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AI-CoV Study: Autoimmune Encephalitis Associated With COVID-19 and Its Vaccines—A Systematic Review

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Background and Purpose Autoimmune encephalitis (AIE) following coronavirus disease 2019 (COVID-19) is an underexplored condition. This study aims to systematically review the clinico-investigational and pathophysiologic aspects of COVID-19 and its vaccines in association with AIE, and identify the factors predicting neurological severity and outcomes.

Methods Relevant data sources were searched using appropriate search terms on January 15, 2022. Studies meeting the criteria for AIE having a temporal association with COVID-19 or its vaccines were included.

Results Out of 1,894 citations, we included 61 articles comprising 88 cases: 71 of COVID-19-associated AIE, 3 of possible Bickerstaff encephalitis, and 14 of vaccine-associated AIE. There were 23 definite and 48 possible seronegative AIE cases. Anti-NMDAR (N-methyl-D-aspartate receptor; *n*=12, 16.9%) was the most common definite AIE. Males were more commonly affected (sex ratio=1.63) in the AIE subgroup. The neurological symptoms included altered mental state (*n*=53, 74.6%), movement disorders (*n*=28, 39.4%), seizures (*n*=24, 33.8%), behavioural (*n*=25, 35.2%), and speech disturbances (*n*=17, 23.9%). The median latency to AIE diagnosis was 14 days (interquartile range=4–22 days). Female sex and ICU admission had higher risks of sequelae, with odds ratio (OR) of 2.925 (95% confidence interval [CI]=1.005–8.516) and 3.515 (95% CI=1.160–10.650), respectively. Good immunotherapy response was seen in 42/48 (87.5%) and 13/13 (100%) of COVID-19-associated and vaccine-associated AIE patients, respectively. Sequelae were reported in 22/60 (36.7%) COVID-19 associated and 10/13 (76.9%) vaccine-associated cases.

Conclusions The study has revealed diagnostic, therapeutic, and pathophysiological aspects of AIE associated with COVID-19 and its vaccines, and its differences from postinfectious AIE.

Systematic review registration PROSPERO registration number CRD42021299215

Keywords COVID-19; autoimmune encephalitis; COVID-19 vaccine; postinfectious encephalitis.

INTRODUCTION

The clinical spectrum of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections has continued to broaden since the emergence of this virus. Previous reviews have provided valuable insights into coronavirus disease 2019 (COVID-19)-associated neurological conditions such as stroke, Guillain-Barre syndrome, acute disseminated encephalomyelitis, critical-illness polyneuropathy/myopathy, myelitis, encephalitis, and multisystem inflammatory syndrome.[1-3] However, autoimmune encephalitis (AIE) in association with COVID-19 and its vaccines represents one of the newer frontiers that has remained poorly explored.[4] In particular, in the current situation where COVID-19-associated encephalitis and postacute sequelae of COVID-19 have also been reported, recognizing AIE amidst its

mimics has been challenging for neurologists worldwide.[5] Seminal papers on COVID-19-associated AIE have reported on the application of current clinical diagnostics to identify these cases.[5-7] Rare cases of AIE after vaccination with COVID-19 vaccines have also been reported.

This situation prompted us to attempt to systematically dissect the spectrum of encephalitis temporally associated with COVID-19 and postvaccination subgroups in accordance with the currently accepted criteria for AIE, and identify the demographic, clinicoinvestigational characteristics, diagnostic challenges, management strategies, and clinical outcomes of these patients.[8,9] We subsequently tried to elucidate the pathophysiological mechanisms underlying COVID-19-associated AIE based on recent evidence.

METHODS

Research question

This study was designed to assess the demographic parameters, clinical presentation, investigational profile, management strategies, and factors affecting the clinical outcomes in patients with definite, possible, or probable AIE associated with COVID-19 or its vaccination. The probable pathophysiological mechanisms were subsequently reviewed.

Protocol registration

This systematic review was performed in accordance with synthesis without meta-analysis guidelines. The protocol was registered under PROSPERO (no. CRD42021299215).

Search strategies

The search strategy was designed to yield optimum results for four different aspects of our study. COVID-19 and its equivalent Medical Subject Headings (MeSH) terms were initially combined with the equivalent terms for AIE which was followed by combination with "encephalitis" and its equivalent terms to capture the entire spectrum. MeSH terms for COVID-19 vaccines were subsequently used to identify vaccine-associated cases. The review of pathogenesis was based on separate search strategy combining COVID-19, encephalitis, and pathogenesis with their equivalent terms. Three authors (SMM, DD, and SG) independently performed the search protocol. The detailed search terms are provided in the Supplementary Material (in the online-only Data Supplement).

Data sources

We searched the database platforms of PubMed/MEDLINE, Scopus, LitCOVID, WHO global COVID-19 database, Web of Science, and Google Scholar. A shadow search based on the reference lists of identified articles was performed, and relevant studies were considered. All articles identified up to January 15, 2022 were included.

Study selection based on inclusion and exclusion criteria

The identified articles were screened based on their title, type of study, sample size, COVID-19 status, primary clinical manifestations, clinical phenotype, investigational profile, management strategies, and clinical outcomes. Each of the patient records was assessed according to the criteria reported by Graus et al.[9] in 2016. Seminal studies on post-HSE (herpes simplex encephalitis)-associated AIE have shown the median interval from the diagnosis of HSE to the onset of AIE to be around 4 weeks in children and 6 weeks in adults.[10,11] Hence, we defined 2 months as the cutoff interval to the onset of compatible neurological syndrome from the index event as indicative of a likely temporal association, where an index event was defined as COVID-19 of any severity and/or administration of any of the currently approved COVID-19 vaccines.

The following inclusion criteria were applied: 1) studies involving patient(s) diagnosed with COVID-19 or who had taken a COVID-19 vaccine, and presenting with a clinical syndrome that met the criteria for definite, probable, or possible AIE within 2 months of the index event, 2) cases who had antineuronal antibody positivity with consistent clinical phenotypes even if they did not satisfy the criteria of Graus et al.,[9] and 3) cases diagnosed as COVID-19-associated encephalitis if the clinicoinvestigational phenotype matched the criteria of Graus et al.,[9] even if the reporting authors did not consider this to be the case. The following exclusion criteria were applied: 1) articles not written in English, 2) articles lacking patient-level data, 3) articles based on perspectives or viewpoints, 4) no temporal association with SARS-CoV-2 infection or vaccination, 5) a clinical profile that could be explained by an alternative diagnosis, and 6) not-peer-reviewed articles.

Data extraction

The included studies were assessed and patient-level data were extracted with regards to predefined variables, which included demographic parameters, clinical features at the primary presentation, neurological symptoms and signs, latency to the onset of the first neurological symptoms, latency to the relapse or nonremission of previous neurological symptoms leading to the diagnosis of AIE, investigational profile including neuroimaging, electroencephalography (EEG), cerebrospinal fluid (CSF) analysis, antineuronal antibody status, and SARS-CoV-2 diagnostics, management strategies, time taken to respond to therapy, clinical outcomes, and sequelae. All of the patients were assigned COVID-19 severity scores in accordance with the WHO clinical progression scale.[12]

Risk of bias

Each study underwent a risk-of-bias assessment based on the type of study. The Joanna Briggs Institute critical appraisal tool published in 2017 was used to assess case reports.[13] Case series were analyzed using the National Institutes of Health quality assessment tool.[14] Each study was assessed independently by two authors (SMM and DD). Finally, the interrater reliability was calculated.

Data synthesis

Categorical variables are expressed as percentages while continuous variables are expressed as median and interquartile range (IQR) values. The characteristics of each patient were assessed with regards to the predefined variables, and a descriptive analysis was performed. Outcome measures were categorized into markers of neurological severity and prognosis. The markers of neurological severity were depicted as the presence of status epilepticus and the need for ICU care due to either a neurological indication per se or a neurological complication as an add-on to respiratory indication. Cases requiring ICU care for pure respiratory indication were not included in the outcome measurements. The prognostic markers were depicted as the response to immunotherapy and sequelae. Response to immunotherapy was defined as clinical or radiological improvement following the initiation of one of the standard immunotherapeutic agents, which included the steroid methylprednisolone (MP) or dexamethasone, intravenous immunoglobulin (IVIg), plasma exchange (PLEX), and monoclonal antibodies including rituximab. Sequelae were defined as the persistence of at least one of the neurological symptoms at the time of discharge or at follow-up. All definitions are provided in the Supplementary Material (in the online-only Data Supplement).

