Journal of Autoimmunity 96 (2019) 24–34

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Prognosticating autoimmune encephalitis: A systematic review

James Broadley[a,*], Udaya Seneviratne[a,b,c], Paul Beech[d,e], Katherine Buzzard[f,g], Helmut Butzkueven[a,f,g], Terence O'Brien[a,g,h], Mastura Monif[a,g,h]

[a] Department of Neuroscience, Monash University, Melbourne, Australia
[b] Department of Neuroscience, Monash Health, Melbourne, Australia
[c] Department of Medicine, St Vincent's Hospital, University of Melbourne, Melbourne, Australia
[d] Department of Radiology, Alfred Health, Melbourne, Australia
[e] Department of Radiology, Monash Health, Melbourne, Australia
[f] Department of Neurosciences, Eastern Health, Melbourne, Australia
[g] Department of Neurology, Melbourne Health, Melbourne, Australia
[h] Department of Neurology, Alfred Health, Melbourne, Australia

ARTICLE INFO

Keywords:
Autoimmune encephalitis
NMDA
Predictor
Prognosis
Outcome

ABSTRACT

Objective: To perform a systematic review of the current scientific literature in order to identify variables associated with patient prognosis in autoimmune encephalitis.

Methods: We performed a systematic literature search using MEDLINE, Embase, PubMed and PsychInfo databases. We selected studies that explored the correlation between early clinical and paraclinical findings, and patient outcomes. Data was extracted, analyzed and recorded in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

Results: Forty four publications detailing 2823 subjects matched our inclusion criteria. There was considerable heterogeneity in methodology, patient profile, investigation results and clinical outcome measures. Findings were often discrepant for cases of anti-NMDAR encephalitis when compared with other causes of autoimmune encephalitis. Delay in immunotherapy contributed to a variety of worse outcomes for patients with different subsets of autoimmune encephalitis. Altered consciousness, ICU admission and no use of immunotherapy were variables associated with poor prognosis in anti-NMDAR encephalitis. Older age, sex, the presence of status epilepticus, CSF abnormalities and MRI changes were unlikely to have significant prognostic value. The influence of antibody titers, autonomic dysfunction and underlying malignancy was unclear.

Conclusions: A number of variables were identified to have potential predictive value for outcomes in autoimmune encephalitis. Heterogeneous study design, size and quality were major limiting factors in this review.

1. Introduction

Autoimmune encephalitis is a rare, debilitating and potentially treatable condition. There are different sub-types of autoimmune encephalitis characterized by antibodies to intracellular antigens (internal part of the synapse, cytoplasmic or nuclear proteins), or extracellular synaptic proteins and cell surface antigens. A large proportion of presumed autoimmune encephalitis cases do not exhibit the known autoantibodies, and are thus named 'sero-negative' autoimmune encephalitis [1]. Some forms of autoimmune encephalitis can start de novo whereas others are associated with an underlying malignancy; the so called paraneoplastic autoimmune encephalitis.

Individuals affected by autoimmune encephalitis usually present with behavioral change, mood alteration, memory and cognitive deficits, seizures as well as movement disorders [1]. During the acute phase of the disease there can be severe disability, and for some the morbidity associated with the illness can persist. Notably, certain subtypes of autoimmune encephalitis have a predilection for younger patients, with otherwise little or no comorbid disease, thus rendering a considerable change in a patient's level of function.

Prognosis is widely variable depending on the subtype, with the best outcomes being reported in patients with cell surface antibodies and poor outcomes are often seen in classic paraneoplastic cases that target intracellular antigens [2]. Even within a subtype, however, there are significant inconsistencies observed in long term morbidity [3–5]. Understanding what factors may influence prognosis is essential in providing an informative perspective to clinicians, patients and families, as well as potentially influencing future treatment decisions.

* Corresponding author. Central Clinical School, Monash University, Level 6 Alfred Centre, 55 Commercial Road, Melbourne, VIC, 3004, Australia.
E-mail address: james.broadley12@gmail.com (J. Broadley).

https://doi.org/10.1016/j.jaut.2018.10.014
Received 28 August 2018; Received in revised form 16 October 2018; Accepted 17 October 2018
Available online 26 October 2018
0896-8411/

A number of observational studies have documented associations between the initial clinical and paraclinical findings, and the patients' outcome. Research articles of this nature have diverse designs, with investigators focusing either on cohorts with a specific antibody or with a single syndrome, such as limbic encephalitis or autoimmune epilepsy. Studies that are designed to look at outcome measures such as mortality, seizure control and cognitive deficits are very helpful, not only in improving our current knowledge regarding autoimmune encephalitis sub-types, but also for the future development of clinical guidelines. However such studies are scarce, and even for comparable research articles the results are frequently conflicting. This forms the basis of this systematic review where we attempt to collate and summarize findings from multiple research publications, and interpret it in a meaningful way.

Research focusing on prognosis is underpinned by three critical aspects: (i) case ascertainment, (ii) defining predictors, and (iii) outcome measures of prognosis [6]. In order to identify markers that have been shown to affect prognosis, we reviewed the published literature focusing on all three aspects of prognosis in patients diagnosed with autoimmune encephalitis.

