal disease caused by severe acute respiratory syndrome 2 (SARS-CoV-2), first emerged in Wuhan, China, in late 2019, and subsequently became a global pandemic that continues to have significant deadly effects.[1–3] In 2020, the global COVID-19 mortality ratio was estimated to be 4.6%[1] and significant consequences continue to be felt worldwide. Various treatment protocols were implemented in hospitals to address the disease-causing mechanisms of the virus, and several scientific studies were initiated to pursue various treatment methods.[4]

Two antimalarial drugs in the aminoquinoline group, chloroquine (CQ) and hydroxychloroquine (HCQ), were among the early choices to treat COVID-19 based on their ability to inhibit other coronaviruses.[2,3] Examination of the mechanism of action suggested that CQ and HCQ suppress the glycosylation of angiotensin-converting enzyme 2 located on the cell surface and draw viral particles into the intracellular space. Subsequently, interleukin 6 (IL-6) produces an anti-inflammatory effect by inhibiting tumor necrosis factor alpha (TNF-α), abnormal interferon, and other pro-inflammatory cytokines that can cause lung damage and acute respiratory distress syndrome.[4]

Compared with CQ, HCQ dissolves better and exhibits fewer toxic effects,[5,6] and is therefore safer. However, these drugs may cause toxicity that predisposes to neuro-psychiatric, sensory, cardiac, and metabolic problems.[7,8] In addition to possible problems caused by drugs used to treat COVID-19, the virus itself is thought to have potential pulmonary, renal, hepatic, psychiatric, neurological, and cardiovascular effects.[9] Psychiatric and neurological disorders that may be seen in-

Address for correspondence: Semra Bülbüloğlu, İstanbul Aydın Üniversitesi Sağlık Bilimleri Fakültesi, İstanbul, Turkey
Phone: +90 532 496 81 15 **E-mail:** semrabulbuloglu@hotmail.com **ORCID:** 0000-0002-7252-9478

Submitted Date: December 31, 2020 **Accepted Date:** August 16, 2021 **Available Online Date:** March 21, 2022

What is presently known on this subject?

- Coronavirus 2019 (COVID-19) is a new entity that is potentially fatal. Full understanding of the infection and ideal treatment procedures remain unclear. Neuropsychiatric symptoms are common and prolong the recovery period.

What does this article add to the existing knowledge?

- At the time of writing, awareness of the significance of neuropsychiatric findings as a result of infection with COVID-19 was limited. The data collected can assist physicians and nurses to improve care.

What are the implications for practice?

- This systematic review is a valuable source of information in terms of neuropsychiatric findings. Greater awareness among physicians and nurses can speed effective care strategies for the management of neuropsychiatric symptoms in COVID-19 patients.

clude headache, confusion, unconsciousness, muscular coordination disorder (ataxia), acute cerebrovascular disease, and convulsive seizures,[9] which may present within 2-3 weeks after infection with the virus.[10]

The literature indicates that after the acute phase of COVID-19, the virus remains in the central nervous system (CNS) and may cause post-infectious neurological and psychiatric complications.[11] The development of such disorders is significantly associated with the degree and severity of the disease. Severe systemic inflammatory responses may induce these problems. The psychoneurological vulnerability of individuals generally increases with older age, a weak immune system, a comorbidity, or chronic disease.[12,13] In patients who recover from COVID-19, conditions such as a urinary tract infection or pneumonia, may trigger confusion, delirium, or encephalopathy.[12,13] Increased awareness of neurological and psychiatric disorders caused by COVID-19 is of great importance to assist in the management, prevention, and treatment of these conditions.

Neurological and psychiatric problems that develop in individuals diagnosed with COVID-19 may be related to treatment protocols. Patients with a severe COVID-19 infection are typically given comprehensive treatment in the intensive care unit or a COVID-19 clinic. Research examining the side effects of the virus and COVID-19 treatment is ongoing. This study was a systematic review of available early research on neurological and psychiatric problems seen in individuals who had been diagnosed with COVID-19 who were followed up and treated in a hospital.