Statistical analysis

The χ^2-test was used to adjust p values for multiple comparisons. A binomial logistic regression was subsequently performed to ascertain the effects on predefined outcome measures of various independent variables such as age, sex, clinical manifestations, severity of COVID-19 illness, MRI and EEG abnormalities, CSF pleocytosis, CSF hyperproteinorachia, CSF oligoclonal bands (OCB), inflammatory markers, antineuronal antibody status, and treatment delay. The Mann-Whitney U test was used to compare time latencies across various groups. The chief effect metric for the binomial logistic regression was the odds ratio (OR). A probability value of $p<0.05$ was considered to be statistically significant. All statistical analyses were carried out using SPSS (version 28; IBM Corp., Armonk, NY, USA). Graphs were created using GraphPad Prism (version 9; GraphPad Software, San Diego, CA, USA). The figures were constructed using BioRender (https://biorender.com/).

RESULTS

Study characteristics

Our search strategy yielded 17,761 articles, of which 1,894 Abstracts were screened after duplicate exclusion, and 61 articles were found to meet the inclusion criteria. These 61 articles comprised 47 on COVID-19-associated AIE, 1 case report on possible Bickerstaff encephalitis, 1 case series on both of the above subgroups, and 12 on vaccine-associated AIE. The articles included 52 case reports[15-66] and 9 case series.[5,6,67-73] Fig. 1 provides the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. The risk of bias was assessed prior to inclusion, the results of which are presented in Supplementary Table 1 (in the online-only Data Supplement). Interrater reliability as quantified by Cohen's kappa score was 0.61, which is suggestive of substantial agreement between the authors. The 88 cases comprised 71 of AIE, 14 of vaccine-associated AIE, and 3 of possible Bickerstaff brainstem encephalitis. The 71 AIE cases comprised 48 (67.6%) identified as possible AIE and 23 (32.4%) as definite AIE (Supplementary Material and Supplementary Tables 2−5 in the online-only Data Supplement). All the analysis was performed on 71 AIE cases. The three cases of Bickerstaff encephalitis has been discussed narratively in the later section.

Demographic profile and timelines

In the overall AIE group, 61/71 (85.9%) cases were adults, with significantly greater representation in the possible-AIE subgroup (OR=6.562, 95% confidence interval [CI]=1.582−28.482, p=0.012). The median age was 55 years (IQR=38−65 years) in the overall-AIE group, and it was higher in the possible-AIE subgroup (60 years, IQR=46−66 years) than in the definite-AIE subgroup (40 years, IQR=17−54 years). Males were more commonly affected, accounting for 44/71 (62%) cases in the overall-AIE group, 30/48 (62.5%) in the possible-seronegative-AIE subgroup, and 14/23 (60.9%) in the definite-AIE subgroup. However, in the pediatric subgroup, males were less frequently affected (3/10, 30%; OR=0.209, 95% CI=0.049−0.865, p=0.035). Patients presented to the neurological facility after a median duration of 7 days (IQR=3−14 days). The median latency to the onset of neurological symptoms was estimated to be 1 day (IQR=0−12 days). The median latency to nonremission of the neurological symptoms despite therapy or relapse, which subsequently led to diagnoses of AIE, was estimated to be 14 days (IQR=4−22 days). The 71 AIE patients included 6 (8.5%) diagnosed as AIE during the second admission, of which 3 cases became positive for one of the antineuronal antibodies (single cases of anti-NMDAR [N-meth-

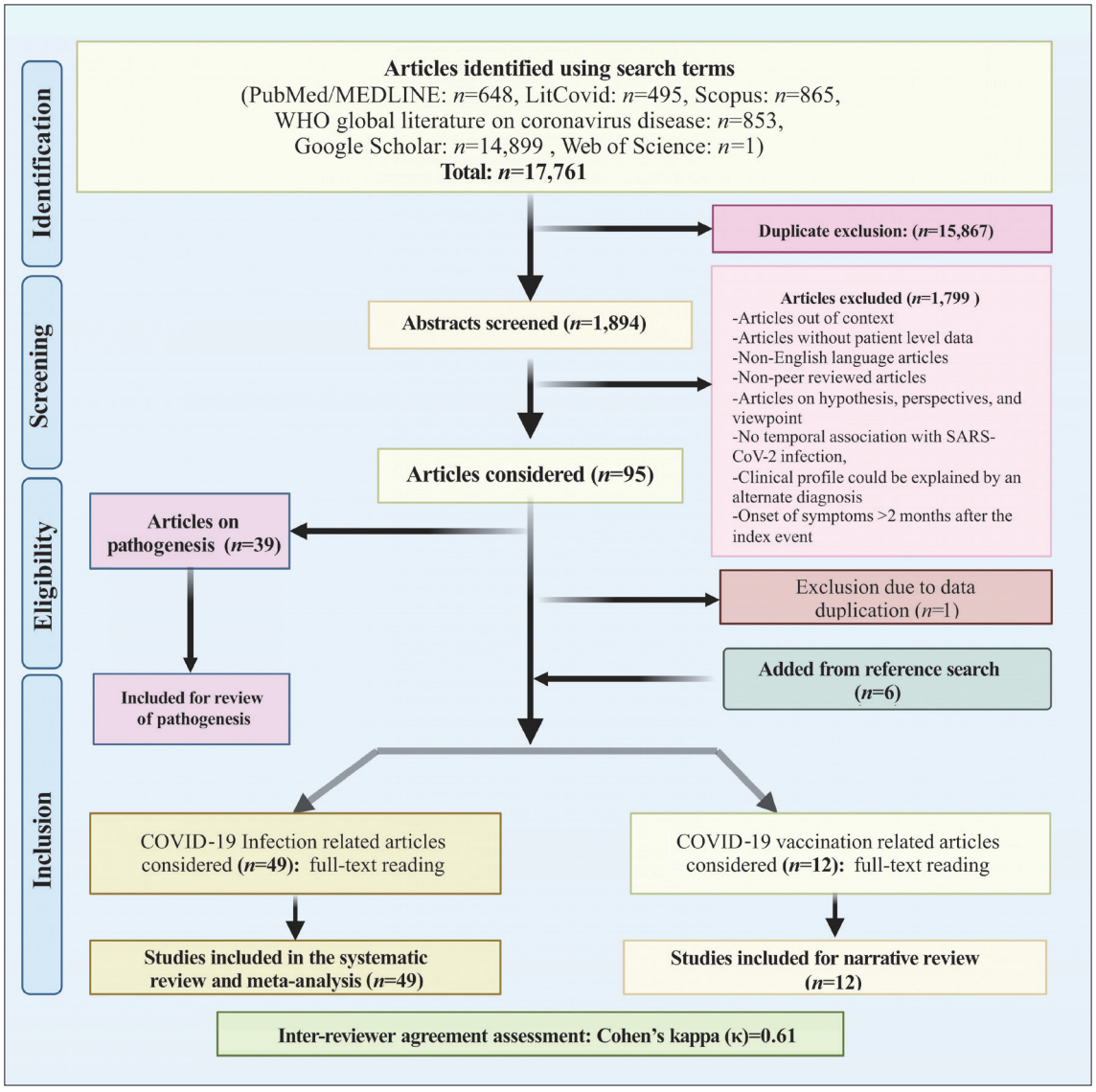

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

yl-D-aspartate receptor], contactin-associated protein-like 2 [CASPR2], and glutamic acid decarboxylase 65-kilodalton isoform [GAD-65]) while 3 (4.2%) were seronegative AIE (Table 1; Supplementary Table 2 in the online-only Data Supplement).

Clinical spectrum

The main clinical manifestations along with subgroup comparisons are provided in Table 1. The possible-AIE subgroup contained a significantly larger number of cases with severe COVID-19 illness (OR=9.643, 95% CI=1.170−79.462, p=0.035). None of the pediatric patients had severe COVID-19 illness. ICU admission due to either pure neurological indication or as an additional factor to respiratory indication was reported in 24/68 (35.3%) overall cases, with no significant difference between the subgroups. The main domains of neurological syndromes included altered mental state (n=53, 74.6%), movement disorders (n=28, 39.4%), seizures (n=24, 33.8%), behavioral and neuropsychiatric symptoms (n=25, 35.2%), speech disturbances (n=17, 23.9%), cognitive symptoms (n=10, 14.1%), eye-movement abnormalities (n=8, 11.3%), insomnia (n=8, 11.3%), and focal weakness (n=7, 9.9%).

