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The association between autoimmune encephalitis mediated by *N*-methyl-D-aspartate receptor autoantibodies and COVID-19: a systematic review

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Neurological complications related to coronavirus disease 2019 (COVID-19) infection have been increasingly reported. One of the most serious neurological complications is encephalitis, which could be due either to direct viral invasion or an immune-mediated inflammatory reaction. In this study, we conducted a systematic review of reported cases of autoimmune encephalitis mediated by *N*-methyl-D-aspartate receptor antibodies in conjunction with or after diagnosis of COVID-19 infection.

Keywords: Autoimmune encephalitis, *N*-methyl-D-aspartate receptor, COVID-19

Introduction

The coronaviruses are one of the RNA virus families characterized by positive charge, envelopment, and a single strand [1]. The novel coronavirus disease 2019 (COVID-19) was reported for the first time in Wuhan, China, in December 2019 [2]. Shortly after that, reports emerged on the effect of COVID-19 on all body systems, including but not limited to the nervous system. Several case reports and systematic reviews have described neurological manifestations of COVID-19, including Guillain-Barré syndrome and seizures. However, one of the rarely reported observations of COVID-19 infection is its association with the onset of autoimmune encephalitis [3]. We conducted this review to outline the association between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and *N*-methyl-D-aspartate r eceptor (NMDA-R) antibody encephalitis.

Methods

Search strategy

We searched the Cochrane Library 2023, MEDLINE (December 2019 to August 2023), EMBASE (December 2019 to August 2023), PubMed (December 2019 to August 2023), Scopus, and Web of Science databases according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [4]. There were no restrictions of language or date during our electronic search for case reports or case series.

The following search strategy was utilized with the following keywords and their synonyms (in all fields): ([SARS-CoV-2] OR COVID OR COVID-19 OR coronavirus) AND (Encephalitis OR [limbic encephalitis]) AND ([Anti-N-Methyl-D-Aspartate Receptor Encephalitis] OR [NMDA] OR [Autoimmune limbic encephalitis] OR [anti-NMDA receptor autoantibody] OR [Receptors, N-Methyl-D-Aspartate]).

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Case series and case reports of COVID-19 with evident autoimmune encephalitis mediated by NMDA-R autoantibodies were confirmed by cerebrospinal fluid (CSF) analysis. After exclusion of duplicates, all articles were evaluated through title and abstract screening by three independent reviewers, followed by a detailed and accurate reading of all full-text articles.

Inclusion criteria

The inclusion criteria for the articles were as follows: (1) Described patients with neurological signs or symptoms concerning autoimmune encephalitis attributed to COVID-19; (2) COVID-19 infection proven via SARS-CoV-2 polymerase chain reaction testing with nasopharyngeal or oropharyngeal swab; (3) Published in a peer-reviewed journal.

Cases of autoimmune encephalitis that occurred after COVID-19 vaccination were excluded. Only cases that occurred with a direct relationship to COVID-19 infection were included.

Study selection and data extraction

All reviewers performed data extraction for patient demographics, COVID-19 testing from a nasal swab and CSF, respiratory or other body system involvement in COVID-19 infection, the time between COVID-19 infection and the onset of autoimmune encephalitis symptoms, CSF analysis, treatment used, and outcome. Symptoms included an altered mental status, seizures (generalized or focal), sleep disturbances, abnormal movements (including dystonia or chorea), cognitive dysfunction, mood symptoms, and psychosis. We defined the outcome using one of the following terms: good, recovering, and poor. A good outcome was defined as discharged home and/or use of the following descriptive terms in the study: "no morbidity" or "good recovery." If the patient was discharged to a rehabilitation facility, then the outcome was defined as "recovering" and/or if any of the following terms were used: "started to improve" or "recovering." A poor outcome was defined as continued worsening of the condition despite adequate treatment and period of observation. If the onset of autoimmune encephalitis symptoms and signs started within 5 days of the onset of COVID-19 respiratory or systemic symptoms, they were labeled as simultaneous onset.

Normal white blood cell (WBC) count results in CSF values were stratified by age. For adult patients, the normal WBC value is <5 cells/mm^3. For people from the age of 5 years to puberty, the normal value is 0–10/mm^3, while people from the age of 1– 4 years have a normal value of 0–20/mm^3. Finally, for patients younger than 1 year, the normal value is 0–30/mm^3 [5]. A normal protein count in the CSF was defined as equal to or less than 45 mg/dL.