Materials and Method

This systematic review sought to determine the neurological and psychiatric signs and symptoms seen in COVID-19 patients and examine if it could be determined if the cause was related to the disease or the treatment applied. The sequence of actions followed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines are summarized in a flowchart in Figure 1.[14]

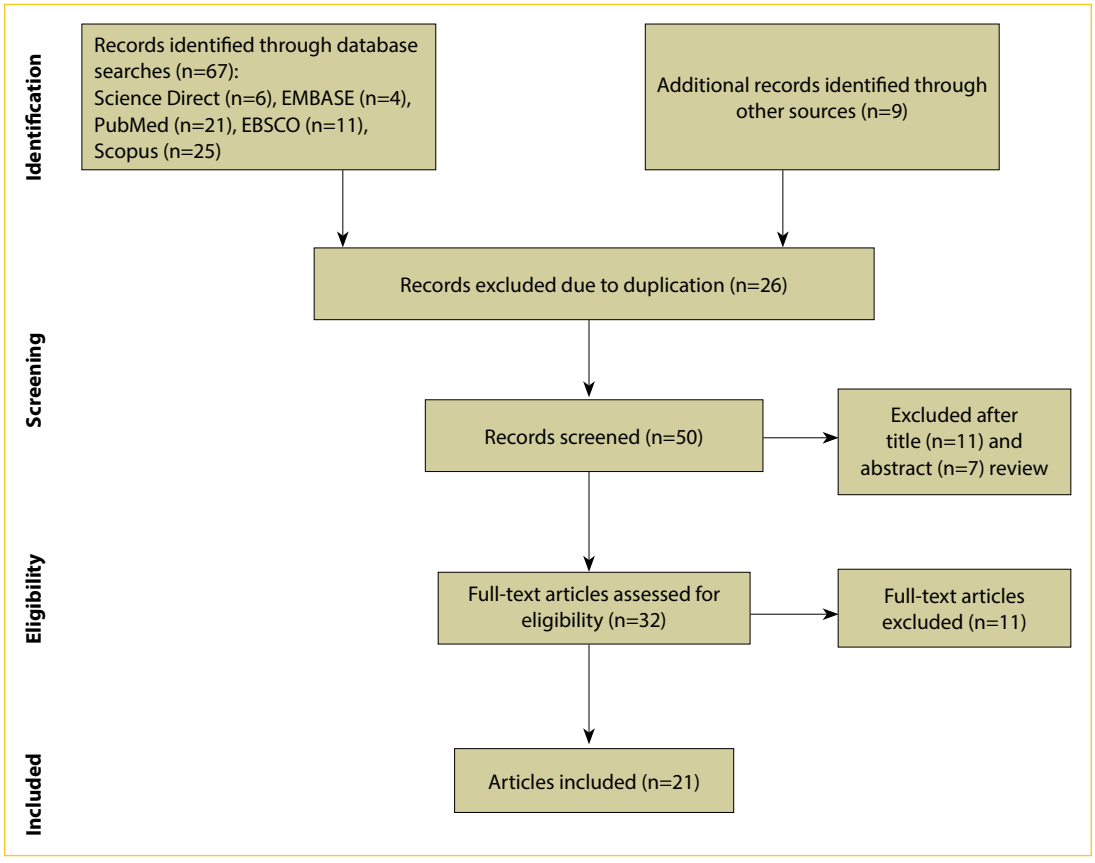


Figure 1. Flow diagram of study selection.[14]

Research Strategy

The research included a review of the Science Direct (n=6), PubMed (n=21), EMBASE (n=4), EBSCO (n=11), and Scopus (n=25) electronic databases, as well as article references and Google Scholar (n=9) using Medical Subjects Headings (MeSH) and Embase Tree (EMTREE) keywords. The search was conducted using the keywords, "COVID-19" or "coronavirus" or "SARS-CoV-2", "brain", "central nervous system" or "CNS", "neurologic", "psychiatric", "disorders", "diseases", and "dysfunction" in English and Turkish (Fig. 2). Various combinations of each term were used in a search of work published during the period of December 1, 2019 to September 1, 2020.