Altered mental state

The prevalence of altered mental state was significantly higher in the possible-AIE subgroup (OR=12.024, 95% CI=1.373−105.260, p=0.025). It was less likely in children than in adults (OR=0.245, 95% CI=0.061−0.984, p=0.047). Possible-AIE cases had lower incidence rates of insomnia (OR=0.123, 95% CI=0.023−0.670, p=0.015) and speech abnormalities (OR=

Table 1. A comparative analysis of demographics, salient clinical manifestations, investigations, management, and clinical outcomes

Parameter	Overall AIE group[¶]	Possible seronegative AIE	Definite AIE	OR (95% CI)	*p*
Cases	71 (100)	48 (67.6)	23 (32.4)	-	-
Age (yr)	55 [38–65]	60 [46–66]	40 [17–54]	-	-
Adults	61 (85.9)	45 (93.8)	16 (69.6)	6.562 (1.582–28.482)	0.012*
Sex, male[†]	44 (62.0)	30 (62.5)	14 (60.9)	1.071 (0.386–2.975)	0.895
Clinical manifestation					
Severe COVID-19 illness[‡]	16/62 (25.8)	15/43 (34.9)	1/19 (5.3)	9.643 (1.170–79.462)	0.035*
ICU admission	24/68 (35.3)	14/45 (31.1)	10/23 (43.5)	0.717 (0.257–2.001)	0.525
Altered mental state	53 (74.6)	40 (83.3)	13 (56.5)	12.024 (1.373–105.260)	0.025*
Movement disorder	28 (39.4)	14 (29.2)	14 (60.9)	0.558 (0.072–4.354)	0.578
Myoclonus	14 (19.7)	9 (18.8)	5 (21.7)	0.659 (0.070–6.178)	0.715
Ataxia	9 (12.7)	4 (8.3)	5 (21.7)	0.561 (0.052–6.053)	0.634
Seizures	24 (33.8)	14 (29.2)	10 (43.5)	0.511 (0.085–3.074)	0.463
GTCS	10 (14.1)	6 (12.5)	4 (17.4)	0.349 (0.029–4.194)	0.407
Status epilepticus	10 (14.1)	8 (16.7)	2 (8.7)	2.100 (0.409–10.794)	0.374
Focal weakness	7 (9.9)	5 (10.4)	2 (8.7)	0.762 (0.059–9.845)	0.835
Behavioral and psychiatric symptoms	25 (35.2)	17 (35.4)	8 (34.8)	3.112 (0.395–24.495)	0.281
Visual hallucinations	6 (8.5)	2 (4.2)	4 (17.4)	1.068 (0.069–16.551)	0.962
Eye-movement abnormalities	8/71 (11.3)	4/48 (8.3)	4/23 (17.4)	1.811 (0.437–7.500)	0.413
Cognitive symptoms	10 (14.1)	8 (16.7)	2 (8.7)	2.060 (0.385–11.033)	0.398
Insomnia	8 (11.3)	2 (4.2)	6 (26.1)	0.123 (0.023–0.670)	0.015*
Speech abnormality	17 (23.9)	8 (16.7)	9 (39.1)	0.313 (0.100–0.977)	0.045*
Mutism	8 (11.3)	4 (8.3)	4 (17.4)	0.358 (0.035–3.704)	0.389
Investigation					
CSF pleocytosis	26/67 (38.8)	14/46 (30.4)	12/21 (57.1)	0.328 (0.113–0.955)	0.041*
CSF OCB positivity	10/34 (29.4)	5/25 (20.0)	5/9 (55.6)	5.0 (0.970–25.771)	0.054
CSF hyperproteinorachia	24/53 (45.3)	15/35 (42.9)	9/18 (50)	0.750 (0.240–2.347)	0.621
Elevation of at least one inflammation marker	23/29 (79.3)	16/21 (76.2)	7/8 (87.5)	0.457 (0.045–4.668)	0.509
MRI abnormality	37/64 (57.8)	31/47 (66)	6/18 (33.3)	4.133 (1.299–13.155)	0.016*
EEG abnormality	36/43 (83.7)	25/29 (86.2)	11/14 (78.6)	1.705 (0.325–8.933)	0.528
Timeline					
Latency to neurological symptoms (days)	1 [0–12]	3 [0–10]	0 [0–14]	-	0.251
Latency to relapse or nonremission of neurological symptoms leading to diagnosis of AIE (days)	14 [4–22]	15 [7–24]	8 [3–22]	-	0.147
Duration at presentation (days)	7 [3–14]	6 [1–10]	10 [4–16]	-	0.096
Time from diagnosis to initiation of immunotherapy (days)	14 [7–27]	17 [10–42]	7 [3–23]	-	0.068
Diagnosis at second admission	6 (8.5)	3 (6.3)	3 (13.0)	1.290 (0.280–5.937)	0.744
Treatment					
At least one form of immunotherapy	47/57 (82.5)	29/38 (76.3)	19/19 (100)	-	-
Parenteral steroids[§]	39/57 (68.4)	23/38 (60.5)	17/19 (89.5)	0.719 (0.117–4.407)	0.721
IVIg	23/57 (40.4)	12/38 (31.6)	12/19 (63.2)	0.205 (0.047–0.898)	0.036*
IVIg (second course)	3/57 (5.3)	-	3/19 (15.8)	-	-
PLEX	8/57 (14.0)	3/38 (7.9)	5/19 (26.3)	1.800 (0.124–26.196)	0.667
Combination[‖]	21/57 (36.8)	10/38 (26.3)	12/19 (63.2)	0.404 (0.122–1.334)	0.137
No immunotherapy	9/ 57 (15.8)	9/38 (23.7)	-	-	-
Clinical outcome					
Response to immunotherapy	42/48 (87.5)	24/29 (82.8)	18/19 (94.7)	0.267 (0.029–2.486)	0.246
Latency to therapeutic response (days)	8 [5–19] (36/71 cases)	7 [5–11] (21/48 cases)	11 [7–30] (15/23 cases)	-	0.095
Sequelae[‡]	22/60 (36.7)	16/45 (35.6)	6/15 (40.0)	1.387 (0.438–4.393)	0.578
Died	4 (5.6)	4 (8.3)	-	-	-

Data are *n* (%) or median [interquartile range] values, except where indicated otherwise.

Note: One patient had both anti-GAD-65 and anti-NMDAR positivity. *$p<0.5$; [†]No information about sex for one study[71]; [‡]Included four deaths; [§]Two patients were given dexamethasone instead of MP[17,40]; [‖]Combination therapy included use of steroids, IVIg, or PLEX individually or in combination. One patient was given IVIg and tocilizumab[57]; [¶]Three patients of Bickerstaff encephalitis are not considered in the analysis.

AIE, autoimmune encephalitis; CI, confidence interval; CSF, cerebrospinal fluid; EEG, electroencephalography; GTCS, generalized tonic–clonic seizures; IV, intravenous; IVIg, intravenous immunoglobulin; MP, methylprednisolone; MRI, magnetic resonance imaging; NA, not available/not applicable; NMDAR, N-methyl-d-aspartic acid receptor; OCB, oligoclonal bands; OR, odds ratio; PLEX, plasma exchange; "-", not available/applicable.

0.313, 95% CI=0.100−0.977, *p*=0.045).

Movement disorders

Movement disorders constituted one of the most frequent presentations, featuring in 14/23 (60.9%) cases of definite AIE and 14/48 (29.2%) cases of seronegative AIE. The plethora of symptoms included myoclonus (*n*=14, 19.7%), ataxia (*n*=9, 12.7%), orolingual dyskinesia (*n*=4, 5.6%), catatonia (*n*=4, 5.6%), choreiform movements (*n*=4, 5.6%), facial myoclonus (*n*=3, 4.2%), and dystonia (*n*=2, 2.8%). Rare presentations in single case reports included hyperekplexia, myorhythmia, rigidity, akinesia, and mirror movements.

Seizures

New-onset seizures that were not explained by a metabolic or previously known epileptic disorder was reported in 24 (33.8%) of the 71 cases, of which 10/23 (43.5%) were definite AIE and 14/48 (29.2%) were seronegative AIE. The seizures were generalized in 10 (13.5%) of the 71 cases and focal in 3 (4.1%), while in the remaining cases the onset was not known. Status epilepticus was noted in 10/71 (14.1%) cases, of which 8/48 (16.7%) were seronegative AIE and 2/23 (8.7%) were definite. In the definite AIE subgroup, both were positive for anti-NMDAR (2/12, 16.7%), and this included the case with dual antibody positivity (anti-NMDAR and anti-GAD-65). One of the cases from the seronegative-AIE subgroup presented with new-onset refractory status epilepticus.

Speech abnormality

Mutism was the most common speech abnormality, reported in 8/71 (11.3%) cases, of which 4/23 (17.4%) were definite AIE and the remaining (4/48, 8.3%) were seronegative AIE. Other abnormalities comprised dysarthria (*n*=4, 5.6%), aphasia (*n*=1, 1.4%), and paraphasia (*n*=1, 1.4%), while the abnormalities remained unclassified in four (5.6%) of the cases.

Behavioral and neuropsychiatric symptoms

Behavioral changes and neuropsychiatric manifestations were seen in 25/71 (35.2%) cases, of which 17/48 (35.4%) were seronegative AIE while 8/23 (34.8%) were definite AIE. The wide range of symptoms included visual hallucinations (*n*=6, 8.5%), anxiety (*n*=5, 7.0%), depression (*n*=3, 4.2%), mood alterations (*n*=3, 4.2%), and emotional lability (*n*=1, 1.4%).

