Complications related to COVID-19 infection in neurological diseases

Nörolojik hastalıklarda COVID-19 enfeksiyonuna bağlı komplikasyonlar

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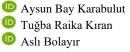**E-mail:** raika.kiran@ozal.edu.tr
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SUMMARY

Neurological signs and symptoms constitute at least 35% of the findings reported from the beginning of the coronavirus-19 (COVID-19) epidemic until now. Neurological symptoms based on myopathy,headache,taste and smell disorders,dizziness, impaired consciousness, encephalitis, and peripheral nervous system disorders such as Guillain-Barré and Miller Fisher syndromes, have been described. We aimed to provide information on how COVID-19 infection affects neurological system and possible damage mechanisms.This review has been prepared by scanning severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19, coronavirus, neurological symptoms, results, pandemic keyword combinations in the database. In the literature review, a total of 57 articles, including case series, case report, letter, article and review, were reached on the neurological disorders associated with COVID-19 in the last two years.If the patient is older, the COVID-19 infection may be more severe. Hypertension, obesity, diabetes, and cardiovascular diseases also make more challenging the clinical cases. In addition, patients with a history of neurological disorders and acute respiratory symptoms appear to be at higher risk of encephalopathy.

Keywords: COVID-19, Guillain-Barré syndrome, Encephalitis, Stroke, Neurological complications

ÖZET

Nörolojik belirti ve semptomlar, koronavirüs-19 (COVID-19) salgınının başlangıcından bugüne kadar bildirilen bulguların en az %35'ini oluşturmaktadır. Miyopati, baş ağrısı, tat ve koku bozuklukları, baş dönmesi, bilinç bozukluğu, ensefalit ve Guillain-Barré ve Miller Fisher sendromları gibi periferik sinir sistemi bozukluklarına dayalı nörolojik semptomlar tanımlanmıştır. Bu derleme ile COVID-19 enfeksiyonunun nörolojik sistemi nasıl etkilediği ve olası hasar mekanizmaları hakkında bilgi vermeyi amaçladık. Bu derleme, veri tabanlarında "şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2), COVID-19, koronavirüs, nörolojik semptomlar" anahtar kelimelerinin kombinasyonlarının sonuçları ile elde edilen yayınlardan hazırlanmıştır. Literatür taramasında son iki yılda COVID-19 ile ilişkili nörolojik bozukluklara ilişkin vaka serisi, vaka sunumu, mektup, makale ve derleme olmak üzere toplam 57 makaleye ulaşılmıştır. Hasta daha yaşlıysa, COVID-19 enfeksiyonu daha şiddetli olabilir. Hipertansiyon, obezite, diyabet ve kardiyovasküler hastalıklar da klinik vakaları daha da zorlaştırmaktadır. Ek olarak, nörolojik bozukluk ve akut solunum semptomları öyküsü olan hastalarda ensefalopati riski daha yüksek görülmektedir.

Anahtar sözcükler: COVID-19, Guillain-Barré sendromu, ensefalit, inme, nörolojik komplikasyonlar.

INTRODUCTION

Infection of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), later renamed coronavirus disease 2019 (COVID-19) infection, first appeared in China's Wuhan Province in late December 2019 and it has extended widely whole to the world.The COVID-19 pandemic is unfortunately still ongoing. Main symptoms of COVID-19 infection are mostly alike with other respiratory illness. Fever, cough, and shortness of breath are mostly reported symptoms of COVID-19 infection. The disease is more severe, especially in individuals who have chronic bronchitis, emphysema, heart failure or diabetes as secondary medical disorders [1]. However, COVID-19 has also been shown to affect other organs, including the brain. Recently, there have been scientific reports that individuals with COVID-19 infection are seen with respiratory tract disease symptoms as well as neurological involvements such as acute cerebrovascular diseases, unconsciousness and skeletal muscle symptoms, paralysis, headache, and paraesthesia [2-4].The increased information shows us that patients with more severe systemic symptoms were more likely to have neurologic symptoms, such as acute cerebrovascular diseases, impaired consciousness and skeletal muscle injury, in comparison with those with milder forms of the infection [5].