Inclusion Criteria

The inclusion criteria were determined according to the Population, Intervention, Comparison, and Outcome (PICO) framework. (i) The sample group consisted of COVID-19 patients with neurological/psychiatric disorders, (ii) The patients were >18 years of age, and (iii) there was a relevant article or case report published in an international refereed journal, using the following criteria:

a) The original and quantitative nature of the studies
b) Published in English or Turkish
c) Conducted December 1, 2019-September 1, 2020

Study Selection Process

In all, 32 articles were evaluated as full text and 44 studies were excluded. The final review included a total of 21 articles: [15–35] 9 descriptive studies and 12 case reports. There were 4 articles from Italy, 7 from China, 3 from England, and 3 from the United States of America (USA), and 1 each from France, Morocco, Iran, and Turkey.

Descriptive studies/case series (cross-sectional, relationship-seeking, comparative) were evaluated using the 9 Joanna Briggs Institute MAStARI Critical Assessment tools, adapted into Turkish by Nakhichevan and Secginli.[36] Both authors of this review conducted an independent methodological quality evaluation of a total of 76 articles. The highest score awarded in the assessment was 8 and the lowest score was 6. The title and abstract of the selected publications were reviewed twice, and studies not meeting the inclusion criteria were excluded. The full text of the remaining studies was examined and the exclusion process of studies not meeting the inclusion criteria was repeated. Author information and details about the method and results obtained were recorded, and the methodological quality of the studies was evaluated. In the event of any inconsistency in a decision to include an article, the final decision was made after detailed examination and discussion.

The fit analysis kappa value was calculated using IBM SPSS Statistics for Windows, Version 25.0 software (IBM Corp., Armonk, NY, USA) to determine inter-rater reliability. The kappa value was determined to be 0.78, indicating that there was a high level of agreement between the raters.

Results

Sample Characteristics and Use of Data Registration Form

The data obtained from the studies reviewed are shown in Table 1. All of the studies were published in 2020, which was early in the pandemic, and includes research and case reports from Asia, Europe, and the USA. A data registration form developed by the authors was used to record the relevant data from all of the literature included in the review. The sample studies consisted of patients who were treated in hospital for COVID-19. Six of the articles were retrospective and 3 were prospective in design. The retrospective studies used data obtained from