Cognitive symptoms

Though less common, diverse cognitive symptoms were reported for 8/48 (16.7%) cases of seronegative AIE and 2/23 (8.7%) cases of definite AIE. The deficits included memory impairment (*n*=6, 8.5%), perseveration (*n*=5, 7.0%), executive dysfunction (*n*=2, 2.8%), disinhibition (*n*=2, 2.8%), apraxia (*n*=1, 1.4%), and palilalia (*n*=1, 1.4%).

Eye-movement abnormalities

Out of 8 patients with eye-movement abnormalities, 4/48 (8.3%) were seronegative AIE and 4/23 (17.4%) were definite-AIE. These abnormalities included nystagmus (*n*=2, 2.8%), opsoclonus (*n*=2, 2.8%), and impairment of pursuits (*n*=2, 2.8%). There were single cases presenting with ocular bobbing, ocular flutter, roving eye movements, and internuclear ophthalmoplegia.

Miscellaneous deficits

Sleep disturbances were reported in 10/71 (14.1%) cases: 7/23 (30.4%) were definite AIE and 3/48 (6.3%) were seronegative AIE. Somnolence was present in 2 (2.8%) of the 71 cases. Alien hand was reported in a single case with a novel antibody. Headache was one of the less-common manifestations, reported in only four (5.6%) cases, while bulbar symptoms were reported in three (4.2%) cases.

Investigational profile

SARS-CoV-2 diagnostics

All patients in the included studies were diagnosed as having COVID-19. PCR of the CSF revealed positivity for SARS-CoV-2 in three cases, all of which were also positive for one of the antineuronal antibodies (two cases had anti-NMDAR and one case had antiamphiphysin antibodies). Antibodies against SARS-CoV-2 were detected in 12 cases, among which 6 (12%) were seronegative AIE and 4 (33.3%) were anti-NMDAR positive, and there was a single case each of anti-GAD-65, anti-CASPR2, and a novel antibody positivity. SARS-CoV-2 antibody positivity in the CSF was reported in only four cases: three were possible seronegative AIE and one had anti-NMDAR positivity.

CSF analyses

CSF analysis revealed pleocytosis in 26/67 (38.8%) cases, hyperproteinorachia in 24/53 (45.3%), and OCB positivity in 10/34 (29.4%). Pleocytosis was more common in the definite-AIE than the possible-AIE subgroup (OR=0.328, 95% CI=0.113–0.955, *p*=0.041).

EEG findings

EEG findings were abnormal in 36/43 (83.7%) cases of the overall AIE group, with no significant difference between the possible-AIE and definite-AIE subgroups. The principal finding in EEG was diffuse slowing, in 27/43 (62.8%) cases. Focal slowing involving temporal regions were reported in 9/43 (20.9%) cases, of which were 5/29 (17.2%) were seronegative

AIE, while frontal predominant slowing was noted in 8/43 (18.6%) cases. Lateralized periodic discharges were reported in 6/43 (13.9%) cases, of which 5 of 29 were seronegative AIE (17.2%) (Supplementary Table 2 in the online-only Data Supplement).

Neuroimaging

Brain MRI scans were available for 64 of the 71 cases, of which 37 (57.8%) were abnormal, comprising 6/18 (33.3%) cases of definite AIE and 31/47 (66.0%) cases of seronegative AIE (OR=4.133, 95% CI=1.299−13.155, p=0.016).

Supratentorial lesions in the form of hyperintensities in T2-weighted FLAIR images were reported in 35/64 (54.7%) cases, with infratentorial lesions in 9 (14.1%) and the involvement of both in 5 (7.8%). Signal changes in temporal lobes were reported in 17/64 (26.6%) cases: 4/18 (22.2%) in the definite-AIE subgroup and 13/48 (27.1%) in the seronegative-AIE subgroup. Brainstem involvement was reported in eight (12.5%) cases, mostly involving the pons (7/64, 10.9%), with all cases belonging to the seronegative-AIE subgroup. It was particularly interesting that MRI abnormalities were less common in children than in their adult counterparts (OR=0.136, 95% CI=0.026−0.705, p=0.017). Cerebellar signal changes were reported in 3/64 (4.7%) cases, and splenial lesions were observed in 3/64 (4.7%) cases. There were two cases each (3.1%) of diffusion restriction, contrast enhancement, and microbleeds.

PET scans were available in 11 (15.5%) of the 71 cases. In the definite-AIE subgroup, data were available for only a single case with antimyelin positivity, with PET revealing basal ganglia hypermetabolism. In contrast, cerebellar hypermetabolism was present in 5/10 (50%) cases in the seronegative-AIE subgroup, of which 4 (40%) showed involvement of the vermis. Basal ganglia hypermetabolism was noted in 4/10 (40%) cases. Other findings included prefrontal hypermetabolism in 3/10 (30%) cases and limbic hypermetabolism in a single case (Supplementary Table 3 in the online-only Data Supplement).

Inflammatory markers

Elevation of at least 1 of the inflammatory markers was reported in 23/29 (79.3%) cases: 7/8 (87.5%) cases of definite AIE and 16/21 (76.2%) cases of seronegative possible AIE. The most commonly tested marker was C-reactive protein, which was elevated in 14/18 (77.8%) cases. Among the other markers, interleukin-6 was elevated in serum in 7/8 (87.5%) cases and in CSF in 6/12 (50%) cases.

Antineuronal antibodies

Numerous antibodies were reported in AIE associated with COVID-19. The antineuronal antibodies comprised antibodies against NMDAR (n=12, 16.9%), GAD-65 (n=3, 4.2%), CASPR2 (n=2, 2.8%), myelin (n=2, 2.7%), and a single case (1.4%) of each of leucine-rich glioma inactivated 1 (LGI-1; also called epitempin), GFAP, Yo, and a novel antibody. Based on the criteria of Graus et al.,[9] possible Bickerstaff encephalitis was considered in three cases.

Management strategies

The principal strategies for management were parenteral steroids, IVIg, PLEX, oral steroids, and their combination. Data on management strategies were available for 57 included subjects. The median time to the initiation of definitive treatment was estimated from the available data to be 14 days (IQR=7−27 days). At least one form of immunotherapy was administered in 47/57 (82.5%) subjects. Intravenous parenteral steroid (MP) was used in 39 (68.4%) cases, while IVIg was used in 23 (40.4%) cases. IVIg was less likely to be administered in the possible-seronegative-AIE than the definite-AIE subgroup (OR=0.205, 95% CI=0.047−0.898, p=0.036). Three (5.3%) cases required a second course of IVIg due to unsatisfactory response to the first dose. PLEX was used in eight (14.0%) cases. Various combinations of steroids, IVIg, and PLEX were applied in 21/57 (36.8%) cases (Supplementary Table 4 in the online-only Data Supplement).

Clinical outcomes

A good clinical response was observed in 42 of 48 (87.5%) cases treated with at least 1 of the immunotherapy modalities. There was a favorable response in 18/19 (94.7%) patients in the definite-AIE subgroup and in 24/29 (82.8%) patients in the seronegative-AIE subgroup. From the available data of 36 patients, the median latency to a clinical response following immunotherapy was estimated to be 8 days (IQR=5−19 days): 11 days (IQR=7−30 days) in 15/23 cases in the definite-AIE subgroup, and 7 days (IQR=5−11 days) in the possible-seronegative-AIE subgroup. Sequelae were reported in 22 patients from the available data of 60 patients (36.7%): 6/15 (40%) in the definite-AIE subgroup and 16/45 (35.6%) in the possible-seronegative-AIE subgroup.

Predictors for neurological severity and clinical outcomes

The results of binomial logistic regression are depicted in Fig. 2. A greater severity of COVID-19 illness was associated with an increased risk of ICU admission (OR=8.409, 95% CI=2.200−32.138, p=0.035). Patients presenting with status epilepticus had increased rates of ICU admission (OR=8.556, 95% CI=1.620−45.195, p=0.011). Female sex and ICU admission were associated with higher risks of sequelae, with OR values of 2.925 (95% CI=1.005−8.516, p=0.049) and 3.515 (95% CI=1.160−10.650, p=0.026), respectively. The response to immunothera-

py was not significantly associated with age, sex, severity of COVID-19, abnormal MRI findings, CSF pleocytosis, CSF hyperproteinorachia, antineuronal antibody positivity, or ICU admission. Sequelae were significantly associated with age, severity of COVID-19, altered mental state, status epilepticus, antineuronal antibody positivity, CSF pleocytosis, hyperproteinorachia, OCB, abnormal MRI findings, EEG findings, treatment delay, and immunotherapy response (Fig. 2).