Coronaviruses are one of the enveloped RNA viruses and they have positive polarity. Coronaviruses can infect different host species. Based on their genomic structures, coronaviruses are clustered into four sub-types: alpha, beta, delta and gamma. Mammals can only be infected with alpha and beta coronavirus [6]. The olfactory nerve is the main enterence area to the nervous system for coronaviruses. It can be cause numerous systemic disorders such as hypoxia, immune damage, hypercoagulability and electrolyte imbalance. Cerebrospinal fluid may also been infected by the virus and findings such as anosmia, dysgeusia, agitation, confusion, epilepsy, cognitive impairment and encephalitis have been seen COVID-19 positive patients.In addition, partial neuronal degeneration has been reported in patients who died due to COVID-19 infection [7,8].

Although the precise mechanism of COVID-19 penetration into the central nervous system (CNS) has not yet been founded, its most likely explanations seem to offer two possibilities: 1) hematogenous spread of COVID-19 from the systemic circulation to the cerebral circulation, where slower flow helps the virus to damage the capillary endothelium and gain access to the brain(neuronal dissemination model of coronavirus invasion) (9) and 2) spread via the cribriform plate and olfactory bulb [10]. In neuronal dissemination model of coronavirus invasion, which is supported by porcine studies, the virus infects a peripheral neuron and relies on the machinery of active transport, synaptic terminals and retrograde transport to the neuronal cell body in remote areas of the brain [9]. Previous experimental models have demonstrated that other coronaviruses can compromise the nervous system and respiratory system by directly targeting neurons located in cardiorespiratory centers [9-11]. However, preliminary observation of patients seen in the COVID-19 pandemic proposes that the COVID-19 virus may have a higher affinity for its CNS target than other coronoviruses.

With this study, we aimed to investigate the literature to ensure a survey of the neurological complications of COVID-19 and the mechanisms of nervous system damage.

MATERIAL AND METHODS

Search strategy and study selection

We actualized searches with PUBMED, MEDLINE and EMBASE databases based on keyword combinations for SARS-CoV-2, COVID-19, coronavirus, neurological symptoms, results, pandemic. The references of the accessed articles were also scanned. All the publication types (reviews, cohort studies, case-control, case reports and series) were included in the searches. Matching publications were removed from the reference list. The last literature review was conducted on September 22, 2021. Detailed features of the scanned studies on the subject are shown in Table 1.

Table 1: Scanned reports of neurological manifestations associated with COVID-19.

Design	Population	Mean Age	Country	Neurological manifestations	References
CS	214	52.7	China	Total:78(36.4%) CNS 53 (24.8) PNS 19 (8.9) Muscle injury 23 (10.7)	Mao et al. (3)
CR	1	74	USA	Encephalopathy	Filatov et al. (4)
CR	58	63	France	Total:49 (84%) Confusion: 26 (65%) Agitation: 40 (69%) Dysexecutive syndrome: 14 (36%) Abnormal corticospinal tract signs: 39 (67%) Cerebral Ischemic stroke: 3 (23%)	Helms et al. (54)
CR	1	24	Japan	Meningitis/Encephalitis	Moriguchi et al. (55)
CR	1	64	Iran	Meningoencephalitis	Mardani et al. (56)
CS	8	MD	Brasil	Meningoencephalitis (12,5%) Encephalitis (12,5%) Facial palsy (25%) Delirium (25%) Intracranial hypertension (12,5%) Headache (12,5%)	Melo Espíndola et al. (57)
CS	5	MD	USA	Ischemic stroke due to large vessel occlusion	Oxley et al. (39)
CR	1	58	NA	Acute haemorrhagic necrotizing encephalopathy	Poyiadji et al. (28)
CS	5	MD	Italy	GBS (0.4-0.5)	Toscano et al. (14)
CS	6	MD	Turkey	Total: 6 Autoimmune Meningoencephalitis: 3	Dogan et al. (29)
CS	1	MD	China	Encephalitis	Yea et al. (30)
CR	1	65	Iran	GBS	Sedaghat et al. (13)
LTR	1	70	Italy	GBS	Padroni et al. (15)
CR	1	71	Italy	GBS	Alberti et al. (16)
ARTC	4	81	USA	Acute stroke	Avula et al. (40)
LTR	1	64	France	GBS	Camdessanche et al. (17)
CR	1	49	Italy	Cryptogenic stroke	Frisullo et al. (41)
CR	1	54	USA	GBS	Virani et al. (58)
CR	2	MD	China	GBS	Zhao et al. (18)
LTR	1	66	Italy	GBS	Bracaglia et al. (19)
LTR	1	53	Turkey	GBS	Oguz-Akarsu et al. (20)
ARTC	43	MD	UK	Encephalopathies CNS Sendroms Stroke Plexopathy GBS	Paterson et al. (49)
CS	276	MD	USA	GBS	Chan et al. (21)
CS	2	56,5	France	GBS	Bigaut et al. (22)
CS	1	57	UK	GBS	Webb et al. (23)
CR	153	71	UK	Encephalopathy Encephalitis Altered mental status	Varatharaj et al. (31)
CS	1	40	UK	Rhombencephalitis	Wong et al. (32)
CR	1	6-week old	USA	Neurologic manifestations	Dugue et al. (33)
CR	1	54	Italy	Acute disseminated encephalomyelitis	Zanin et al. (35)
LTR	1	30	Spain	GBS variants, Acute vestibular Syndrome, horizontal nystagmus, oscillopsia	Pellitero et al. (51)

