Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

Autoimmune encephalitis associated with COVID-19: A systematic review

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ABSTRACT

Introduction: There are increasing reports of COVID-19 related neurological complications which may be due to direct viral invasion, or immune mediated inflammatory diseases such as autoimmune encephalitis and ADEM (acute demyelinating encephalomyelitis). In this study, a systematic review is presented of the reported cases infected by the COVID-19 who were diagnosed with various forms of autoimmune encephalitis (AE).
Methods: The authors searched three databases including PubMed, Scopus, and Web of science for extracting original articles on coronavirus/ COVID-19 and AE.
Results: Eighteen articles were considered in this study, including 15 case reports, and three case series with a total of 81 patients. Among the studies, 19 cases were reported with AE including 7 (37%) cases of limbic encephalitis, 5 (26%) patients with anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, 2 (11%) with AE presenting as new-onset refractory status epilepticus (NORSE), 1 (5%) case of steroid-responsive encephalitis, and 4 (21%) cases with an unknown type of AE.
Conclusion: Our systematic review revealed evidence on AE development in patients infected with the COVID-19. Clinicians should be aware of the possible diagnosis of AE when considering other neurological differential diagnosis in SARS-CoV-2 infected patients.

1. Introduction

The novel coronavirus disease (COVID-19) appeared for the first time in Wuhan of China in December 2019 (Lu et al., 2020). Caused by the SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus 2), it is a member of the family of coronaviruses infecting humans which is responsible for lower respiratory infection and can cause acute respiratory distress syndrome (ARDS) (Zhou et al., 2020; Chen et al., 2020).

According to previous reports, there are confirmed cases with neurological manifestations who developed the disease either via direct attack to the central nervous system (CNS) or via autoimmune processes (Sánchez-Morales et al., 2021a; Bhagat et al., 2021). New evidence has identified an association between the COVID-19 and systemic autoimmune diseases like autoimmune hemolytic anemia or one-organ-specific diseases like Guillain-Barre syndrome (Toscano et al., 2020; Lazarian et al., 2020). Several neurological complications have now been described: encephalitis, meningitis, and cerebrovascular diseases including ischemic stroke and hemorrhage, ADEM, encephalopathy, and myopathy (Liu et al., 2020a; Helms et al., 2020; Guilmot et al., 2021).

In the following, a systematic review can be found of the reported cases who were infected by the COVID-19, and diagnosed with various forms of autoimmune encephalitis (AE).

2. Methods

2.1. Design

This systematic review was conducted based on Preferred Reporting for Systematic Review and Meta-Analysis (PRISMA) (Moher et al., 2009).