2. Methods

2.1. Search strategy

We used the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines as the basis for this review [7]. We identified relevant studies by searching abstracts in MEDLINE, Embase, PsychInfo and PubMed databases from their inception to 30/04/2018. Search terms including autoimmune encephalitis, autoimmune antibody subtypes, outcome and prognosis were combined with Boolean operators (Table 1). Furthermore, we searched the reference lists of included publications to identify additional studies undetected in the initial search.

Table 1
A list of the search terms used in MEDLINE, Embase, PsychInfo and PubMed to identify the research studies that were analyzed as part of this study. For inclusion, abstracts had to contain at least one of the search terms from each column.

Encephalitis	Autoimmune encephalitis	Outcome
	Paraneoplastic encephalitis	Prognosis
	Limbic encephalitis	Predict*
	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	
	Hashimoto	
	Anti Neuronal	
	Anti Hu	
	Anti Yo	
	Anti Ri	
	Anti CV2	
	Anti CRMP5	
	Anti Ma	
	Anti Recoverin	
	Anti Tr	
	Anti Ta	
	ANNA-1	
	ANNA-2	
	ANNA-3	
	Anti Purkinje	

2.2. Eligibility criteria

Studies were eligible for this review if they were original research on patients diagnosed with autoimmune encephalitis that provided a statistical analysis of factors that correlated with the patient outcome. We included publications based on cases with features of encephalitis that were suspected or confirmed to have an autoimmune cause. We excluded studies focusing on other antibody associated CNS or non-CNS syndromes, such as paraneoplastic cerebellar degeneration, stiff person syndrome, isolated myelitis or paraneoplastic neuropathy. We also excluded studies that reported such cases in a wider cohort of patients with encephalomyelitis, where the statistics could not be isolated for cases of encephalitis only. Inclusion criteria were English language publications and the availability of full text. Animal studies, grey literature and case studies reporting less than 10 patients were excluded. Studies performed solely in children were also excluded as childhood cases are likely to represent distinct clinical entities when compared with adult cases [8,9]. Finally we excluded studies where autoimmune encephalitis was a subset of a larger study on encephalitis due to multiple aetiologies.

2.3. Data extraction

Each study underwent a detailed review, during which the following details were extracted: number of patients, antibody subset, clinical syndrome, age, sex, abnormal investigation findings, outcome measures, factors tested for outcome correlation and study results. We made particular note of papers that tested early magnetic resonance imaging (MRI) findings and/or cerebrospinal fluid (CSF) characteristics as possible markers for prognosis. The CSF parameters we considered applicable were those identified by routine testing, such as protein, glucose, white cell count, or differential cell counts. We recorded MRI abnormalities likely due to encephalitis, or any MRI abnormality if these details were not specified.

For the most common antibody subtypes we reviewed details on seizure frequency, cognitive impairment, psychosis, underlying neoplasia, immunotherapy, follow-up timeframes and reported outcomes. Reported rates of immunotherapy usage were in the original cohort unless otherwise stated. In papers where there was loss to follow-up, we took reporting of outcomes in the most complete group of patients, even if that follow-up was significantly shorter than the longest follow-up. This was meant to reduce the error in the collection and reporting of data. We used the outcomes that were defined as good or favorable by the study authors, or where patients were left with no or only mild deficits when no definition was given. For studies with an adequate description of relevant outcome data, we noted the patients' median follow-up timeframe, the numbers of patients with follow-up information and the proportion to have a positive outcome. We excluded any information that was unclear or incomplete, in particular noting if it was unclear for the antibody subset of interest. A breakdown of constituent antibodies was documented in studies that included intracellular autoantibodies.

2.4. Study quality evaluation

Included studies were reviewed independently by two authors (JB & US), and classified based on the study design. Where discrepancy was found, consensus agreement was reached. The studies were objectively assessed for quality, using the Newcastle-Ottawa Scale for cohort and case-control studies [10], an adapted version of the Newcastle-Ottawa

Table 2
Matrix used to rate the quality of the studies. Case series were assessed using the tool proposed by Carmen Moga et al., and are scored out of 18 [12]. Cohort and case control studies were evaluated using the respective Newcastle-Ottawa Scales [10]. Cross-sectional studies were evaluated using an adapted Newcastle-Ottawa Scale [11], but used the same thresholds to convert to categorical values.

Case series		Cohort/case-control/cross-sectional
Good	≥14 points	3-4 stars in selection domain AND 1–2 stars in comparability domain AND 2–3 stars in outcome/exposure domain
Fair		2 stars in selection domain AND 1–2 stars in comparability domain AND 2–3 stars in outcome/exposure domain
Poor	< 14 points	1-1 star in selection domain OR 0 stars in comparability domain OR 0–1 star in outcome/exposure domain

Scale for cross-sectional studies [11], and the quality assessment tool for case series proposed by Moga et al. [12]. We characterized each study as having good, fair or poor quality based on the scoring of these quality assessment tools as shown in Table 2.