Clinical syndromes

Anti-NMDAR associated encephalitis (*n*=12)

Anti-NMDAR associated encephalitis constituted the most common group of definite AIE, accounting for 12/71 (16.9%) cases.[5,17-19,23,26-28,33,35,37,69] Males were affected twice as often as females (sex ratio=2:1). With a median age of 26 years (IQR=15−52 years), the disease had a younger onset than that of overall-AIE group. Altered mental state was the most common presentation of the 12 (*n*=9, 75%) cases, followed by movement disorders (*n*=7, 58.3%), new-onset seizures (*n*=7, 58.3%), and behavioral symptoms (*n*=5, 41.7%). Various movement disorders were described, which included orolingual dyskinesia (*n*=3, 25%), myoclonus (*n*=2, 16.7%), choreiform movements (*n*=2, 16.7%), catatonia (*n*=2, 16.7%), and ataxia (*n*=1, 8.3%). The median duration of illness at presentation was 15 days (IQR=3−21 days). The median latency to the relapse or non-remission of neurological symptoms leading to the diagnosis was 4 days (IQR=3−14 days). Neuroimaging showed abnormal signal changes in the temporal lobe in 4/11 (36.3%) cases, with bilateral involvement in 3 (27.3%) cases. EEG showed slowing in three (42.9%) of seven confirmed cases of anti-NMDAR AIE. Management strategies included parenteral steroids (8/11, 72.7%), IVIg (8/11, 72.7%), and their combination (7/11, 63.6%). A favorable response to immunotherapy was observed in 10/11 (90.9%) cases, and sequelae were reported in 4/11 (36.3%) cases.

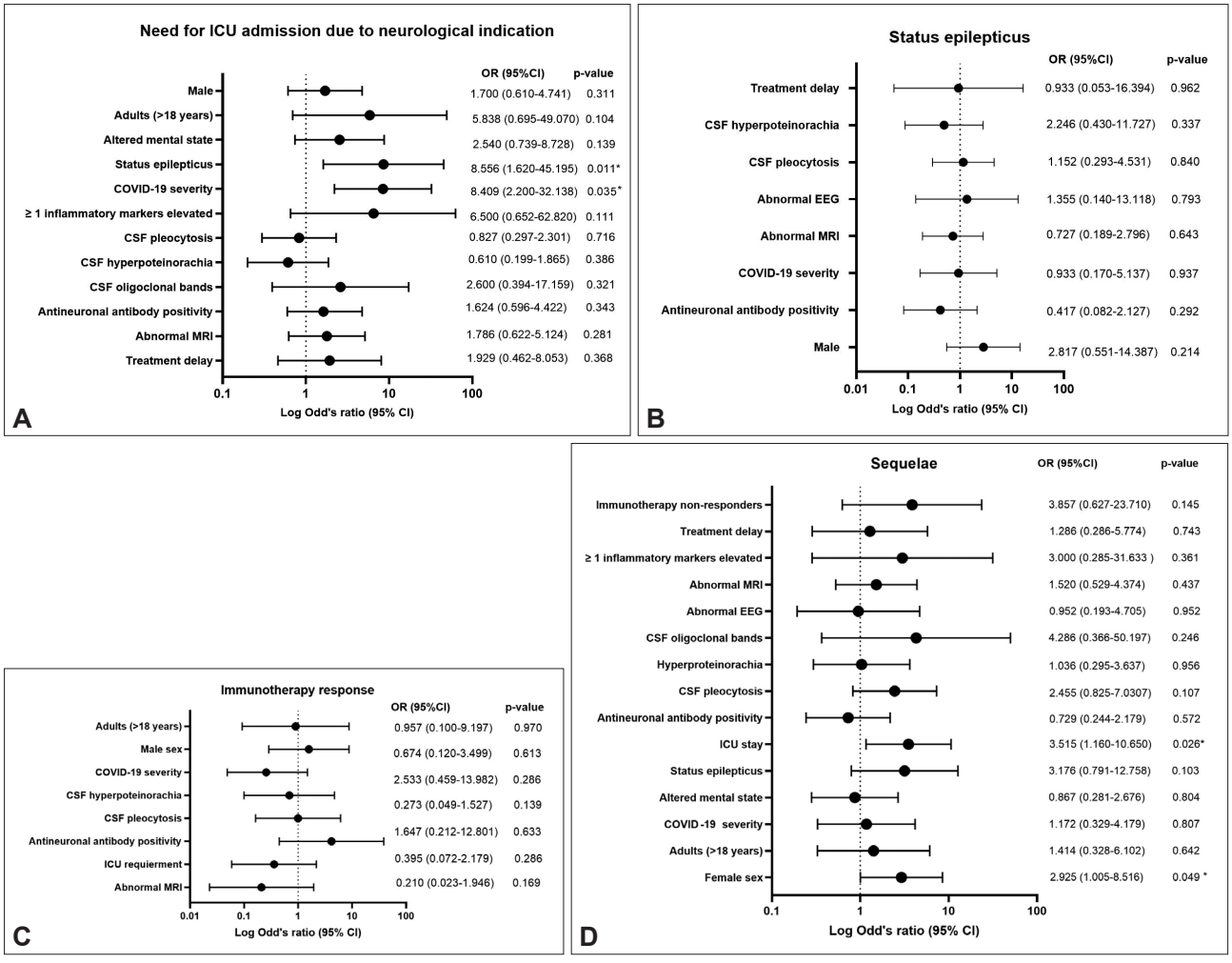

Fig. 2. Factors predicting neurological severity (A, B) and clinical outcomes (C, D). CI, confidence interval; CSF, cerebrospinal fluid; EEG, electroencephalography; MRI, magnetic resonance imaging; OR, odds ratio.

Anti-GAD-65-associated AIE (*n*=3)

We identified two cases with anti-GAD-65 positivity and a single case with dual positivity for anti-NMDAR and GAD-65.[20,32,35] Altered mental state, seizures, and movement disorders were the common presentations, occurring in two of the three cases. None of the cases had CSF pleocytosis or hyperproteinorachia. Neuroimaging showed cerebellar signal changes in one case, and bilateral temporal and anterior cingulate signal changes in another. Although all of the patients responded to immunotherapy, two of them (66.7%) reported sequelae at the last follow-up.

Bickerstaff encephalitis (*n*=3)

Three cases[16,71] partially met the criteria of Graus et al.[9] for possible Bickerstaff encephalitis. All of these patients had recently been affected by COVID-19. Altered mental state and ataxia were the primary neurological presentation in all three cases. Brain MRI revealed cerebellar signal changes in one case, while MRI findings were normal in the other two cases. EEG was suggestive of diffuse slowing. CSF analysis produced no evidence of pleocytosis or elevation of protein levels. The antibody profiles showed anti-GD1b positivity in two cases and anti-GD1a positivity in one case. The response to immunotherapy was favorable in two cases while data were not available in the third case.

Other antibodies associated (*n*≤2)

Rare reports of antineuronal-antibody-associated AIE included two cases of CASPR2[30,71] and single reports of antimyelin,[69] LGI-1,[39] GFAP,[34] amphiphysin,[58] Yo,[69] and a novel antibody detected against mouse brain neuronal proteins[24] associated with AIE. All of the cases showed a temporal association with SARS-CoV-2 infection. The demographic, clinical, investigational, and management profiles are summarized in Supplementary Tables 2 and 3 (in the online-only Data Supplement).

Seronegative AIE (*n*=48)

Our inclusion criteria identified 48 (67.6%) cases of possible seronegative AIE in association with COVID-19.[6,15,16,21,22,29,31,36,38,40-44,53-57,59-63,67,68,70,73] Males were more commonly affected than females (sex ratio: 1.67). The median age was 60 years (IQR=46−66 years), which was higher than that in the definite-AIE subgroup. Similar to the definite-AIE subgroup, altered mental state was the most common manifestation (*n*=40, 83.3%), followed by seizures (*n*=14, 29.2%), movement disorders (*n*=14, 29.2%), and behavioral and neuropsychiatric symptoms (*n*=17, 35.4%). The median latency to the onset neurological symptoms was 3 days (IQR=0−10 days), while the median latency to the relapse or nonimprovement of neurological symptoms was 15 days (IQR=7−24 days). EEG findings were similar to those in the definite-AIE subgroup, except for additional findings of lateralized periodic discharges in 5/29 (17.2%) cases. MRI data were available for 47 cases. It was particularly interesting that brain MRI revealed brainstem involvement in 7/47 (14.9%) cases, mostly in the pons. PET was applied in 11/48 (22.9%) cases, with the findings including basal ganglia hypermetabolism in 4/11 (36.3%) cases and cerebellar (particularly vermian) hypermetabolism in 4/11 (36.3%) cases. CSF pleocytosis and hyperproteinorachia were reported in 14/46 (30.4%) and 15/35 (42.9%) cases, respectively. Immunotherapy was administered in 29 of 38 (76.3%) cases: MP (*n*=29, 76.3%), IVIg (*n*=23, 60.5%), PLEX (*n*=3, 7.9%), or their combination (*n*=10, 26.3%). A response to immunotherapy were noted in 24/29 (82.8%) cases. One of the nine cases who did not receive any form of immunomodulation had sequelae at follow-up, while data were not available for two cases (Supplementary Tables 2 and 3 in the online-only Data Supplement).