CS: Case series, CR: Case report, LTR: Letter, ARTC: Article, MD: Missing Data, GBS: Guillain Barre Syndrome

RESULTS and DISCUSSION

Neurological Manifestations of COVID-19 Infection

Neurological symptoms associated with COVID-19 disease include dizziness, headache, taste disturbance, neuromuscular symptoms, altered mental status, stroke, Guillain-Barré syndrome (GBS), myoclonic tremor, seizure, Horner's syndrome, acute hemorrhagic necrotizing encephalopathy, meningoencephalitis and cerebral vein thrombosis[12-15].

Specific neurological disorders associated with COVID-19

A total of 417 patients with moderate COVID-19 disease, 263 of whom were women, showed overall symptoms of cough, myalgia and loss of appetite. 85.6% of the patients reported complaints about olfaction and 88% of them for taste disorders. According to the results of the study, women were significantly more affected by olfactory and taste disorders than men [16]. In their cohort study, Mao et al. reported that 88 of 214 patients they examined in three COVID-19 hospitals in China were severe. They reported that 78 (36.4%) of the 214 hospitalized patients had neurological symptoms such as impaired consciousness, acute cerebrovascular disease, and skeletal muscle injury, and 6 of these patients had a stroke [3].

Guillain–Barré (GBS) and Miller Fisher syndromes:

Sedaghat et al. demonstrated that a 65 years old male patient diagnosed with COVID-19 disease was an AMSAN (acute motor and sensory axonal neuropathy) variant of the immune-mediated disorder GBS according to the electrodiagnostic test result [17]. The effect of decreased vital capacity due to neuromuscular failure could not be determined in 5 patients with the first signs of GBS 5-10 days after the onset of COVID-19 disease symptoms [18]. Neurophysiological findings of a patient with COVID-19 infection who was intubated as a result of worsening muscle weakness after 24 days of isolation indicated GBS [19]. A 71 years old male patient was diagnosed with the presence of a severe form of acute poly-radiculoneuritis with prominent demyelinating features and COVID-19-associated GBS in line with the findings obtained [20]. Camdessanche et al. reported a COVID-19 positive patient was again diagnosed with GBS due to findings. It was also emphasized that GBS can lead to requirement of intensive care unit (ICU) and that possible ICU-induced weakness should be distinguished after ICU treatment [21]. GBS was associated with the COVID-19 disease in line with the findings of a 61 years old female patient and her relative [22]. Asymptomatic patient's diagnosis of GBS was made with motor and antidromic sensory nerve conduction studies. There was an increase in creatine phosphokinase-2, C-reactive protein, interleukin 6, total protein levels, lymphocytopenia; moderate increase in aspartate transaminase, alanine transaminase and lactate dehydrogenase (LDH) and of patient's blood parameters. She had negative anti-ganglioside antibodies in cerebrospinal fluid (CSF) and serum but her COVID-19 PCR test was positive. They performed motor and antidromic sensory nerve conduction studies consistent with demyelinating polyneuropathy [23]. An asymptomatic, 53 years old female patient with a positive diagnosis of COVID-19 and negative CSF test for COVID-19 disease was treated with the diagnosis of GBS [24].