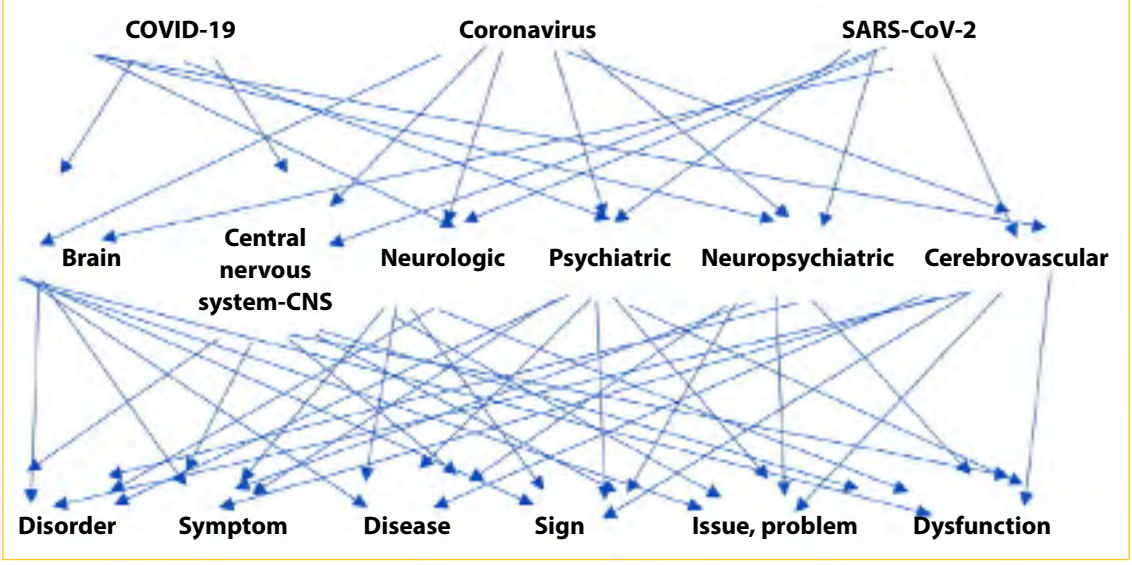


Figure 2. Word combinations used in literature search.

Table 1. Data obtained from the studies included in the systematic review

Author and publication year	Location	Sample size	Method	Neurological and psychiatric signs and symptoms
Alberti et al., 2020	Milan, Italy	n=1	Case report	Polyneuropathy (+)
Beyrouti et al., 2020	London, England	n=6	Case report; Brain MRI (+)	Ischemic stroke 33%
Cavalcanti et al., 2020	New York, NY, USA	n=3	Case report; Brain MRI (+)	Cerebral venous sinus thrombosis 100%
Chen et al., 2020	Wuhan, China	n=99	Retrospective and descriptive, n=99; Data were obtained from epidemiological, demographic, clinical, and radiological records.	Confusion 9%, headache 8%
Hanafi et al., 2019	Lille, France	n=1	Case report; Brain MRI (+)	Polyneuropathy (+), Encephalopathy (+)
Huang et al., 2020	Wuhan, China	n=41	Prospective and descriptive	Headache 8%
Karadaş, Öztürk and Sonkaya, 2020	Ankara, Turkey	n=239	Prospective and descriptive; During data collection: - Comprehensive neurological examination was performed by 2 neurologists - Brain CT/MRI/EEG were performed on patients with neurological findings - Laboratory findings, IL-6, D-dimer, and CK values were examined.	Headache 26.7%, eye movement pain 1.3%, dizziness 6.7%, tinnitus 2.1%, hearing deficit 1.3%, visual impairment 3.3%, tongue numbness 1.7, voice bifurcation 1.3%, facial numbness 3.3%, cerebrovascular disorders 3.8%, confusion 9.6%, sleep disturbance 12.6%, balance disorder 2.5%, muscle pain 15.1%, Guillain-Barré syndrome 0.4%, restless leg syndrome 1.7%
Li et al., 2020	Wuhan, China	n=221	Retrospective and descriptive	Acute ischemic attack 5%, cerebral venous sinus thrombosis 0.5%, cerebral hemorrhage 0.5%
Mao et al., 2020	Wuhan, China	n=214	Retrospective; Data were obtained from electronic records. Neurological findings were reviewed and classified by 2 neurologists.	CNS problems 25%, headache 13%, dizziness 17%, confusion 8%, acute cerebrovascular problems 3%, impaired muscle control 0.5%, convulsive seizure 0.5%
El Otmani et al., 2020	Casablanca, Morocco	n=1	Case report	Polyneuropathy/Guillain-Barre syndrome (+)
Oxley et al., 2020	New York, NY, USA	n=5	Case report	Ischemic stroke 20%
Padroni et al., 2020	Ravenna, Italy	n=1	Case report	Polyneuropathy/Guillain-Barre syndrome (+)
Paterson et al., 2020	London, England	n=43	Descriptive; Brain MRI (+)	Encephalopathy/delirium/ psychosis 23%, acute disseminated encephalomyelitis 20.9%, hemorrhage 11.6%, CNS problems 27.9, and isolated myelitis 2.32%
Sedaghat and Karimi, 2020	Sari, Iran	n=1	Case report	Polyneuropathy/Guillain-Barre syndrome (+)
Toscano et al., 2020	Sari, Iran	n=1	Case report	Polyneuropathy/Guillain-Barre syndrome (+)
Varatharaj et al., 2020	Southampton, England	n=125	Descriptive, retrospective; Data were obtained from electronic records.	CVA 62%, ischemic stroke 74%, intracerebral hemorrhage 12%, altered mental status 31%, Guillain-Barré syndrome 67%
Virani et al., 2020	Pittsburgh, PA, USA	n=1	Case report	Polyneuropathy/Guillain-Barre syndrome (+)
Vollono et al., 2020	Rome, Italy	n=1	Case report; EEG (+)	Focal status epilepticus (+)