2.2. Search strategy

We searched three databases of Pubmed, Scopus, and Web of science

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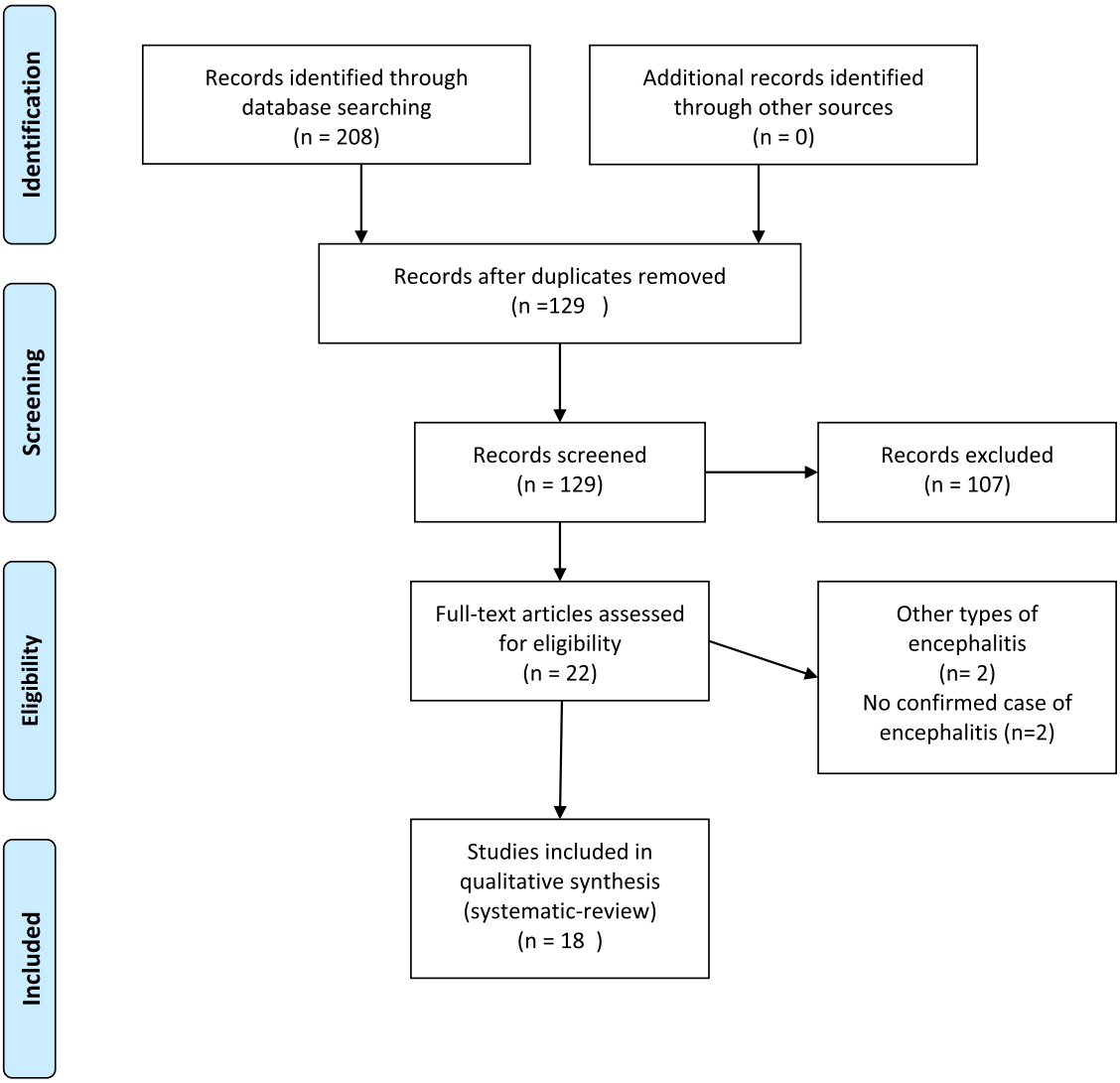

Fig. 1. PRISMA flow diagram depicting the flow of information through the different phases of a systematic review.

for extracting original articles on coronavirus/ COVID-19 and autoimmune encephalitis (AE) on the 1st of April. The search strategy consisted of keywords including "Autoimmune encephalitis", "Limbic encephalitis", "Anti NMDA", "Anti VGKC", "Anti LGI1", "Anti CASPR2", "Anti AMPA", "Anti GAD65", "Anti GABA", "Anti GABAA", "Anti GABAB", "Anti D2", "Anti Dopamine-2″, "Anti DPPX", "Anti Glycine", "Anti GlyR", "Anti Glutamate", "Anti mGluR1", "Anti mGluR5", "Anti amphiphysin", "Anti Neuronal", "Anti CV2", "Anti Ta", "Anti Purkinje", "COVID-19″, "Sars-Cov-2″, and "coronavirus".

2.3. Eligibility criteria

We included the studies have reported the AE related to COVID-19 infection. The studies with other types of encephalitis or unconfirmed cases of autoimmune encephalitis were excluded.

2.4. Study selection

Articles were independently selected by two investigators (M.B and M.R) following two steps. First, the title and abstract were screened. In the next step, the full texts of the selected studies were reviewed according to eligibility criteria. At the end of each step, any disagreements were resolved by discussing the issue with the third investigator (F.N).

2.5. Data extraction

The same reviewers (M.B and M.R) independently extracted the following data manually: author, year, country, study design, number of patients, mean age, sex, number of AE cases, type of AE, and symptoms.

2.6. Data syntheses and analyses

The quantitative data was represented as percentage or mean ± standard deviation. Studies and results were qualitatively compared.

3. Results

3.1. Eligible publications

Our comprehensive literature search yielded a total of 208 articles. After removing duplicates and screening titles and abstracts, 22 reports remained; however, after full text reviews, four studies did not meet the inclusion criteria. Finally, qualitative synthesis was performed on18 studies (Fig. 1).

3.2. Study characteristics

Among the included studies, there were 15 case report studies, two

Table 1
Charcteristics and autoimmune encephaltis of included studies.