Vaccine-associated AIE (*n*=14)

Our search strategy identified 14 cases of possible AIE that was temporally associated with SARS-CoV-2 vaccination.[45-52,64-66,72] Patient-level data were not available for one of these studies.[50] The median age of the patients was 32 years (IQR=22−57 years), and there was female preponderance (sex ratio=5:8). The data from 13 cases comprised 7 (53.8%) that were temporally associated with the ChAdOx1-S vaccine and 6 (46.2%) that followed the administration of the mRNA-1273 vaccine. The median interval to the onset of symptoms was 5 days (IQR=5−8) days. Three of the 14 cases occurred after the second dose. The clinicoinvestigational profile was suggestive of possible AIE according to the currently accepted criteria in 12/14 (85.7%) cases. Two cases were definite AIE with positivity for anti-NMDAR and anti-LGI-1 antibodies. Altered mental state was the most frequently reported symptom (6/13,46.2%), followed by speech disturbances (5/13, 38.5%), and memory deficits (4/13, 30.8%). Brain MRI showed signal changes in temporal lobe in 4/14 (28.6%) cases. One of the cases showed mild hypoperfusion in the right temporal region in SPECT.[65] CSF pleocytosis was observed in 12/14 cases. Parenteral steroids were administered in 11/13 (84.6%) cases (10 were given MP and 1 was given dexamethasone), while 3/13 (23.1%) cases received a combination of steroids, IVIg, and rituximab. While all of the treated patients showed a response to immunotherapy, sequelae occurred in 10/13 (76.9%) cases (Table 2).

DISCUSSION

Postinfectious AIE is a well-described condition in the literature.[74] Herpes simplex virus (HSV), varicella zoster virus,

Table 2. Summary of included studies of SARS-CoV-2-vaccine-associated AIE cases based on current diagnostic criteria for AIE, and the management and clinical outcomes

Study	Case number	Age (yr)	Sex	Vaccine	Dose	Latency from vaccination (days)	Clinical features	Criteria 1*			Criteria 2				Criteria 3	Diagnostic certainty	Neuronal antibody	CSF OCB	AEACN anatomical classification†	EEG	Tx	Tx response	Sequelae
								Altered sensorium	Working-memory deficits	Neuropsychiatric symptoms	New focal CNS findings	Seizures	MRI suggestive of encephalitis	CSF pleocytosis	Exclusion of alternative etiology								
Zuhorn et al. 2021[72]	1	21	Female	ChAdOx1-S	1	5	Headache and progressive neurological symptoms including attention and concentration difficulties	✓	✓	×	×	✓	Normal	✓	✓	Possible	Negative	NA	NA	Diffuse abnormally slow theta rhythms without epileptiform activity	Dexamethasone	Yes	Yes
	2	63	Female	ChAdOx1-S	NA	6	On day 2 developed DVT of left lower limb, and on day 6 developed vigilance disorder and severe immobilizing opsoclonus-myoclonus syndrome	×	✓	×	✓	×	Normal	✓	✓	Possible	Negative	NA	NA	Diffuse abnormally slow theta and delta rhythms without epileptiform activity	IV MP (1 g for 5 days)	Yes	Yes
	3	63	Male	ChAdOx1-S	NA	8	Isolated aphasia, fever, and decreased intrinsic readiness to react (alertness)	×	✓	×	✓	×	Normal	✓	✓	Possible	Negative	NA	NA	Normal	No	NA	Yes
Kwon and Kim 2021[48]	4	57	Female	ChAdOx1-S	NA	6	Generalized convulsive seizure, cognitive decline including attention and memory deficits, and gradually worsening dysphasia	×	✓	×	✓	✓	FLAIR hyperintensities in left insular and mesial temporal cortices with diffusion restriction and contrast enhancement	✓	✓	Possible	Negative	Positive	Limbic	Intermittent generalized rhythmic delta activity	IV MP, IVIg, rituximab	Yes	Yes
Takata et al. 2021[46]	5	22	Female	ChAdOx1-S	NA	NA	Confusion, hallucinations (visual and tactile), and delusion. Known case of nonsyndromic retinitis pigmentosa	×	✓	✓	×	×	Normal	✓	✓	Possible	Negative	Positive	NA	Normal	Symptomatic	Yes	Yes

Table 2. Summary of included studies of SARS-CoV-2-vaccine-associated AIE cases based on current diagnostic criteria for AIE, and the management and clinical outcomes (continued)

Study	Case number	Age (yr)	Sex	Vaccine	Dose	Latency from vaccination (days)	Clinical features	Criteria 1*			Criteria 2				Criteria 3	Diagnostic certainty	Neuronal antibody	CSF OCB	AEACN anatomical classification†	EEG	Tx	Tx response	Sequelae
								Altered sensorium	Working-memory deficits	Neuropsychiatric symptoms	New focal CNS findings	Seizures	MRI suggestive of encephalitis	CSF pleocytosis	Exclusion of alternative etiology								
Shin et al. 2022[47]	6	35	Female	ChAdOx1-S	1	5	Dysarthria, slow activities of daily living, extreme anxiety, severe rigidity in all extremities, catatonia, motor aphasia, jaw-opening dystonia, hypophonia, drooling, and abnormal movements. Patient with known intellectual disability	✓	✓	×	✓	×	Mild swelling of right hippocampus. Chronic encephalomalacia in both frontoparietal lobes	✓	✓	Possible	Negative	Negative	Limbic	Diffuse beta-wave activity, with intermittent generalized delta waves	IV MP, IVIg, rituximab	Yes	Yes
Torrealba-Acosta et al. 2021[52]	7	77	Male	mRNA-1273	1	2	Confusion, fever, generalized rash, headache, dizziness, and double vision, which progressed gradually to severe encephalopathy, myoclonus, and orofacial movements over 5 days	✓	✓	×	✓	✓	Normal	✓	✓	Possible	Negative	Negative	NA	Generalized slow background activity in the theta band, with state changes and reactivity but no sleep features	IV MP (1 g for 4 days)	Yes	Yes
Al-Mashdali et al. 2021[45]	8	32	Male	mRNA-1273	1	2	Agitation, disorientation, confusion, aggressiveness, and forgetfulness	✓	✓	×	×	×	Normal	×	✓	Possible	Negative	Negative	NA	Slowed background activity	IV MP	Yes	No

Table 2. Summary of included studies of SARS-CoV-2-vaccine-associated AIE cases based on current diagnostic criteria for AIE, and the management and clinical outcomes (continued)

Study	Case number	Age (yr)	Sex	Vaccine	Dose	Latency from vaccination (days)	Clinical features	Criteria 1*			Criteria 2				Criteria 3	Diagnostic certainty	Neuronal antibody	CSF OCB	AEACN anatomical classification†	EEG	Tx	Tx response	Sequelae
								Altered sensorium	Working-memory deficits	Neuropsychiatric symptoms	New focal CNS findings	Seizures	MRI suggestive of encephalitis	CSF pleocytosis	Exclusion of alternative etiology								
Walter et al. 2021[51]	9	30	Male	mRNA-1273	2	≈2 months	Generalized malaise and moderate headache, taste disorders, and facial paralysis on the left side	✓	✓	×	✓	×	FLAIR hyperintensities in the brainstem, mesencephalon, and cerebellum and around the fourth ventricle, No contrast enhancement	✓	✓	Possible	Negative	Negative	NA	Slowed background activity	IV MP	Yes	Yes
Flannery et al. 2021[49]	10	≈20	Female	mRNA-1273	1	7	Anxiety, decreased mental acuity, insomnia, hypochondriacal delusions, catatonia, grand mal seizure, and transient aphasia	✓	✓	✓	✓	✓	Normal	✓	✓	Definitive	Anti-NMDAR antibodies	Negative	NA	No abnormality	IV MP, IVIg, rituximab	Yes	Yes
Kaulen et al. 2021[50]	11	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Bilateral hippocampal hyperintensities	✓	✓	NA	NA	Positive	Limbic	NA	NA	NA	NA
Zlotnik et al. 2022[64]	12	48	Male	mRNA-1273	2	~18	Anterograde amnesia, and impairment of temporal orientation, abstraction, and language skills, with hyponatremia	×	✓	×	×	×	Bilateral medial, temporal, and parahippocampal hyperintensities (left>right)	×	✓	Definite	Anti-LGI-1 antibodies	NA	Limbic	No abnormality	IV MP, oral steroids	Yes	Yes
Solís Tarazona et al. 2021[65]	13	28	Female	ChAdOx1-S	1	10	Disorientation, stereotypy, catatonia, and reduced word output	✓	×	✓	×	×	Normal	✓	✓	Possible	Negative	NA	NA	Diffuse slowing	IV MP	Yes	No
Fan et al. 2022[65]	14	22	Male	mRNA-1273	2	5	Fever, blurring of vision, status epilepticus, impaired consciousness, slurred speech, and memory loss	✓	✓	✓	×	✓	Normal MRI. SPECT showed mild hypoperfusion in the right temporal region	×	✓	Possible	Negative	NA	Limbic	Diffuse slowing	IV MP	Yes	No

*Criteria for possible AIE according to Graus et al. in 2016.[9]; †Anatomicoclinical classification for AIE proposed by the Autoimmune Encephalitis Alliance Clinicians Network (AEACN).[8]

AIE, autoimmune encephalitis; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalography; IV, intravenous; IVIg, intravenous immunoglobulin; MP, methylprednisolone; MRI, magnetic resonance imaging; NA, not available/not applicable; NMDAR, N-methyl-d-aspartic acid receptor; OCB, oligoclonal bands.