2.5. Synthesis of results

We found considerable heterogeneity in study designs and populations, and subsequently we focused on describing the results and synthesizing them in a qualitative manner. Using the information obtained from the studies, we calculated average rates of seizure presentations, cognitive impairment, psychosis, tumor diagnoses and immunotherapy usage as well as the average rates of favorable outcomes for the major antibody groups. We evaluated the publications for their most commonly analyzed prognostic markers, and whether or not an association was found. We carefully examined studies for repeated reporting of the same patients on a per variable basis. In studies reporting the same outcome measures in the same patients, the results of the study with the highest quality (or patient number when the quality category is the same) took precedence and the superseded study was discounted from the analysis of that variable. In situations where the patients were the same but the outcome measures were different, we still included both studies. We used information about the target populations, outcomes and quality of each paper to evaluate the prognostic value of each marker. Our final conclusions were based on the findings of the body of evidence, the results of high quality studies and the methodological rigor in key publications.

3. Results

3.1. Search results

Using the search parameters, we found a total of 1411 citations, which adjusted to 753 citations after removing duplicates. After an initial assessment, 497 citations were excluded due to one or more of the following reasons: full text being unavailable, no English translation available or being unrelated to the topic matter. A further 224 studies were excluded after evaluating abstracts as they did not meet our inclusion criteria. A total of 32 studies fulfilled our inclusion criteria through our initial search, and 12 additional papers were added by reviewing the reference lists. This made a total of 44 studies to be included in our final analysis (Fig. 1).

3.2. Study evaluation

In the final analysis, we reviewed 32 case series, 11 cohort studies and 1 cross-sectional study. A total of 2823 patients were described, ranging from 10 to 557 cases per study with a median of 33 cases. The most commonly evaluated clinical entity was anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis in 17 studies, followed by anti-voltage-gated potassium channel (VGKC) encephalitis in nine. Thirteen publications described a mixed group of autoimmune encephalitis with multiple antibody subtypes and two publications examined cases of anti-γ-aminobutyric acid receptor B (GABAb) encephalitis. Quality was generally poor amongst most of the studies with only 5 case series, 5 cohort studies and the sole cross-sectional study fulfilling the criteria of good quality. In depth analysis of each study is provided in an attached Data in Brief article (see Table S1 in Ref. [13]).

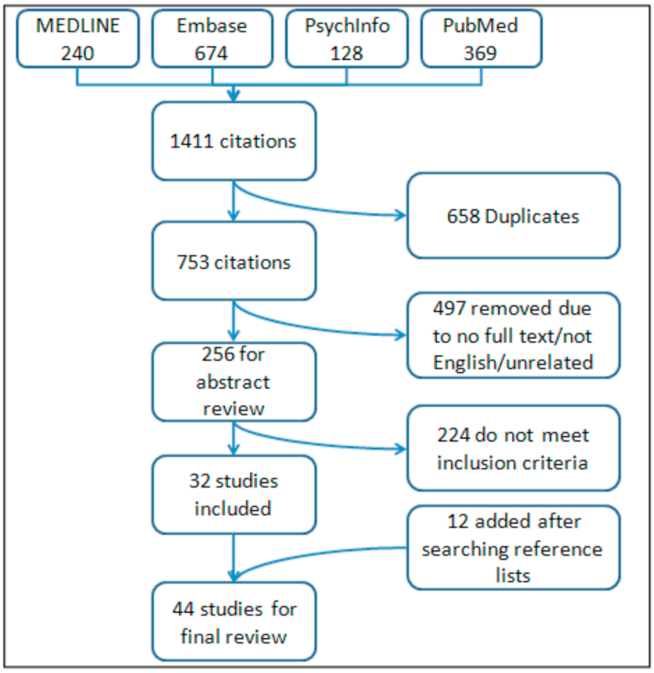

Fig. 1. Study flow-chart.

3.3. Case ascertainment and antibody subtypes

The majority of cases were identified retrospectively, either at the level of tertiary hospital care or specialist referral center following a positive antibody test. There were eight prospective studies [2,8,14–19]. All cases were described based on their symptom onset or acute presentation, and therefore represent incident cases of autoimmune encephalitis. Detailed breakdown analyses of substituent antibodies are provided in an attached Data in Brief article (see Tables 1–4 in Ref. [13]).

3.3.1. Anti-NMDAR encephalitis

There were a total of 1566 cases with anti-NMDAR encephalitis evaluated in 27 studies. Of the associations that were reviewed, seizure was the most common symptom (81.2%), followed by psychosis (70.5%) and cognitive impairment (47%). Tumor associations were relatively uncommon at 22.1% and on average 93.1% of cases received immune modulating treatment. The clinical outcome could be

Table 3
Measures used to assess outcomes in this review.