Results

Our search strategy identified 19 peer-reviewed case reports of confirmed COVID-19 infection and autoimmune encephalitis mediated by NMDA-R autoantibodies. The total number of patients involved was 19 (Figure 1).

The number of adult patients (age, >17 years) included was 13, and the mean age was 35.8 years (range, 18–65 years). The number of pediatric patients was six, and the mean age was 5.6 years (range, 1–11 years). There was equal inclusion of both sexes, with 53% of patients being female (n = 10) (Table 1 [6-24]).

CSF testing for COVID-19 was performed in three patients only, one of whom was positive. In addition, 58% of patients (n = 11) had respiratory infection manifestations (including upper or lower respiratory tract involvement). In patients with no respiratory infection manifestations prior to the onset of neurological manifestations, COVID-19 infection was discovered incidentally by nasal or oropharyngeal swab test (Figure 2).

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of study selection for this review

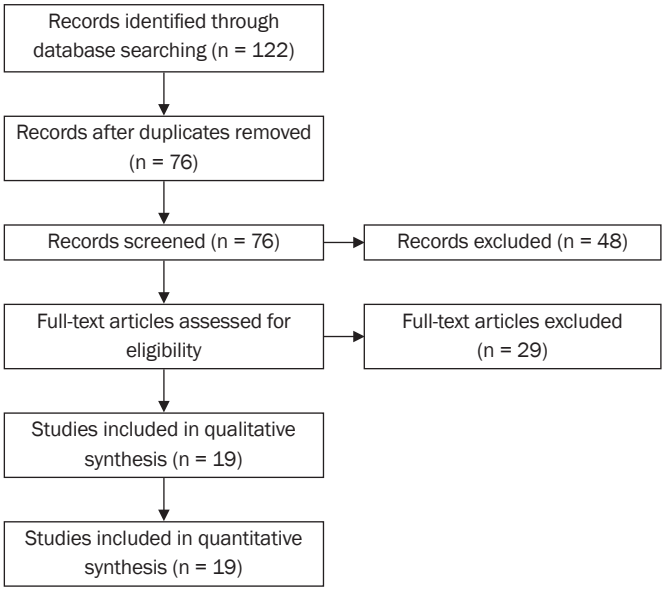


Table 1 Patients' demographics and chronological summary of hospital course

Study	Year	Age (yr)	Sex	MRI brain findings	COVID-19 systemic symptomsa)	Fever at the time of presentation of neurological symptoms	Time from COVID-19's first systematic symptoms to the onset of the neurological manifestations	CSF WBC count (/mm^3)	CSF glucose (mg/dL)	CSF protein (mg/dL)	Main clinical features	Treatment	Outcome
Adauto Luizaga et al. [6]	2022	2	M	Normal	None	Absent	NA				Choreoathetotic movements in all extremities	IVMP	Good
											Language deficits	IVIG	
											Cognitive dysfunction		
Allahyari et al. [7]	2021	18	F	Diffuse subcortical edema	Respiratory	Present	Simultaneous	27	55	241	Altered mental status	IVIG	Good
											Depression		
Álvarez Bravo [8]	2020	30	F	Hippocampal Unilateral	Respiratory	Present	Simultaneous	44		54	Altered mental status	IVMP	Poor
											Focal and generalized seizures	IVIG	
											Psychosis: psychomotor agitation, paranoid ideation, and visual hallucinations	Rituximab	
Ariza-Varón et al. [9]	2022	48	F	Hippocampal Bilateral	Respiratory	Present	Simultaneous	Normal		Normal	Altered mental status	IVMP	Good
Burr et al. [10]	2021	2	F	Normal	None	Present	NA	7	56	25	Altered mental status	IVMP	Good
											Seizures		
Derakhshani et al. [11]	2023	11	F	Normal	None	Present	NA	0	51	9	Altered mental status	IVIG	Good
											Psychosis	Rituximab	
											Seizures		
											Cognitive dysfunction		
Khan et al. [12]	2022	18	M	Normal	None	Absent	NA	21		Normal	Altered mental status	IVMP	Good
											Seizures	Plasmapheresis	
											Psychosis		
											Dystonic posturing		
Hara et al. [13]	2021	65	M	Normal	Respiratory	Present	After 7 days	18		115	Altered mental status	IVMP	Good
											Cognitive dysfunction	IVIG	
Kaur et al. [14]	2022	1	M	Normal	Respiratory	Present	Simultaneous	Normal		Normal	Altered mental status	IVMP	Poor
											Seizures	IVIG	
											Perioral dyskinesias	Rituximab	
Lee et al. [15]	2022	21	F	Hippocampal Bilateral	None	Absent	After 10 days	500	57	402	Altered mental status	IVMP	Recovering
											Psychosis	IVIG	
											Cognitive dysfunction		
McHattie et al. [16]	2021	53	F	Hippocampal Unilateral	Respiratory	Present	Simultaneous	141		54	Altered mental status	IVIG	Good
											Psychosis		
											Cognitive dysfunction		