Epstein-Barr virus, and mycoplasma infection are some of the common infections that have been previously reported as potential triggers of AIE, but most large-scale studies have focused on HSV.[75] The current study has revealed several important aspects of AIE associated with COVID-19 and its vaccines. The demographics of our study showed an adult and male predisposition in the overall AIE group as well as in the definite-AIE and possible-seronegative-AIE subgroups. In the anti-NMDAR-AIE subgroup, males were affected twice as often as females, which contrasts the findings from fairly large-scale observational studies on post-HSE AIE.[10,11] Females predominated among the pediatric and vaccine-associated subgroups. With regards to the clinical aspects, although movement disorders dominated the neurological spectrum in children, ataxia was a more-common manifestation, unlike choreoathetosis, which appears more frequently in post-HSE AIE.[10] The clinical profile in adults was comparable with that of post-HSE AIE. While the onset of neurological symptoms occurred at a median latency of 1 day (IQR=0−12 days) from the diagnosis of COVID-19, the median latency to the relapse or nonremission of neurological symptoms that ultimately led to the diagnosis of AIE was estimated to be 14 days (IQR=4−22 days). There was no significant variation across the subgroups of definite and possible AIE, or of children and adults. The latency to diagnosis was shorter compared with that for post-HSE AIE, which has been estimated to be 4 weeks in children and 6 weeks in adults.[10,11]

Contrast enhancement on brain MRI (3.1%) was a very rare finding in COVID-19-associated AIE, which contrasts the findings of studies on post-HSE AIE.[10,76] CSF analyses revealed lower frequencies of pleocytosis and hyperproteinorachia compared with the post-HSE cohorts.[11] Similar to previous experience with postinfectious AIE, the response to immunotherapy was favorable in cases with COVID-19-associated AIE.[76] Though rare, postvaccination AIE—and particularly anti-NMDAR encephalitis—has been reported in association with H1N1 influenza, Japanese encephalitis, yellow fever, and Tdap-P-IPV (diphtheria and tetanus toxoids and acellular pertussis adsorbed and inactivated poliovirus vaccine) vaccination.[77-80] Although causality could not be established in all of those previously reported cases, a temporal association was found. Most of the patients had sequelae despite management, which is similar to our findings for cases associated with COVID-19 vaccines.

Anti-NMDAR associated encephalitis represents one of the most-studied types of AIE worldwide. In contrast to previous literature, the clinical, demographic, and investigational profiles of COVID-19-associated anti-NMDAR associated encephalitis showed a male preponderance (sex ratio=2:1), along with a lower incidence of psychiatric events (41.6%) and lower frequency of CSF lymphocytic pleocytosis.[81] The incidence of sequelae in these patients (36.4%) was higher than that reported in the case series by Dalmau et al. (25%),[81] review by Barry et al.,[82] and observational study by Saraya et al.[83] reporting similar findings. Lee et al.[84] found a near-equal male-to-female distribution in 37 patients with seronegative AIE. The most frequently reported symptoms were psychosis (86.5%), altered mental state (78.4%), seizures (75.7%), and speech abnormalities (78.4%). In our study, COVID-19-associated AIE had a male predisposition and lower incidence rates of seizures, movement disorders, and psychiatric symptoms. In 12 seronegative cases of AIE, Pradhan et al.[85] found a lower frequency of altered mental state and higher incidence rates of seizures, psychosis, and movement abnormalities compared with our observations of cases with COVID-19-associated seronegative AIE. These differences provide critical insights into the uniqueness of COVID-19-associated AIE, but they require further validation in future large-scale studies.

Proposed pathophysiological mechanisms

We performed a scoping review of various pathogenesis-based studies to identify the probable pathophysiological mechanisms involved in the genesis of AIE associated with COVID-19 (Fig. 3).[86,87]

Systemic infection, cytokine storm, neurotropism, and dysfunction of the blood–brain barrier

The SARS-CoV-2 virus infects the host cell via angiotensin-converting enzyme 2 (ACE-2) receptors and TMPRSS2 (transmembrane protease, serine 2), in conjunction with a plethora of other molecules including basigin, NRP-1, CD-147 (cluster of differentiation 147/basigin/also known as extracellular matrix metalloproteinase inducer [EMMPRIN]), DPP4, ATGR2, ANPEP, cathepsin, and furin.[88-99] The various pathways of CNS invasion include retrograde axonal transport via olfactory mucosa, trans-synaptic transmission across infected neurons, endothelial invasion, direct hematogenous spread to the CNS through blood–brain barrier (BBB)-deficient circumventricular organs, and transport of intracellular virus through infected host immune cells (Trojan horse mechanism).[100-109] A pulmonary SARS-CoV-2 infection leads to the activation of inflammatory cascades, which builds up to a cytokine storm.[110-113] This induces endothelial dysfunction that disrupts neurovascular units, leading to breakdown of the BBB.[110,114-118] Based on experience from SARS-CoV-1 infection and various theories, the involvement of the hypothalamopituitary axis has also been postulated in immune dysregulation.[119,120]