Category	Measure
Fatal events	Mortality, modified Rankin Scale 6
Nonfatal events	Cognition, first line treatment failure, duration of movement disorders, seizure reduction/remission, mood disorder (Beck Depression Inventory), relapse
Patient-centered events	Functional outcome (modified Rankin Scale, Glasgow Outcome Scale, subjective measures), symptoms
Wider burden	N/A

Table 4
Potential predictive variables and the studies that examine their statistical correlation with patient outcome in autoimmune encephalitis. Numbers in brackets are the numbers of publications examining each variable after adjusting for studies that report the same outcomes in the same patients. Underlined studies identified a relationship with outcome that was opposite to remaining publications in that field.

Variable	Number of studies to look for correlation	Number studies to find correlation	Studies finding correlation	Studies not finding correlation
Age	22 (18)	5 (4)	[20,24–26,51]	[4,8,9,18,19,22,27–30,33,35,36,38,39,44,46]
Sex	19 (17)	2 (2)	[23] [28]	[4,8,18–20,22,24,27,29,30,33,35,36,38,44–46]
Autonomic dysfunction	5 (3)	2 (1)	[39] [28]	[24,29,35]
Altered GCS	6 (4)	3 (2)	[19,24,39]	[29,30,35]
Status epilepticus	5 (5)	0 (0)		[18,19,22,25,31]
Presence of tumor	16 (14)	5 (5)	[9,32–34] [8]	[18,19,22,24,25,28,35–39]
MRS at presentation	2 (2)	0 (0)		[18,38]
High MRS at nadir	3 (2)	1 (1)	[35]	[8,39]
Antibody titre	6 (6)	3 (3)	[40,41] [26]	[42–44]
CSF abnormality	14 (11)	3 (3)	[22,24] [45]	[14,18,19,28–30,33,35,36,38,46]
MRI abnormality	14 (11)	2 (2)	[18,47]	[19,22,24,28–30,33,35,36,38,46,52]
Use of immunotherapy	8 (8)	4 (4)	[8,36,37,48]	[19,20,22,30]
Delay in immunotherapy	20 (16)	14 (12)	[8,17,22,27,28,33,34,37,43,45,46,50–52]	[19,30,35,38,39,44]
ICU admission	5 (4)	3 (2)	[8,19,51]	[30,35]
Mechanical ventilation	3 (3)	0 (0)		[19,24,47]

Table 5
Conclusions drawn from the data obtained in this review regarding possible correlations with outcome in autoimmune encephalitis due to any antibody and in anti-NMDAR encephalitis. Relationships are described as being likely, possible, unlikely, inconclusive or not sufficiently studied.

Association with poor outcome in		
Variable	Autoimmune encephalitis	Anti-NMDAR encephalitis
Age	Unlikely	Unlikely
Sex	Unlikely	Unlikely
Autonomic dysfunction	Inconclusive	Not sufficiently studied
Altered conscious state	Unlikely	Possible
Status epilepticus	Unlikely	Unlikely
Presence of neoplasm	Inconclusive	Unlikely (may have positive influence on remission)
MRS on presentation	Unlikely	Not sufficiently studied
MRS nadir	Possible	Unlikely
Antibody titer	Inconclusive	Inconclusive
CSF abnormalities	Unlikely	Inconclusive
MRI abnormalities	Unlikely	Unlikely
Use of immunotherapy	Not sufficiently studied	Likely
Delay in immunotherapy	Likely	Likely
ICU admission	Not sufficiently studied	Likely
Mechanical ventilation	Not sufficiently studied	Unlikely

ascertained in 22 studies representing 1294 patients. A good outcome was demonstrated in 72.6% of cases, depending on the study and follow-up timeframe. A definition of a good outcome is described in Section 3.2 of the methods.

3.3.2. Anti-VGKC encephalitis

Twenty-two studies reported a total of 430 cases of anti-VGKC encephalitis. This number was inclusive of cases with VGKC complex antibodies; LGI1 and CASPR2. Rates of seizures were high amongst this cohort (90.2%) as was cognitive impairment (78.5%). Associations with psychosis and underlying malignancy were relatively uncommon (21.8% and 13.7% respectively). Immunotherapy usage was also high in this group (97.7%). The outcome of 249 patients across 14 studies was described, with an average of 83.7% achieving a good clinical outcome.

3.3.3. Anti-GABAb encephalitis

Anti-GABAb encephalitis was a relatively rare entity amongst the studies, with 38 cases reported across eight studies. A single patient was described as having co-existing anti-Hu antibodies [18]. Seizures were very common amongst this group (94.4%), while cognitive change and psychosis were less frequently found (63.6% and 51.3% respectively). Underlying tumor associations were found in 37.3%. Six publications described outcomes in these cases, totaling 34 patients. On average, 67.4% had positive outcomes.