Author	year	country	Study design	number of patients	age	gender	total number of encephalitis cases	SARS-CoV-2 laboratory results	Encephalitis laboratory results	type of autoimmune encephalitis	presenting signs
Ayatollahi	2020	Iran, Canada	case report	1	18	Female	1	SARS-CoV-2 rRT-PCR: positive, SARS-CoV-2 CSF PCR: negative, Lung CT scan: normal	MRI: normal, EEG: showed moderate intermittent nonepileptiform abnormality over the frontocentrotemporal regions	NM	drowsiness, confusion, urinary retention, generalized tonic-clonic seizure
Zambreanu	2020	UK	case report	1	66	Female	1	SARS-CoV-2 rRT-PCR: positive, SARS-CoV-2 IgG: negative, SARS-CoV-2 CSF PCR: negative	MRI: symmetrical T2 and FLAIR hyperintensities, Diffusion MRI: punctate bright signal on the B1000 map in the medial temporal lobes, thalami and fornices, Autoantibody testing of immunemediated encephalitis: negative	Limbic encephalitis	confusion, amnestic
Grimaldi	2020	France	case report	1	72	Male	1	Lung CT scan: peripheral bilateral ground-glass lesions and consolidative opacities, SARS-CoV-2 rRT-PCR: positive first then turned to negative, SARS-CoV-2 IgG and IgM: negative	EEG: symmetric diffuse background, MRI: normal, F-FDG PET: putaminal and cerebellum hypermetabolism associated with diffuse cortical hypometabolism, serum IgG isotype autoantibodies: High	NM	action tremor, ataxia, dysarthria and upper limbs dysmetria
Manganotti	2021	Italy	case report	2	54	Male	1	SARS-CoV-2 rRT-PCR: positive	EEG: generalized epileptic discharges with bilateral frontal high amplitude delta waves, MRI: normal	autoimmune encephalitis presenting as new-onset refractory status epilepticus (NORSE)	convulsive status epilepticus, generalized myoclonic jerks of axial muscles and face
Pilotto	2020	Italy	case series	25	65/9	15 Male/10 Female	2	RT PCR: positive	NM	Limbic encephalitis	altered mental status, aphasia, seizure, focal motor deficits
Khoo	2020	UK	case report	1	65	Female	1	SARS-CoV-2 rRT-PCR: positive, Chest X-ray: bilateral peripheral pulmonary infiltrates	MRI: normal, CSF white cell count: normal, Autoantibody testing of immunemediated encephalitis: negative, EEG: normal,	NM	involuntary movements, only speak in native language, speaking difficulties and increasing confusion.
Pilotto	2020	Italy, UK, sweden	case report	1	60	Male	1	SARS-CoV-2 rRT-PCR: positive, Chest X-ray: moderate bilateral interstitial pneumonia, SARS-CoV-2 CSF PCR: negative	CSF: mild lymphocytic pleocytosis and moderate increase of CSF protein, EEG: generalized slowing with decreased reactivity to acoustic stimuli, MRI: normal, Autoantibody testing of immunemediated encephalitis: negative	Steroid-responsive encephalitis	severe akinetic syndrome, unable to carry out simple orders, palmomental and glabella reflexes, nuchal rigidity,
Wang	2020	China	case report	1	68	Male	1	Lung CT scan: groundglass shadows in both lungs, PCR: negative, SARS-CoV-2 IgG and IgM: negative and positive, respectivly,	Brain CT scan: lacunar lesions in the left basal ganglia region	NM	unable to walk, uroclepsia, coprolalia, and persecution delusion.

(*continued on next page*)

Table 1 (*continued*)