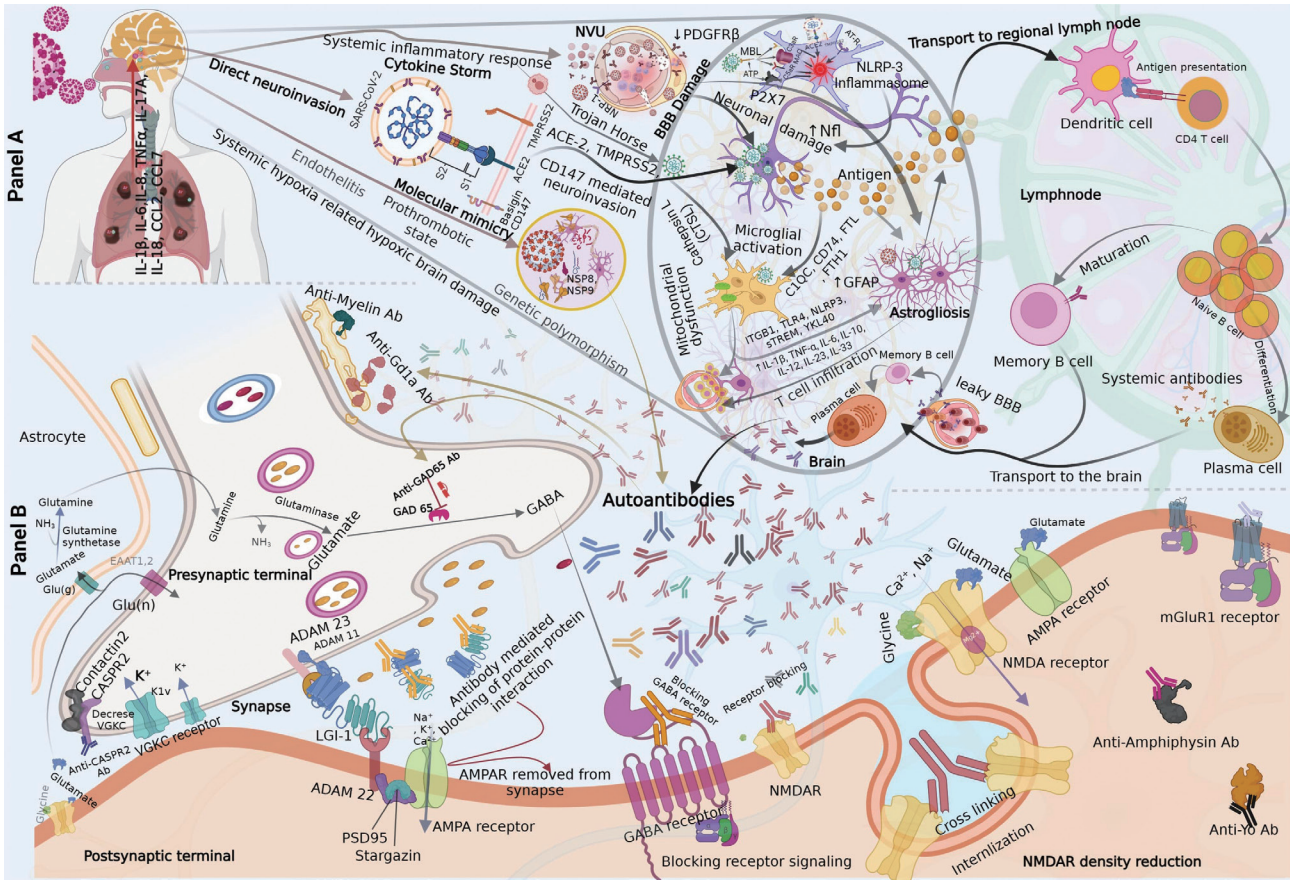

Fig. 3. Proposed pathological process underlying the development of AIE in COVID-19. A: The cytokine storm, neuroinvasion, Trojan horse mechanism, damage to the neurovascular unit, and entry of SARS-CoV-2 into the brain and subsequent neuroinflammation, inflammasome activation, microglial activation, astrogliosis, and ultimately neuronal damage, which in turn leads to intraneuronal substances being exposed of to the immune system. This is followed by the transport of these antigens to nearby lymph nodes and antigen presentation through dendritic cells and T-cell interactions. This ultimately leads to B-cell activation and the formation of memory B cells and plasma cells. Upon reaching the brain, the latter lead to B-cell restimulation, clonal expansion, and differentiation into plasma cells. Finally, autoantibodies are formed against various cell surface and intraneuronal antigenic targets. B: Actions of autoantibodies against various synaptic receptors and intraneuronal targets. Autoantibodies bind to NMDA receptors to cause cross-linking of receptors, disruption of the ephrin-B2 receptor, and interaction with NMDAR. This leads to NMDAR internalization, and then to a decrease in the density of synaptic receptors. After the generation of an action potential, the voltage-gated potassium channels (VGKCs) complex comprising VGKCs (Kv1), LGI-1, CASPR2, and contactin-2 play roles in returning the cell to the resting state. Autoantibodies against LGI-1 decrease the LGI-1–ADAM (a disintegrin and metalloproteinase)23/22 interaction and reversibly reduce the density of postsynaptic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors. Autoantibodies against CASPR2 lead to decreased clustering of Kv1, which leads to a decrease in the neurons returning to baseline after an action potential has been generated.

Microglia activation, astrogliosis, neuronal damage, and autoimmunity

Having entered the CNS, the virus infects the neighboring neurons, oligodendrocytes, astrocytes, and microglia. The viral S1 protein triggers microglia to release an abundance of inflammatory mediators, which lead to activation of the ACE-2 receptor, HIF-1α (hypoxia-inducible factor 1-alpha), NOS (nitric oxide synthase), P2X7 (ATP-activated P2 purinergic receptors), NLRP-3 (NLR family pyrin domain containing 3), and TNF-α (tumor necrosis factor alpha) expression.[119,121-125] The astrocytes start functioning as 'replication hubs' of the virus.[126,127] The exposure of immune-privileged neuronal content to the activated immune system induces the activation of naïve B cells, which differentiate into memory cells and plasma cells. These memory B-cells subsequently enter CNS and undergo restimulation, clonal expansion, and differentiate into plasma cells, which start releasing autoantibodies against the neuronal antigens against the cell surface as well as intracellular targets.[128-131] These autoantibodies in turn interfere with the transmission of neuronal signals and synaptic plasticity, leading to neurological manifestations.[128,130-132]

Molecular mimicry

The structural similarities of the NMDAR GluN1 and Glu-

N2a subunits with SARS-CoV-2 nonstructural proteins 8 and 9, respectively, may induce immune-mediated cross-reactivity to the NMDAR.[133] The autoantibody receptor complexes subsequently activate the downstream pathways leading to alterations at the cellular level, thereby contributing to the wide range of clinical manifestations. Some studies have also highlighted the probable role of genetic polymorphisms, but further research is needed to confirm this.[133-136]

Limitations

Given the rarity of the clinical entity of AIE associated with COVID-19 and its vaccines, our analysis was primarily based on published case reports and series, and hence the findings were susceptible to publication bias. There were few cases of definite AIE, which decreased the power of the statistical analyses. Some of the studies that were purportedly on COVID-19-associated encephalitis were found to instead meet the currently accepted criteria for possible seronegative AIE. Considering the current limitations of antineuronal antibody testing and the possibility of many undiscovered antibodies, we adhered to the currently accepted criteria for diagnosing these cases, and included them in our analyses. However, the possibility of COVID-19-associated encephalitis causing these clinical syndromes could not be completely ruled out based on the current level of understanding. Another potential confounder that should be mentioned is incidental SARS-CoV-2 infection among AIE patients. We considered 2 months as the appropriate cutoff interval for the presence of a temporal association based on previous studies on postinfectious AIE, but the possibility of outliers cannot be completely excluded. Moreover, the current setting of a global pandemic increases the probability of a chance association with COVID-19, which represents a stark contrast to the scenarios underlying previous reports of postinfectious AIE. It is also noteworthy that seroprevalence rates of various antineuronal antibodies in the healthy population have been reported in the literature (Fig. 4).[137]

Conclusion

We attempted to systematically review all of the reported cases in the literature of definite and possible AIE with a temporal association with COVID-19 and its vaccines. To our knowledge, this is the largest aggregation of data on COVID-19-associated and COVID-19-vaccine-associated AIE. This study has revealed that the disease can manifest as a great masquerade, and hence presents critical diagnostic challenges. This review is expected to increase awareness among clinicians about the disease entity, which will facilitate rapid diagnosis, prompt management, and the prevention of sequelae.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.18.6.692.

Availability of Data and Material

All data generated or analyzed during the study are included in this published article (and its supplementary information files).

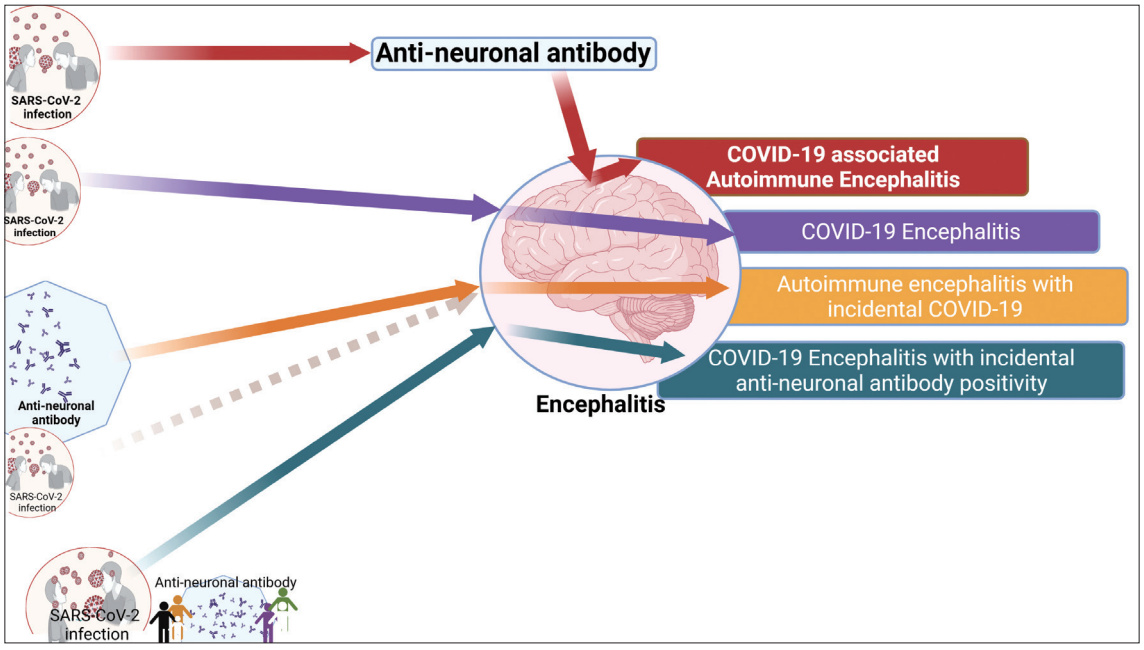

Fig. 4. The spectrum of encephalitis with COVID-19.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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