3.3.4. Autoimmune encephalitis with antibodies to intracellular antigens

Cases of autoimmune encephalitis associated with intracellular antibodies are a relatively diverse cohort. In total, this group accounted for 90 cases across 12 studies. The included antibodies and number of cases are as follows: 55 Ma2 (18 with co-existing Ma1 and 6 with Ta), 14 Hu, 11 amphiphysin, 4 Yo, 4 CV2, 1 Ri, and 1 described as atypical. Psychosis was relatively uncommon amongst this group (33.3%), while rates of patients with seizures (69.1%) or cognitive impairment (71.3%) were similar. Unsurprisingly, tumor diagnoses were the most common in this group (43.6%). Of these studies that described immunotherapy usage, only one had less than 100% immune treatment rates [20]. A number of patients in this study received cancer treatment (34.2%). Adequate follow-up information was available for 73 patients in nine studies. Of these, the prognosis was generally poor with only 45.6% achieving a good clinical outcome.

3.4. Outcome measures

We classified outcomes as being fatal events, nonfatal events, patient-centered events or those with the wider burden as shown in Table 3 [21]. The majority of articles (26 studies) evaluated outcomes using the Modified Rankin Scale (MRS), however there was some variability as to how these results were interpreted. The MRS is recorded as follows: 0 – no symptoms, 1 -minor symptoms but no disability, 2 -symptoms that results in disability preventing premorbid activities but allowing independent living, 3 - disability that prevents completely independent living but able to walk independently, 4 -

disability that prevent independent mobilization but can walk when supervised, 5 - bed bound and fully dependent for all care, 6 – dead [22, Supplemental Table E1].

The MRS was reported either as a continuous value, or dichotomized as good versus poor outcomes. Rarely, the MRS was evaluated by an incremental increase or decrease. Functional outcome was the focus of three other studies, which used different standardized or non-standardized tools to assess this. The cognitive outcome was the next most frequently measured variable (7 studies), followed closely by the seizure outcome (6 studies). Mortality was measured inconsistently amongst these papers; either as an MRS of 6, and therefore included as a poor outcome, or evaluated in its own right. Death was the sole outcome measured in two publications. Only one study examined the long term effects on psychiatric outcomes [23]. While Chi et al. recorded each patient's results on the Zung Depression and Anxiety Scales, these results were not used in their final analysis as the major outcome of interest was mortality [19]. No study evaluated the self-reported quality of life assessments.

3.5. Predictor variables and their association with outcome

Table 4 shows 15 of the most commonly referenced factors that were tested for patient outcome. Although the use of second line immunotherapy was a frequently tested prognostic marker, we excluded this from our analysis as there is insufficient data and variability in indications for second line therapy. Patients may be prescribed further therapy for a variety of reasons including; failure of first line treatment, ICU admission, high MRS on presentation, or even clinician preference. Given this variability, the use of second line agents as a marker of prognosis was excluded. Our conclusions are summarized in Table 5. Anti-NMDAR encephalitis is described separately due to the large number of dedicated studies and frequently polarized results.

3.5.1. Age

Age featured in 18 studies and therefore the most commonly reviewed factor, but only four of these found a relationship with outcome [20,24–26]. This variable was examined either continuously or as categorical values of younger or older age groups. We noted amongst the latter some variability of the age cut-off defining the older age group, but most commonly described as 60 years. We assessed the quality of five publications to be good, all of which found no association with prognosis [8,18,27–29]. One study in the no correlation group was found to have fair quality and the remainder were poor. Functional outcome was the most commonly assessed and was featured in 12 studies, four of which represented the publications that found an association between patient outcome and older age.

There was a discrepancy in the number of cases with intracellular antibodies between the two groups (38 with association vs 17 without). We found that the sole publication reported exclusively in such patients was amongst the studies that identified a correlation between older age and worse outcomes [20]. We also found that amongst encephalitis cases with intracellular antibodies there was a discrepancy in reported rates of cancer diagnoses between the groups (34 of 38, 89.5% in correlation group; 3 of 7, 42.9% in non-correlation group).

3.5.2. Sex

Seventeen studies evaluated the influence of sex on the outcome. While two of these identified a correlation, their results were conflicting. Von Rhein et al. examined 28 patients who were treated with immunotherapy for suspected antibody negative autoimmune limbic encephalitis [23]. After a median follow-up of 18 months (+/- 17 months), executive function recovery was more common amongst females than males ($p = 0.004$). However, there were only 3 patients in the cohort that demonstrated any such recovery. We also note that screening for alternate diagnoses, such as CNS infection, was not part of the study protocol.

Another case series reviewed 77 patients with suspected autoimmune epilepsy who received treatment with immunotherapy [28]. The authors defined immunotherapy responsiveness as > 50% seizure reduction. The study found that on univariate analysis immunotherapy response appeared to be more common amongst males ($p < 0.05$), but results of their multivariate regression analysis were not given.

3.5.3. Autonomic dysfunction

There were three publications that searched for a correlation between autonomic instability and outcome [24,28,29]. Only one of these studies did find an association, but their results were contrary to expected. Dubey et al., as discussed above, found that autonomic dysfunction was associated with responsiveness to immunotherapy both in their univariate ($p < 0.01$) and multivariate regression ($p < 0.05$) analyses [28]. It is possible that this cohort contained some cases that did not actually have an autoimmune etiology and autonomic dysfunction was a specific finding associated with true autoimmune epilepsy, therefore explaining why these cases responded to immunotherapy. The publications that found no relationship with the outcome all examined MRS in cohorts of either anti-NMDAR encephalitis or mixed antibody profiles. Only one of these studies was of good quality [29].