Author	year	country	Study design	number of patients	age	gender	total number of encephalitis cases	SARS-CoV-2 laboratory results	Encephalitis laboratory results	type of autoimmune encephalitis	presenting signs
Burr	2020	USA	case report	1	2	Female	1	SARS-CoV-2 CSF IgG and IgM: positive, SARS-CoV-2 PCR: positive, SARS-CoV-2 CSF PCR: negative, SARS-CoV-2 IgG: positive	MRI: normal, serum and CSF NMDA receptor autoantibody: positive	Anti-NMDA receptor encephalitis	fever, fussiness, poor sleep, constipation, decreased oral intake, fussy, not talking, constant kicking and thrashing movements of arms and legs.
Dhillon	2021	UK	cohort	29	68/9	16 Male/13 Female	1	SARS-CoV-2 CSF PCR: negative	MRI; Lesions in the limbic system, predominantly in the left amygdala and hippocampus with partial restricted diffusion, Autoantibody testing of immunemediated encephalitis: negative	Limbic encephalitis	acute-onset delirium, altered mental status, status epilepticus, cognitive impairment
Sánchez-Morales	2021	Mexico	case series	10	11/8	5 Male/5 Female	1	SARS-CoV-2 CSF PCR: positive, Serum SARS-CoV-2 IgM and IgG: negative, CSF antibodies SARS-CoV-2 IgG: positive	NM	Anti-NMDA receptor encephalitis	Altered behavior and mental status, seizures, insomnia, orolingual dyskinesias
Dono	2020	Italy	case report	1	81	Male	1	Chest X-ray: normal, Lung CT scan: ground-glass pattern in both the inferior lobe segments, SARS-CoV-2 PCR: positive, SARS-CoV-2 CSF PCR: negative	EEG: normal, MRI: hyperintense lesions of the bilateral parietal cortex, left temporal cortex, and right cingulate cortex, Autoantibody testing of immunemediated encephalitis: negative	autoimmune encephalitis presenting as new-onset refractory status epilepticus (NORSE)	drowsy with Glasgow coma scale (GCS) of 5 (no eyes opening both to verbal and pain stimulation, no verbal response, and flexion of the upper limbs to pain), Contemporarily, frequent jerky myoclonic contractions of the abdomen and the right lower limb appeared.
Bhagat	2020	USA	case report	1	54	Male	1	SARS-CoV-2 rRT-PCR: positive, Chest X-ray: normal	MRI: hyperintensity on right posterior medial temporal lobe, Autoantibody testing of immunemediated encephalitis: negative, EEG: right posterior quadrant lateralized periodic discharges	Limbic encephalitis	nonradiating pressure type holocranial headache, diaphoresis, palpitation, nausea drowsy, oriented to time, place, and person with intact language, cranial nerves, motor, sensory, and cerebellar functions
Monti	2020	Italy	case report	1	50	Male	1	SARS-CoV-2 rRT-PCR: positive, Lung CT scan: normal	anti-NMDA receptors antibodies in CSF: positive, MRI: normal	Anti-NMDA receptor encephalitis	confabulations and delirious ideas, focal motor seizures with impaired awareness and oro-facial dyskinesia/automatisms,

(*continued on next page*)

Table 1 (*continued*)

Author	year	country	Study design	number of patients	age	gender	total number of encephalitis cases	SARS-CoV-2 laboratory results	Encephalitis laboratory results	type of autoimmune encephalitis	presenting signs
											refractory status epilepticus
Hosseini	2020	UK	case report	2	62/5	Male	1	SARS-CoV-2 rRT-PCR: positive, SARS-CoV-2 CSF PCR: negative, Lung CT scan: bilateral pleural effusion	MRI: partial diffusion restriction in limbic system	Limbic encephalitis	dysphasia and impaired orientation, attention and memory.
Pizzanelli	2021	Italy	case report	1	74	Female	1	Lung CT scan: bilateral diffuse areas of ground-glass pattern with subpleural parenchymal consolidations, SARS-CoV-2 rRT-PCR: positive, SARS-CoV-2 CSF PCR: negative	Brain CT scan: normal, EEG: focal seizures with impaired awareness and oral automatisms, Autoantibody testing of immunemediated encephalitis in CSF and serum: negative, MRI: bilateral symmetric mesial temporal lobes hyperintensity and mild hippocampal thickness	Limbic encephalitis	mild confusion and a brief episode of non-responsivity with staring
Moideen	2020	India, UK	case report	1	17	Male	1	NM	MRI: normal, EEG: normal, anti-NMDA receptors antibodies in CSF: positive	Anti-NMDA receptor encephalitis	over-familiar attitude, increased psychomotor activity, and labile affect
Panariello	2020	Italy	case report	1	23	Male	1	Chest X-ray: bilateral ground glass opacities, Lung CT scan: patchy bi-basilar consolidations	Brain CT scan: normal, EEG: unstable non reactive to visual stimuli, anti-NMDA receptors antibodies in CSF: positive	Anti-NMDA receptor encephalitis	psychomotor agitation, anxiety, thought disorganization, persecutory delusions, auditory hallucinations, and global insomnia

NM: Not Mentioned; NMDA: N-Methyl-D aspartate, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, rRT-PCR: Real-time reverse-transcription polymerase chain reaction analysis, CT scan: Computed tomography, MRI: Magnetic resonance imaging, PET: Positron emission tomography, F-FDG: Fludeoxyglucose, EEG: Electroencephalography.

case series, and one cohort article with a total of 81 patients. 62.6% of these patients were men. Three studies were multicenter (Ayatollahi et al., 2020; Pilotto et al., 2020a; Moideen et al., 2020), six from Italy (Manganotti et al., 2021; Pilotto et al., 2021; Dono et al., 2021; Monti et al., 2020; Pizzanelli et al., 2021; Panariello et al., 2020), four from UK (Zambreanu et al., 2020a; Khoo et al., 2020a; Dhillon et al., 2021; Hosseini et al., 2020), two from USA (Bhagat et al., 2021; Burr et al., 2021), one from Mexico (Sánchez-Morales et al., 2021a), one from China (Wang et al., 2020a), and one from France (Grimaldi et al., 2020a).