Two patients applied with GBS after COVID-19 disease at his hospital in New York, which is at the epicenter of the COVID-19 pandemic. Examination of a SARS-CoV 2 positive 68 years old male patient, 4+/5 weakness in the hip flexors, absence of vibration and proprioceptive sensation in the toes, +2 arm reflexes, no reflex in the legs were found. Lumbar puncture was performed when the patient developed bilateral facial weakness, neck flexion weakness, dysarthria, dysphagia and inability to move three days after hospitalization. CSF results were compatible with GBS. In another case reported from the same hospital, the CSF results of a patient with positive SARS-CoV 2 test were compatible with GBS [25]. A male patient presented with cough, asthenia, myalgia in the legs, and acute anosmia. It was reported that the complaints of the patient with positive SARS-CoV-2 test and ground glass opaques on chest computed tomography (CT)resolved spontaneously after 21 days. The same patient was admitted to the hospital with rapidly progressive paresthesia, hypoesthesia, and distal weakness in the lower extremities. He was hospitalized because of the development of right peripheral facial paralysis, with symptoms radiating to the mid-thigh and fingertips associated with ataxia.Findings of a 70 years old obese female patient who applied to the hospital with similar complaints are consistent with GBS. CSF SARS-CoV 2 test results were negative in both patients [26]. Sensory nerve conduction tests were performed on a male patient with positive SARS-CoV-2 (COVID-19) nasopharyngeal swab test. It has been reported that patient results meet the electrodiagnostic criteria for acute inflammatory demyelinating polyneuropathy/GBS [27].

Acute motor axonal neuropathy (AMAN) and acute necrotizing myelitis (ANM) a variant of GBS were reported in a 61 years old female patient with positive nasopharyngeal RT-PCR COVID 19 test and negative COVID-19 CSF test. Cervical magnetic resonance imaging (MRI) was consistent with transverse myelitis and EMG was consistent with the diagnosis of AMAN. Plasma exchange was applied to the patient after high-

dose steroid treatment and clinical improvement was noted [28]. Antiganglioside antibody GD1b-IgG in the serum of a 50 years old patient who applied with the complaints of fever, headache, cough, weakness, low back pain for 5 days, and lymphopenia in the blood test results; high CRP and positive oropharyngeal swab RT-PCR COVID-19 test was detected. The COVID-19 disease test of a 39 years old male patient with three-day complaints of diarrhea, fever, ageusia, bilateral abducens palsy, areflexia and albuminocytological dissociation was positive. These two patients infected with COVID-19 were diagnosed with acute Miller Fisher syndrome (MFS) [29]. Li et al., reported that the most common symptoms of 7 COVID-19 related MFS cases were ataxia, perioral paresthesia, ophthalmoplegia, blurred vision and generalized areflexia [30]. It has been reported that orthostatic hypoperfusion syndrome, orthostatic intolerance and painful small fiber neuropathy, chronic fatigue, orthostatic dizziness and brain fog developed in a patient who had Covid-19 infection [31].

Encephalitis, Encephalopathy, Variable Mental Status and Demyelination:

A 58 years old female patient was admitted to the hospital with complaints of 3 day fever, cough and altered mental status. The patient's brain MRI showed hemorrhagic rim-enhancing lesions. A case of acute hemorrhagic necrotizing encephalopathy was detected in a female patient diagnosed with COVID-19 infection [32]. Dogan et al. obtained findings consistent with meningoencephalitis in terms of white matter hyperintensity, increased contrast, and sulcal hemorrhagic features in 3 patients (33). The patient who was positive for COVID-19 disease diagnosed with encephalitis associated with COVID-19 disease by a neurologists. 220 mmHg CSF pressure and negative bacterial or tuberculosis infection finding in the CNS were detected [34].