3.5.4. Altered conscious state

Four publications performed analysis on altered conscious state as a possible prognostic factor [19,24,29,30]. However, only one of these studies gave a definition of altered conscious state [19], where coma was regarded as Glasgow Coma Scale ≤8. The two studies that identified a correlation were both focused on cases of anti-NMDAR encephalitis and were of poor quality. Wang et al. reported MRS outcomes of 51 cases to be correlated with poorer functional performance at a median of 12 months ($p = 0.019$) [24]. Mortality was the outcome of interest for the final study, which found that after an average of 24.5 months coma was associated with a higher risk of death in their multivariate analysis ($p = 0.015$) [19]. In contrast, the studies that did not find a correlation all examined MRS outcomes in cohorts containing cases of encephalitis with variable antibody results. Quality was good in one of these publications [29].

3.5.5. Status epilepticus

Of the five studies that evaluated for an association between status epilepticus and outcome, none of them identified a correlation [18,19,22,25,31]. While most of these were looking at functional outcomes, only one was evaluating the seizure outcome. Among their 41 cases with autoimmune encephalitis with mixed antibody profiles, Byun et al. found that while patients with status epilepticus were less likely to achieve seizure remission at 2–4 weeks after initial treatment, this correlation appears to disappear at the 6-month mark [18]. On review, only 5 patients in their cohort had status epilepticus, which corresponded to a relatively higher percentage of the non-remission compared to remission group (18.2% vs 10%), but this failed to reach statistical significance.

3.5.6. Presence of an underlying neoplasm

Our review identified 14 studies that examined the effect of a tumor diagnosis on prognosis [8,9,18,19,22,24,25,28,32–37]. Five of these found that the presence of a tumor was correlated with worse functional, seizure and mortality outcomes. One retrospective study found that among 64 cases of autoimmune encephalitis, improvement in the patients' major symptom was more commonly seen in patients without an underlying malignancy ($p < 0.05$) [34]. This outcome measure utilized objective and subjective measurements to show this improvement depending on whether the outcome of interest was seizure, cognitive impairment, behavioral change or movement disorder. It was unclear, however, the methods used to determine what the major symptom was for each patient. In a separate publication, Dubey et al.

identified 34 patients with autoimmune epilepsy that were hospitalized for seizures [33]. They evaluated the response rate to immunotherapy as defined by a 50% reduction in seizures after a median of 53.5 days. The authors found that patients with underlying malignancy had a lower response rate ($p < 0.05$).

Another series reviewed cases of anti NMDAR encephalitis of different age groups and followed their MRS outcomes at six months [9]. They found that amongst female patients, those with ovarian teratoma had higher MRS scores on follow-up. We note, however, that more severe symptoms were only demonstrated in three patients. Irani et al. examined 29 cases of Morvan syndrome, 26 of which had demonstrable antibodies to the VGKC complex [32]. Twelve patients in this cohort were found to have a tumor, but 91.7% of these were thymoma with consequently high rates of myasthenia gravis (81.8%). The authors found that the presence of tumor was associated with higher rates of mortality ($p = 0.0016$). In this group, however, at least half the cases of death may have been attributed to myasthenia gravis. Another study reported a very large prospective analysis of 577 patients with anti-NMDA receptor antibodies [8]. They found that while tumor was not significantly associated with MRS outcomes ($p = 0.57$), those that had underlying malignancy were, in fact, less likely to have clinical relapse within the first 24 months ($p = 0.0007$).

Of the 11 studies that found no association with outcome, five only included cases of anti-NMDAR encephalitis [19,22,24,36,37]. In this group, seven studies evaluated MRS, two examined seizure and the remaining two studies looked at relapse and mortality rates. The publications that examined tumor were generally of poor quality. The exceptions were two studies that found an association with outcome [8,34] and three amongst those that did not [18,28,35], all of which were good quality.

3.5.7. MRS on presentation/MRS nadir

There were only two studies that reported an analysis of the association between presenting MRS and outcome [18,38]. Both studies were performed in cohorts of encephalitis with mixed antibody profiles and used a cut-off of severe functional disability on presentation of MRS ≥ 4. There was no significant relationship with seizure remission at 6 months ($p = 0.795$) [18] or MRS improvement at 4 weeks ($p = 0.068$) [38]. In the latter publication, there was a trend for immunotherapy unresponsiveness in the group with high MRS on presentation (66.7% vs 30%), but this was deemed insignificant within the power of the study.