3.3. Autoimmune encephalitis

Findings from the studies on the AE are summarized in Table 1. Among the included studies, 19 cases were reported with AE, including 7 (37%) cases of limbic encephalitis, 5 (26%) patients with anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, 2 (11%) with AE presenting as new-onset refractory status epilepticus (NORSE), 1 (5%) case of steroid-responsive encephalitis, and 4 (21%) cases with unknown type of AE (Table 1, Fig. 2).

A cohort study from UK reported one case of limbic encephalitis out of 29 COVID-19 cases (Dhillon et al., 2021). Also, there was a case series study reporting two patients with limbic encephalitis among 25 COVID-19 patients (Pilotto et al., 2021). The other cases of limbic encephalitis were reported in four case reports (Bhagat et al., 2021; Pizzanelli et al., 2021; Hosseini et al., 2020). The patients were more likely to develop acute-onset delirium, altered mental status, status epilepticus, cognitive impairment, aphasia, seizure, focal motor deficits, headache, diaphoresis, palpitation, nausea drowsy, mild confusion, and a brief episode of non-responsivity (Table 1). In limbic encephalitis, when measured, no cases of LGI1 or CASPR2 antibodies were found.

Five studies reported cases of Anti-NMDA receptor encephalitis. Among the cases, there was a two-year-old girl with symptoms such as fever, poor sleep, constipation, decreased oral intake, not talking, constant kicking, and thrashing movements of arms and legs (Burr et al., 2021). Furthermore, three other cases were patients aged 17, 23, and 50 years old with Anti-NMDA receptor encephalitis (Sánchez-Morales et al., 2021a; Moideen et al., 2020; Monti et al., 2020). It seems that this type of AE affects younger individuals infected with COVID-19. These patients were reported with altered behavior and mental status, seizures, insomnia, dyskinesia, refractory status epilepticus, over-familiar attitude, increased psychomotor activity, anxiety, and labile affect (Table 1).

Moreover, there were two cases with AE presenting as new-onset refractory status epilepticus (NORSE), both from Italy (Manganotti et al., 2021; Dono et al., 2021). The clinical symptoms including convulsive status epilepticus, and generalized myoclonic jerks of axial muscles and face were reported in these patients (Table 1).

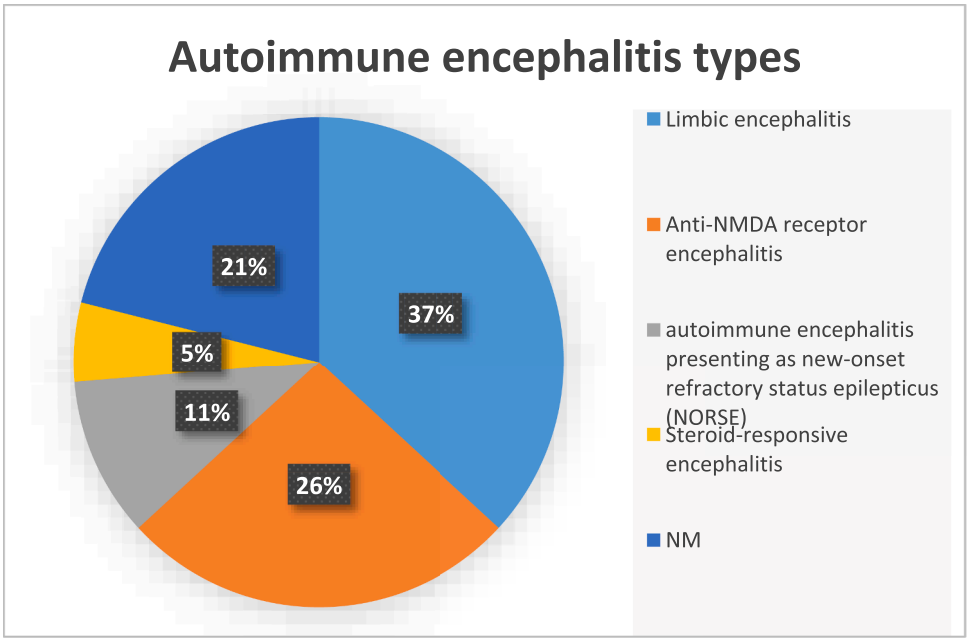

Fig. 2. Types of autoimmune encephalitis expressed as percentage.