Varatharaj et al., reported that of 153 positive SARS-CoV 2 test results, seven (44%) had encephalitis, 16 (41%) had encephalopathy, and 39 (31%) had variable mental status. In addition, it has been reported that altered mental status is present at all ages, and this rate is high in young people [35]. A 40 years old male patient who was positive for COVID-19 disease and showed signs of brain stem and upper cervical cord inflammation according to MRI results was diagnosed with rhombencephalitis. The patient's abnormal neurological findings could not be explained in any other way [36]. Bilateral leg stiffness, decreased response for up to ten seconds, and a continuous upward gaze episode were detected in a 6 weeks old baby boy with a positive nasal COVID-19 test. In addition to the confirmed rhinovirus, the presence of COVID-19 and accompanying neurological symptoms were reported

in the patient [37]. The presence of 80 to 110 nm viral particles in the frontal lobe brain sections was detected in the transmission electron microscopy results of the sections obtained in the postmortem examination of a 74 years old patient with a COVID-19 disease positive nasopharyngeal swab test result [38]. Demyelinating lesions were detected in MRI results of a COVID-19 positive patient. The patient's CSF was normal, white matter lesions and multiple lesions with high signals from bulbomedullary junctions were detected in the brain and spine MRI [39]. RT-PCR test is positive in a 40 years old female patient with a history of headache and myalgia, as well as left-sided facial weakness, fever, dysphagia, dysarthria and dyspnea. Mild leukocytosis accompanied by lymphopenia and irregular consolidation in the right lower lung were detected. MRI results showed large areas of high signal in the basal ganglia, anterior temporal lobes, bilateral frontoparietal white matter, outer capsules and thalamus; diffusion-weighted imaging changes and corresponding visible diffusion coefficient changes were detected in some foci. Patient findings were described as acute disseminated encephalomyelitis associated with COVID-19 [40]. A 72 years old male patient diagnosed with encephalomyelitis had a clinical picture of weakness, dizziness, difficulty in breathing, hypoglycemia, and altered mental status. In addition to these, RT-PCR was positive, chronic microvascular ischemic changes in head CT, left temporal seizures and epileptogenic left temporal sharp waves were detected in 24-hour electroencephalogram (EEG) [41]. A male patient with COVID-19 infection, was diagnosed with postinfectious acute myelitis [42].

A 60 years old male patient with a history of fever and cough, felt pain and weakness in his lower extremities on the 9th day of hospitalization and was diagnosed with rhabdomyolysis based on laboratory test results [43]. Tutar et al. reported 3 cases in the presence of inflammatory/demyelinating lesions, which they thought to be associated with COVID 19. In the neurological examination of a male patient who applied to the clinic with left hemiparesis (4/5) and hemihypoesthesia complaints and globally extremity hyperreflexia were observed. The patient's blood tests showed normal sedimentation but a slight elevation in ferritin level. The patient reported positive for COVID-19 with multiple areas of ground glass opacity on chest CT scan. The patient's brain MRI showed hyperintense nodular lesions with diffusion restriction and contrast in both centrum semiovales adjacent to the lateral ventricles. An 18-year-old female patient had visual acuity at finger movements 40 cm away and signs of pyramidal pathway dysfunction with global limb hyperreflexia. Nasopharyngeal exudate and immunological SARS-CoV-2 PCR analysis were found to be negative for IgG and positive for IgM, and

possible active infection was considered suspicious. The patient's orbital MRI revealed a left optic nerve lesion on T2-weighted images, multiple T2-FLAIR hyperintense lesions in the supratentorial, posterior fossa and corpus callosum on brain MRI, and an uncontrasted T2-hyperintense tense lesion at the C4 level in cervical spine MRI. Chest CT scan of a 48-year-old male patient who applied with complaints of joint pain, weakness and cough was compatible with viral pneumonia and SARS-CoV-2 RT-PCR test was positive. After 10 day, he diagnosed with right hemiparesia. Brain MRI of the patient showed T2-FLAIR hyperintense lesions with contrast fixation and diffusion restriction in the corpus callosum and the right cerebellum adjacent to the fourth ventricle. Tutar et al, demonstrated by radiologic studies that demyelinization occurs in various regions of the central nervous system in COVID-19 patients. It is thought that the spectrum of neurological involvement expands with SARS-CoV-2 infection [44].