Table 1. Data obtained from the studies included in the systematic review *(continue)*

Author and publication year	Location	Sample size	Method	Neurological and psychiatric signs and symptoms
Wang et al., 2020	Wuhan, China	n=138	Retrospective and descriptive; Data were obtained from electronic records.	Headache 7%, dizziness 9%
Yang et al., 2020	Wuhan, China	n=52	Retrospective and descriptive	Headache 6%
Zhao et al., 2020	Hubei, China	n=1	Case report	Polyneuropathy/Guillain-Barre syndrome (+)

CK: Cytokine; CNS: Central nervous system; CT: Computed tomography; CVA: Cerebrovascular accident; EEG: Electroencephalography; IL-6: Interleukin 6; MRI: Magnetic resonance imaging.

electronic patient records, and the prospective studies and case reports used data obtained from patient files, electronic records, or findings detected during examination. Neurological and psychiatric findings were based on the results of electroencephalography (EEG), magnetic resonance imaging (MRI), and computed tomography (CT) examination. Laboratory tests and direct chest radiography provided other findings.

Neurological and Psychiatric Findings Associated with COVID-19 and Treatment

Guillain-Barré syndrome, ischemic stroke, encephalopathy, and cerebral venous sinus thrombosis were among the findings observed. Also, the level of D-dimer in the blood of patients with at least 1 neurological symptom was significantly higher ($p<0.05$) compared with that of patients without neurological symptoms. The IL-6 level was significantly higher in patients with headache than those without ($p<0.05$) and the creatine kinase (CK) level was significantly higher in patients with muscle pain than those without ($p<0.05$).

The study conducted by Mao et al.,[24] which had the second highest sample size (n=214), neurological findings were found to be common: CNS problems were recorded in 25%, muscle control impairment in 0.5%, and acute cerebrovascular problems in 3%. Among the CNS manifestations, headache was seen in 13%, dizziness in 17%, confusion in 8%, and convulsive seizures in 0.5%.

Chen et al.[18] reported findings of headache in 8% and confusion in 9%. Similarly, Huang et al.[21] observed headache in 8%. Both Huang et al.[21] and Sedaghat and Karimi[28] noted an increase in plasma cytokine and chemokine (IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNF-α) levels in addition to the symptoms and findings in Table 1. In the study performed by Li et al.,[23] neurological findings included rates of 5% for acute ischemic attack, 0.5% for cerebral venous sinus thrombosis, and 0.5% for cerebral hemorrhage. Li et al. also reported high levels of D-dimer, leukocytes, neutrophils, and C- reactive protein levels, and low levels of lymphocytes.

Paterson et al.[27] found that the incidence of encephalopathy/delirium/psychosis with both neurological and psychiatric dimensions was 23%. Among other neurological findings, acute disseminated encephalomyelitis was reported to be 20.9%, hemorrhage 11.6%, CNS problems 27.9%, and isolated myelitis 2.32%.

Varatharaj et al.[30] reported neurological findings of cerebrovascular accident 62%, Guillain-Barré 67%, ischemic stroke 74%, and intracerebral hemorrhage 12%. Notably, an altered mental state was seen in 31%. Wang et al.[33] also stated that headache was seen in 7% and dizziness in 9% of COVID-19 patients.