A case report also described a patient with steroid responsive encephalitis after COVID 19 infection (Pilotto et al., 2020a). The case was unable to carry out simple orders and presented severe akinetic syndrome, palmomental and glabella reflexes, and nuchal rigidity.

Also, seven other studies reported AE in COVID-19 the patients without mentioning the exact type (Ayatollahi et al., 2020; Khoo et al., 2020a; Wang et al., 2020a; Grimaldi et al., 2020a). All the clinical symptoms of encephalitis in reported cases are detailed in Table 1.

4. Discussion

Different theories have been postulated to explain the pathophysiology of SARS-CoV-2 CNS invasion. SARS-CoV-2 reaches to CNS through systemic circulating system. The virus cannot easily cross the blood brain barrier (BBB) and invade the CNS (Achar and Ghosh, 2020). However, virus recruits three main strategies to cross the BBB. These mechanisms include transcellular migration, paracellular migration, and Trojan horse (Dahm et al., 2016).

There is another important mechanism explaining the development of AE in the COVID-19 infection. It has been demonstrated that cytokine-mediated neuroinflammation in response to SARS-CoV-2 infection plays an important role in the pathogenesis of AE (Dhillon et al., 2021). Severe case of COVID-19 infection induces overproduction of inflammatory cytokines, known as cytokine storm (Achar and Ghosh, 2020). Supportably, patients with a severe condition of COVID-19 show higher levels of inflammatory cytokines such as IL-2R, IL-6, IL-8, IL-10, and TNF-α compared to cases with non-severe COVID-19 condition (Liu et al., 2020b). Elevated IL-6 which is known as a common feature of the disease during the inflammatory phase can be a linking factor due to its role in facilitating autoantibody production in anti-NMDA-R encephalitis (Byun et al., 2016). Overproduction of inflammatory cytokines seems to affect BBB integrity, increase its permeability, and lead to viral transmission through BBB (Achar and Ghosh, 2020). Furthermore, it has been shown that SARS-CoV-2 induces production of anti-NMDA-R autoantibodies and causes AE (Sánchez-Morales et al., 2021b). Based on the reviewed articles in this study, hyperinflammation syndrome is a leading cause for the development of AE in the majority of COVID-19 patients. Moreover, the results indicate that the AE is mostly presented several days after respiratory symptoms, suggesting a trigger role for COVID-19 infection in autoimmune induced CNS disorders.

Based on the reviewed articles in this study, limbic encephalitis is the most frequent type of encephalitis among patients with AE, followed by anti-NMDA receptor encephalitis. This type of encephalitis is caused by autoantibodies that target NMDA receptors located in CNS. Infection-induced anti-NMDA-R encephalitis has been reported after herpes simplex virus (HSV1) infection (Monti et al., 2020). In a prospective study, AE was observed in about 27% of patients with HSV1 infection (Armangue et al., 2018). Among patients who developed AE after the COVID-19, only one case was reported with positive CSF PCR and there was one positive case for IgG and IgM in CSF for SARS-CoV-2 (Table 1). Based on this finding, the presence of undetectable virus in the CSF of COVID-19 patients with AE maybe due to transient presence of the virus in cerebrospinal fluid (CSF) or immunological response-induced CSF injury (Ayatollahi et al., 2020; Zambreanu et al., 2020b). Moreover, the absence of virus RNA is not associated with the severity of neurological disorders (Matschke et al., 2020). Positive autoimmune antibody and high level of proteins in CSF are applied as diagnostic criteria for AE (Wang et al., 2020b). However, antibody test could be negative in some patients (Khoo et al., 2020b). Studies have reported that corticosteroids and intravenous immunoglobulin are considered as first-line therapies for AE treatment (Manganotti et al., 2021; Khoo et al., 2020b; Pilotto et al., 2020b; Grimaldi et al., 2020b).

5. Conclusion

Our systematic review revealed evidence on the probability of developing AE in patients infected with the COVID-19. Clinicians should be aware of the possible diagnosis of AE when considering other neurological differential diagnosis in SARS-CoV-2 infected patients.

Declaration of Competing Interest

The authors declare there is no conflict of interest

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.103795.

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