Acute Cerebrovascular Complications:

Large blood vessels occlusion is the major cause of ischemic stroke which evaluated in patients younger than 50 years old (n=5) with confirmed but non-critical COVID-19 [45]. Avula et al. reported the effects of the treatment applied to four patients with a history of hypertension, who were positive for COVID-19 disease, diagnosed with ischemic stroke with radiographic findings and clinical course [46]. A case of ischemic stroke was described in a 49 years old COVID-19 positive female patient who had no cerebrovascular risk factors and no family history of neurological disease [47]. Beyrouti et al. reported that in addition to demographic, clinical, radiological and laboratory findings of 6 patients aged 53 years and older, all patients had large vessel occlusion, and recurrent strokes occurred in two patients despite therapeutic anticoagulation. They reported that ischemic stroke can be seen in five out of six COVID-19 patients in between 8 to 24 days [48]. Acute ischemic stroke in 4.6% of 219 COVID-19 patients and intracerebral hemorrhage in 0.5% were reported at Union Hospital in Wuhan. It has been reported that 6 of 10 patients with ischemic stroke received antiplatelet therapy, 3 of the patients died, the other 4 patients received anticoagulant therapy and 2 of these patients died [49]. Out of 22 COVID-19 positive clinical cases, 17 cases of acute ischemic stroke, 3 cases of aneurysm rupture and 2 cases of sinus thrombosis were reported [50].

Morassi et al. identified 6 patients with a mean age of 69, COVID-19 positive, with liver enzyme changes and elevated LDH. They reported that four of the patients were diagnosed with ischemic stroke, two with hemorrhagic stroke, and five patients died and the remaining one was severely affected neurologically (modified Rankin score(mRS):4) [51]. A 31 years old male patient, diagnosed with a ruptured Hunt, 3rd Hess degree subarachnoid hemorrhage, who developed severe headache and unconsciousness, tested positive for COVID-19. The PCR test was also positive in a patient who had an ischemic stroke with massive hemorrhagic conversion requiring decompressive hemicraniectomy [52].

Cranial Multineuritis and Horner's Syndrome:

A 65 years old female patient with hypothyroidism, rheumatoid arthritis and Factor V Leiden deficiency was consulted to the emergency room (ER) service with shortness of breath, atony and fever. The patient's nasal and pharyngeal samples were positive for the RT-PCR COVID-19 test. Chest CT revealed ground-glass infiltrates consistent with pneumonia. On the day after his hospitalization, ptosis and miosis were detected on his right side without anhidrosis and the patient was diagnosed with Horner's Syndrome (HS) [53]. A male patient, who was consulted to the clinic with ptosis, weakness, fever and mild headache, was characterized by HS as a result of neurological examination [54]. Another study summarized the neurological disorders of 43 patients aged 18 to 85 years. Among these, para-infectious or septic encephalopathy with delirium was found in 10 patients, mostly over 50 years of age. Inflammatory CNS syndromes were detected in 12 patients, stroke in 8 patients, GBS in 7 patients, plexopathy in a 60 years old male patient, and the findings of 5 patients could not be characterized [55].

Gennaro et al. detected hyperactive delirium, asymmetrical distribution cranial multineuritis in a 42 years old male patient who was hospitalized in the intensive care unit with COVID-19 pneumonia. Another case, in 67 years old male, they reported cranial neuritis accompanying dyslaxia and dysphagia [56]. The PCR COVID-19 test of a 30 years old female patient, who was consulted for a sense of instability and loss of balance, was positive. It has been reported that the patient showed anosmia and vestibular symptoms, respectively, in line with the clinical course observed in the patient, suggesting that the virus may have directly accessed the nervous system [57].

CONCLUSION

The COVID-19 epidemic, which broke out in Wuhan in December 2019, has become a crisis in the whole world, both in the economy and in the health sector. Although respiratory complaints are among the most prominent symptoms in patients, different neurological complications reported during and after COVID-19 are increasing day by day. It is known that COVID-19 infection can be more severe if the patient is aged. Hypertension, obesity, diabetes, and cardiovascular

diseases also make more challenging the clinical cases. In addition, patients with a history of neurological disorders and acute respiratory symptoms appear to be at higher risk of encephalopathy. It should not be forgotten that a diet rich in fat and refined carbohydrates and a low-fiber diet impair immunity and lead to impaired defense against inflammation and viruses.

In the pathology of the deadly COVID-19 epidemic, oxidative stress and inflammatory cytokine storm are among the main features. Co-administration of immunomodulatory agents with current treatment approaches may attenuate the pathology leading to immune-mediated neurological disorders associated with COVID-19. In the light of the literature reviewed in this study, understanding the neurological complications in individuals with severe COVID-19 infection will contribute to diagnosis and management of the disease.

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