Case reports usually addressed 1 or 2 findings. These included Guillain-Barré syndrome, ischemic stroke, encephalopathy, and cerebral venous sinus thrombosis. Oxley et al.[25] noted

Table 2. Grouping of neurological and psychiatric symptoms in terms of short- and long-term effects*

	Case report		Research article	
	During COVID-19	Post-infectious	During COVID-19	Post-infectious
Brain	2	7	6	2
Neurological	3	3	6	2
CNS	5	1	7	5
Psychiatric	0	0	6	2

*Some findings appeared during the acute phase of COVID-19 and continued to occur in the later period. CNS: Central nervous system.

that ischemic stroke was detected in 2 of 5 patients. Similarly, Beyrouti et al.[16] observed ischemic stroke in 2 of 6 patients. The case report submitted by Vollono et al.[32] reported the presence of focal status epilepticus, and the presence of polyneuropathy and encephalopathy was reported by Hanafi et al.[20] Polyneuropathy and Guillain-Barré syndrome were observed in all of the other case reports.

Table 2 illustrates the findings analyzed in 4 groups. Neurological findings were grouped as related to the brain (acute ischemic attack, ischemic stroke, cerebral venous sinus thrombosis, cerebral hemorrhage, etc.), CNS (CNS disorders, impaired muscle control, etc.), or neurology (polyneuropathy, Guillain-Barre syndrome, etc.). The final category was psychiatric symptoms, such as headache, dizziness, altered mental status, encephalopathy/delirium/psychosis, sleep disturbance, convulsive seizures, and confusion.

Discussion

This systematic review is an important source of early information, as it examined the results of 21 studies and addressed a wide range of psychiatric and neurological disorders in patients diagnosed with COVID-19. Although the findings of the studies included in this systematic review have been categorized as neurological and psychiatric, the synergy should not be forgotten. The work of Karadaş, Öztürk, and Sonkaya noting that headache and dizziness may occur as a result of cerebrovascular disorders should not be disregarded; likewise, it should be kept in mind that confusion, eye movement pain, and sleep disturbance may be interrelated.

It is highly possible that the potential lethality of COVID-19 and generalized fear due to worldwide disruption on many levels may cause anxiety or fear of death. However, the data recording forms included in the scope of this investigation do not allow us to draw specific conclusions. Specific scales should be used to assess the presence and causes of stress, anxiety, and fear of death. Findings of encephalopathy/delirium/psychosis with both neurological and psychiatric dimensions, as well as acute disseminated encephalomyelitis, hemorrhage, CNS problems, and isolated myelitis reported by Paterson et al.[27] are nonetheless noteworthy.

The studies conducted by Karadaş, Öztürk and Sonkaya[37] and Mao et al.,[24] the studies with the largest sample size, mostly record psychiatric problems, including headache, dizziness, confusion, restless leg syndrome, convulsive seizures, Guillain-Barre syndrome, and sleep disturbance. The same studies reported neurological problems, such as cerebrovascular problems, CNS disorders, and imbalance.

In a prospective study, Karadaş, Öztürk and Sonkaya[37] determined that patients with a high serum D-dimer level had more neurological disease findings than those with a low level; that is, there was a direct proportion between D-dimer level and neurological disease findings ($p<0.05$). The authors also found that patients with a high serum D-dimer level had more neurological disorder symptoms than those with a low level, suggesting a direct correlation between D-dimer level and neurological disorder symptoms ($p<0.05$).[22] In addition, it was stated that there was a greater likelihood of headache in patients with a high IL-6 level ($p<0.05$). In the same patient group, the CK level was high in patients with muscle pain ($p<0.05$). It is thought that high CK and lactate dehydrogenase levels are associated with muscle damage. This suggests that systemic inflammatory response syndrome (SIRS) may have a role in the pathogenesis of muscle damage.[38] SIRS has been observed in cases of pneumonia caused by COVID-19, and patients with severe infections can be presumed to be predisposed to multiorgan failure.[38]