Peak functional disability was examined by three studies [8,35,39], but only one identified a significant correlation [35]. This cohort consisted of 161 cases of autoimmune encephalitis, equally divided based on whether each patient received second line immunotherapy with rituximab. The authors examined two types of functional outcomes; a favorable MRS defined as values 0–2, and an improvement in MRS as defined by its decrease by at least one point during the follow-up period. The whole cohort underwent statistical analysis for predictors of outcome. They found that while an MRS ≥ 4 at worst neurological status had little correlation with future MRS improvement ($p = 0.655$), their multivariate analysis revealed this variable to have a significant relationship with unfavorable MRS outcomes ($p = 0.037$). Conversely, Titulaer et al. found that in their series of 577 anti-NMDAR encephalitis cases, the relationship between maximum MRS and 24 month functional outcome was insignificant (multivariate analysis, $p = 0.51$) [8]. An analogous, albeit smaller, study with a shorter follow-up of 4 months reported similar findings, although they did not provide their statistics [39].

3.5.8. Antibody titers

There were six publications to evaluate the correlation between outcome and initial antibody titer [26,40–44], but only three of these found a relationship [26,40,41]. Five studies were isolated to cases with cell-surface antibodies, with publications on anti-NMDAR encephalitis and anti-VGKC encephalitis divided on whether a relationship with outcome exists. Of those that did not find a correlation the quality was generally higher, with two of good quality [42,43] and one fair [44]. The publications that found an association, however, were all of poor quality. A description of the origin of the titer, serum or CSF, was provided in all studies except one [41]. Regarding outcome measures, cognition was represented in all publications with two exceptions, which examined MRS [40] and Glasgow Outcome Scale [26]. Two publications also reviewed MRS outcomes [42,43], while another study documented relapse rates [44].

One series studied 45 cases of anti-NMDAR encephalitis with serial serum and/or CSF analysis and reviewed their MRS outcomes after a median of 26 months [40]. Among patients with a monophasic illness, the authors found a correlation between both serum and CSF, and the ultimate outcome. While the association with CSF titers barely reached statistical significance ($p = 0.049$) and had overlapping confidence intervals (75–211 vs 158–735), a much stronger association was identified with serum titers ($p = 0.0025$). It was unclear in their methods, however, whether these relationships were identified with initial samples or included an average of the serial titers. A different retrospective study reviewed the cognitive outcomes following anti-VGKC limbic encephalitis in 19 cases [41]. With an interval of 254 days between assessments, the authors found that higher antibody titers on presentation were associated with worse verbal memory scores on follow-up ($p = 0.039$). Litmeier et al. reported a retrospective analysis of 11 cases of Steroid-Responsive Encephalopathy associated with Autoimmune Thyroiditis (SREAT) [26]. The authors determined that higher serum thyroid peroxidase (TPO) antibodies correlated with better functional outcomes at a median of 11 months ($p = 0.03$); an outcome that was contrary to other positive findings in this field.

3.5.9. CSF/MRI findings

12 publications included CSF and/or MRI findings as part of their analysis [18,19,22,24,28–30,33,36,45–47]. There were only three studies that found an association between abnormal CSF and long term outcome. One retrospective series examined 51 cases of anti-NMDAR encephalitis and reviewed their functional outcome by MRS after a median of 12 months [24]. On univariate analysis, the authors found a correlation between abnormal CSF and a poor outcome, but this barely reached significance with a p-value of 0.049. The results of their multivariate regression analysis were not described. A separate study reviewed a group of 72 cases that received immunotherapy for dementia on the basis of having a possible autoimmune etiology [45]. Pre and post treatment cognitive domains were assessed, and the resultant cohort outcomes classified the cases as being either responders or non-responders. The authors, in fact, found a strong correlation between abnormal CSF and better cognitive outcomes ($p = 0.02$). The likely explanation for this is that the selection criteria for autoimmune dementia in this paper lacked specificity, and therefore a response to immunotherapy was identifying patients with a truly inflammatory etiology to their cognitive impairment. This is demonstrated by a lower than expected rate of abnormal investigations in the cohort (CSF 28%, MRI 22%, EEG 18%), as well as by four patients who were considered immunotherapy responsive, but had a pathological diagnosis of Alzheimer's disease. Finally, de Montmollin et al. found that amongst cases of anti-NMDAR encephalitis requiring ICU admission, higher CSF white cell counts were associated with worse MRS values at 6 months [22]. A CSF white cell count > 50 cells/mm^3 was used as the reference for this analysis, with statistically significant p-values found when compared to cell counts of 5–50 cells/mm^3 and < 5 cells/mm^3 ($p = 0.03$ and 0.04 respectively). All three of these papers were of poor quality. There were eight studies that found no association between CSF findings and outcome [18,19,28–30,33,36,46]. Of these, quality was assessed to be poor in five and good in three. Two publications in this group reported cases of anti-NMDAR encephalitis, while the remainder examined encephalitis with a mixture of antibody profiles. The outcomes of the

studies are summarized as follows: two MRS, four seizure outcomes, and one each for relapse and mortality rates.