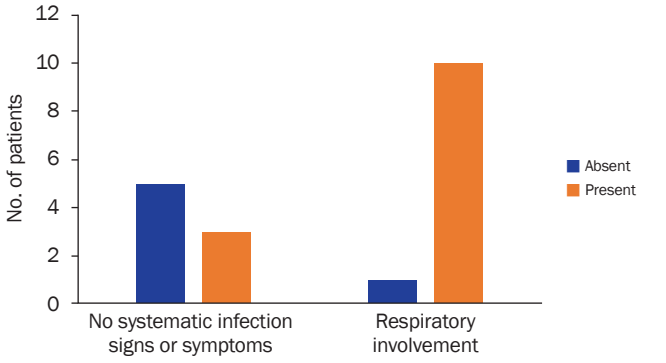
(Continued to the next page)

Table 1 Continued

Study	Year	Age (yr)	Sex	MRI brain findings	COVID-19 systemic symptomsa)	Fever at the time of presentation of neurological symptoms	Time from COVID-19's first systematic symptoms to the onset of the neurological manifestations	CSF WBC count (/mm^3)	CSF glucose (mg/dL)	CSF protein (mg/dL)	Main clinical features	Treatment	Outcome
Monti et al. [17]	2020	50	M	Normal	None	Present	Simultaneous	25	68	48	Altered mental status Seizures (refractory status epilepticus) Orofacial dyskinesia/ automatisms	IVMP IVIG Plasmaphere-sis	Good
Naidu et al. [18]	2023	50	F	Diffuse subcortical edema	Respiratory	Present	Simultaneous	0	54	770	Altered mental status Seizures	IVMP IVIG Plasmaphere-sis	Recovering
Panariello et al. [19]	2020	23	M	Normal	Respiratory	Present		0	70	65	Psychosis Insomnia	IVIG	Good
Sanchez-Larsen et al. [20]	2023	22	F	Normal	Respiratory	Present	Simultaneous	7		Normal	Altered mental status Seizures Psychosis	IVMP IVIG Rituximab	Good
Sarigecili et al. [21]	2021	7	M	Normal	None	Absent	NA	Normal		Normal	Altered mental status Seizures Choreiform move-ments in the hands and feet, tongue protrusion, bruxism, and lip smacking Psychosis, catatonia	IVMP IVIG Plasmaphere-sis	Good
Simonavičiutė et al. [22]	2023	11	M	Hippocampal Bilateral	None	Absent	NA	Normal			Altered mental status Seizures Psychosis	IVMP IVIG	Good
Tiraboschi et al. [23]	2021	40	F	Normal	Respiratory	Present	After 14 days	Normal		Normal	Altered mental status Seizures Psychosis Dyskinesias and parkinsonism	IVIG	Good
Valadez-Calderon et al. [24]	2022	28	M	Hippocampal Bilateral	Respiratory	Absent	After 14 days	Normal		Normal	Altered mental status Seizures Incoherent speech, somnolence, auditory hallucinations, suicidal ideation	IVMP IVIG	Poor

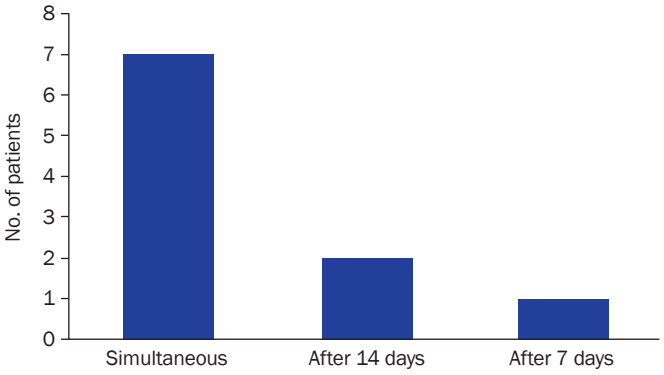
MRI, magnetic resonance imaging; COVID-19, coronavirus disease 2019; CSF, cerebrospinal fluid; M, male; F, female; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; NA, not available or not applicable.
[a)]Other than fever.