A direct relationship cannot yet be established between the emergence of neurological and psychiatric symptoms and the clinical condition of COVID-19 patients. Neurological and psychiatric findings may be associated with the toxicity caused by the drug therapy administered. Also, the emergence of multiple organ failure in patients with muscle damage may indicate that the inflammatory response may be a predisposing factor to skeletal muscle damage. In addition to an increase in CK and D-dimer levels, the neutrophil count, C-reactive protein level, coagulation activation, and inflammatory response measures are high and the lymphocyte count is low in COVID-19 patients.[24,39] In this context, although there may be a link between high coagulation activation and ischemic stroke and cerebrovascular disease, no similar studies were found in a review of the literature. Autopsy results of some COVID-19 patients have, however, confirmed that the virus appears to trigger neurological damage.[40,41]

The results of this systematic review indicated that the increase in cytokines, TNF-α, and IL-6 values may be associated with the function of cytokines as pain mediators.[42] The increase in IL-6 level might explain the headaches seen in COVID-19 patients, just as in migraine patients.[37] IL-6 enables the activation of proinflammatory cytokines released from T cells and macrophages. This causes inflammation, in situations such as infection and trauma. In addition, cytokines initiate fever, acute phase response, and PGE2 synthesis.[43] All of these processes explain the increase in cytokines and chemokines observed.

Guillain-Barré syndrome may develop as a result of neurological disorders that progress in parallel with infection. The syndrome is caused by an abnormal autoimmune response to various viral or bacterial infections that leads to a cross-reactivity between the ganglioside components of the peripheral nerves and can lead to nerve damage.[29] Guillain-Barré syndrome can cause acute paralytic attacks.

Polyneuropathy (chronic inflammatory demyelinating polyneuropathy, CIDP) is a multifocal demyelinating syndrome or disease. It is very similar to Guillain-Barré syndrome, so there is a possibility of misdiagnosis. However, the response to immunosuppressive therapy suggests that it is an autoimmune disease. Guillain-Barre syndrome demonstrates symptoms within the first 4 weeks after the onset of the disease,

while in cases of polyneuropathy, symptoms may not appear for 8 weeks or longer.[44]

Convulsive seizures have been reported in COVID-19 patients.[24] Disruption of the blood-brain barrier following viral encephalitis or excessive proinflammatory cytokine release is thought to be the cause of cortical irritation that initiates the seizures associated with COVID-19 infection.[12,45,46]

The studies included in this systematic review were based solely on data record forms; no scales were used to measure neurological and psychiatric problems, as is ordinary practice. Given the pandemic conditions, this is understandable; however, it also suggests that some problems may not have been thoroughly evaluated. Nonetheless, this systematic review is an important source of information as a comprehensive study of the early records of neurological and psychiatric problems in COVID-19 patients.

Clinicians should be aware of possible psychiatric and neurological problems in COVID-19 patients, and these disorders should be diagnosed and treated at an early stage. Additional research of this subject is recommended, including experimental research based on the data we have in this systematic review.

Conclusion

The results obtained confirmed that COVID-19-associated psychiatric and neurological disorders are frequently observed and should not be ignored. The long-term effects of the virus and side effects that may develop due to drug administration to treat COVID-19 are not yet fully known. The pandemic has limited the ability to conduct research and confirm available evidence using advanced diagnostic methods due to financial limitations and restrictions on movement that reduce the workforce and capabilities. Therefore, additional studies are required. It is likely that not all COVID-19 patients undergo a psychiatric and neurological examination. This is an indication that some problems may go unnoticed. Clinicians should be aware of possible psychiatric and neurological disorders, and these problems should be diagnosed and treated at an early stage, and additional research is needed to determine a fuller understanding.

Conflict of interest: There are no relevant conflicts of interest to disclose.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – N.G.; Design – N.G., S.B.; Supervision – N.G.; Fundings - N.G., S.B.; Materials – N.G., S.B.; Data collection &/or processing – N.G., S.B.; Analysis and/or interpretation – N.G., S.B.; Literature search – N.G., S.B.; Writing – N.G., S.B.; Critical review – N.G., S.B.

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