Figure 2 The number of patients who had a fever at the time of presentation among COVID-19-infected individuals



The graph illustrates the comparison between patients who had respiratory involvement with COVID-19 infection and those who did not.
COVID-19, coronavirus disease 2019.

Figure 3 The time of onset of neurological manifestations after COVID-19 infection respiratory involvement according to the number of patients



COVID-19, coronavirus disease 2019.

Of the 11 patients who had no systematic involvement of COVID-19, three had fever.

It was found that 70% of the patients (n = 7) who had respiratory manifestations with COVID-19 infection had a simultaneous onset of the neurological manifestations of autoimmune encephalitis. Two patients had onset after 2 weeks, and one had onset of neurological manifestations after 1 week (Figure 3).

Among patients with confirmed NMDA-R antibodies in the CSF, six had a positive serum test for NMDA-R autoantibodies. One patient demonstrated co-expression of NMDA-R antibodies and anti-glutamic acid decarboxylase 65 (GAD 65) antibodies.

The CSF analysis of WBCs was normal in 100% of pediatric cases (n = 6) and five of the 13 adult patients (38%). The average CSF WBC count in patients with elevated WBCs was 97.8/mm^3 (range, 7–500/mm^3). Unfortunately, most of the articles did not mention if the WBCs were predominantly composed of lymphocytes or polymorphonuclear cells.

All pediatric patients and five adult patients (38%) had a normal protein count. The average protein count in patients with elevated protein in the CSF was 218.6 mg/dL (range, 48–770 mg/dL).

The most prevalent neurological manifestation was an altered mental status (n = 17, 89%), which is defined by a reduced level of consciousness or disorientation. This condition was followed by focal or generalized seizures (n = 12, 63.1%). Around half of the patients had psychosis (n = 9), and 36.8% had cognitive dysfunction (Figure 4).

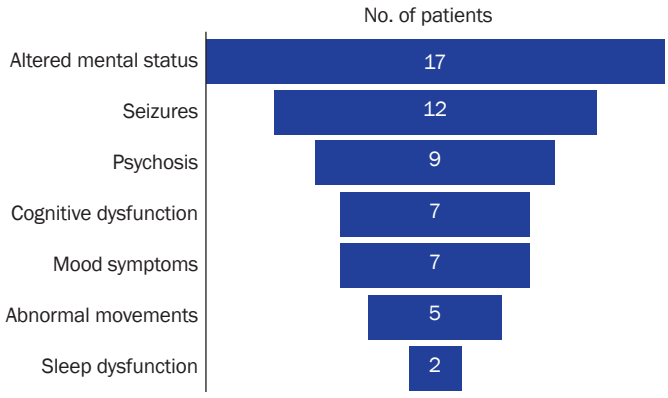
In total, 58% of the patients had a normal brain magnetic resonance imaging (MRI) scan at the time of presentation with neurological manifestations (n = 11). The most common abnormality noted on brain MRI was hyperintensity on T2 sequences involving the hippocampus (32%, n = 6), with bilateral involvement (n = 4) being more common than unilateral involvement (n = 2). This abnormality was followed by diffuse subcortical hyperintensity on T2 sequences (n = 2, 11%).

The majority of the patients experienced a good outcome (n = 14, 74%). The therapeutic interventions used were high-dose intravenous (IV) methylprednisolone, IV immunoglobulins (IVIG), rituximab, and plasmapheresis. Three patients had a poor outcome, and two patients had a “recovering” outcome.

Discussion

Our systematic review indicates that COVID-19 infection is not only a respiratory illness, but that neurological complications also may occur. Autoimmune encephalitis is a rare disorder; however, the cases included in our review are indicative of a potential association between COVID-19 infection and autoimmune encephalitis mediated by NMDA-R autoantibodies. None of the female patients in our study had ovarian teratoma, which is an established risk factor for NMDA-R autoimmune encephalitis.

Figure 4 Neurological manifestations in *N*-methyl-D-aspartate receptor autoantibody-positive patients (n = 19)



Our analysis showed that commonly used CSF markers of inflammation (WBC count and protein) are not helpful in the diagnosis of autoimmune encephalitis, and this trend was more pronounced in the pediatric population in which none of them had an elevated WBC count or protein count. This finding was based on the first lumbar puncture analysis findings, which can be a limitation as those numbers could change in the subsequent CSF analyses [25]. Immunoglobulin G synthesis and oligoclonal band analysis were not assessed, which is another limitation in the CSF analysis in this review because these substances are sensitive markers for inflammation [26].

Serum analysis of NMDA-R autoantibodies was not carried out in all patients; however, our data are in concordance with the current evidence of serum NMDA-R autoantibodies as a limited marker for autoimmune encephalitis. This trend illustrates the importance of NMDA-R autoantibodies in CSF to confirm the diagnosis [27].

Brain MRI also had its limitations in assisting with the diagnosis of autoimmune encephalitis, especially in the acute phase, with almost half of the patients having normal brain MRI. The most common finding was the involvement of the hippocampal region of the temporal lobes, which is one of the most common sites of involvement in NMDA-R autoimmune encephalitis [28].

An altered mental status was the most common neurological manifestation (n = 17, 89%), followed by seizures. Half of the patients experienced acute psychosis, and about one-third of patients demonstrated cognitive dysfunction. The neurological manifestations did not correlate with MRI-specific findings.

None of the inflammatory biomarkers (WBCs or protein count), MRI findings, or clinical symptoms correlated with the need for aggressive immunotherapy or the outcome, which could be indicative of the temporary presence of COVID-19 infection in the initiation and augmentation of encephalitis mediated by NMDA-R autoimmune encephalitis.

The distributions of the ages and genders of the affected patients were the same between adults and pediatric patients, which emphasized the pathogenic role of COVID-19 infection in this disorder.

The exact pathological role of COVID-19 infection in autoimmune encephalitis is not yet established. While some patients did not have respiratory symptoms and their positivity for COVID-19 was a coincidence, the majority of the patients had respiratory symptoms, and most neurologic manifestations started within 5 days of the onset of respiratory symptoms. Nonstructural protein mimicry of the SARS-CoV-2 virus with NMDA-R subunit epitopes was suggested as the underlying cause of the autoimmune response against NMDA-R in the brain. However, this link has not yet been proven [29]. T-helper 17 (Th17) and interleukin-6 involvement in the pathophysiology of COVID-19 infection has been linked to the pathophysiology of neuropsychiatric symptoms that may arise with COVID-19 infection [30,31]. The proinflammatory response produced by activated Th17 can disrupt the blood-brain barrier and could lead to autoimmune neurological manifestations [32].

Our systematic review is unable to provide a strong association between the SARS-CoV-2 virus and the emergence of NMDA-R. Due to the limited availability of autoimmune antibody testing around the world and the variations in testing modalities, some cases likely were missed. The approach to encephalopathy may also vary among providers. Patients who had a normal brain MRI or CSF analysis upon presentation could have had an abnormal MRI or CSF results on repeated testing. No such data were available from the outpatient follow-up visits.

The prognosis was favorable for most patients. There was no correlation between the outcome and the degree of inflammation found in the CSF, MRI findings, or therapeutic interventions used. However, all patients received IV methylprednisolone, IVIG, rituximab, or plasmapheresis as solo therapy or combined treatment. This review highlights the potential association between COVID-19 infection and autoimmune encephalitis mediated by NMDA-R antibodies and indicates

the importance of early immunotherapy upon diagnosis. Further research is also needed to follow up on the patients affected by this syndrome to determine the rate of recurrence and if this is a monophasic syndrome caused by COVID-19 infection or a chronic syndrome.

Conclusions

Our systematic review highlights the potential association between COVID-19 infection and autoimmune encephalitis mediated by NMDA-R antibodies. It also suggests the importance of early immunotherapy upon diagnosis. Further research is needed to establish the prevalence of neurological complications of COVID-19 and to further investigate its biological background.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization, Investigation, Visualization: all authors; Data curation, Methodology, Project administration: AS; Formal analysis: AS, HA; Writing–original draft: AS, HA; Writing–review & Editing: all authors

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