Two studies found an association between MRI findings and patient outcome. Byun et al. reported a case series of 41 patients with autoimmune encephalitis [18]. They found that in their cohort a normal MRI on presentation was associated with seizure remission at 6 months ($p = 0.036$). While this case series was of good quality, it is unclear, however, whether the authors included faciobrachial dystonic seizures (FBDS) in their grouped analysis of seizure outcomes. As a typically early manifestation of LGI1 encephalitis, MRIs are often normal and patients usually respond well to immunotherapy [17,27]. Another retrospective series described the MRS outcomes of 15 patients with anti-NMDAR encephalitis after a median of 68 months [47]. They found that the development of cerebellar atrophy on subsequent MRIs was negatively correlated with outcome ($p = 0.01$). While initial MRIs were recorded, these investigations were used as baseline measures only in order to identify brain atrophy in the subsequent 1–2 months. Notably, only two patients in this case series had cerebellar atrophy and a poor outcome.

A total of nine studies found no association between MRI changes and outcome [19,22,24,28–30,33,36,46]. MRS was the reported outcome in four studies, while three examined seizure rates, and one each described relapse and mortality outcomes. Several different encephalitic illnesses were studied, including four publications on anti-NMDAR encephalitis and five included cases with a mixture of different antibody profiles.

3.5.10. The use of immunotherapy

We found eight studies that examined whether the use of any immunotherapy affected outcomes [19,20,22,30,36,37,48], and four of these found an association. Twenty five cases of anti-NMDAR encephalitis were described in one series, which found that after a median follow-up of 20 months relapse rates were higher amongst those that did not have immunotherapy in their first episode ($p = 0.009$) [36]. In a similar series of 44 patients with anti-NMDAR encephalitis, it was found that among cases without tumor those that did not receive immunotherapy or had delayed treatment had significantly worse MRS scores ($p < 0.0001$) [37]. Lancaster et al. reported 15 cases of anti-GABAb encephalitis [48]. The authors found that after a median of 6 months follow-up, the four patients who did not have immunotherapy did not demonstrate any neurological improvement compared to 90% of those that did have such treatment ($p = 0.005$). Neurological improvement was defined in the study by their ability to live independently or with little assistance. While non-standardized, this measure would correlate to MRS values of 0–3. A series of 577 cases found that patients that had immunotherapy during the first episode of anti-NMDAR encephalitis were less likely to have relapses within the first two years of follow-up ($p = 0.038$) [8]. MRS outcomes were not examined for a correlation. Notably, all of these papers only reviewed cases with encephalitis associated with cell-surface antibodies.

Among the studies that found no association between the use of immunotherapy and outcomes, one series reported cases of autoimmune encephalitis of any antibody profile [30]. They found that during their median follow-up period of 31 months the use of immunotherapy was not significantly different between those that had good and poor MRS outcomes ($p = 0.16$). We note that a trend for more immunotherapy uptake existed in the group with favorable MRS scores (89.5% vs 64%). Also, nearly half their cohort was considered probable autoimmune encephalitis, but the criteria used to define this population were unconventional compared to more frequently referenced recommendations [49]. A retrospective study from 2004 found that immunotherapy was not significantly correlated to higher rates of neurological improvement or stabilization, as defined by change in MRS scores [20]. Their cohort consisted of 38 patients with anti-Ma2 associated encephalitis, and represents the only study in this review dedicated towards cases of encephalitis with intracellular antibodies. Rates of immunotherapy usage were lower in those with neurological deterioration, but this failed to reach significance (53.3% vs 77.8%, $p = 0.13$). Chi et al. found that among their series of anti-NMDAR encephalitis, mortality rates were not significantly different in patients that did not receive immunotherapy ($p = 0.673$) [19]. In fact, all patients who died had received some type of immunotherapy. Finally, another publication also failed to find a significant difference in immunotherapy usage between those with good and poor MRS outcomes following ICU admission for anti-NMDAR encephalitis ($p = 0.85$) [22]. Immunotherapy usage was very high in this series with 97.4% receiving immune treatment of some kind. Among publications in this category, only one met the criteria of good quality [8].

3.5.11. Time to immunotherapy

Most studies within this category evaluated the influence of delay in immunotherapy from symptom onset. However, two series evaluated the time from admission to immunotherapy [19,22]. Four studies found no association between time to immunotherapy and outcomes [19,30,35,44]. Of these, we determined quality to be poor in two, fair in one and good in one. The latter found that in their cohort of 161 autoimmune encephalitis cases there was no association between time to first line immunotherapy and either improvement in MRS or a favorable MRS during the follow-up period of around 2 years ($p = 0.982$, 0.560 respectively) [35]. We note that the mean time to treatment was 7 months, with 48.8% of cases receiving therapy within the first month. This suggests that there were cases in the cohort with a very long time to treatment. Much wider standard deviations are found in time to treatment in groups with improved and favorable MRS at follow-up than those without, suggesting the aforementioned cases are amongst these groups. Should such cases be removed from analysis, mean time to treatment of these groups would be significantly shorter.

The 12 studies that found an association between early immunotherapy and better outcomes were generally of better quality with six rating good [8,17,27,28,34,43], one fair and seven poor [22,33,37,45,46,50]. Among the high quality publications, there was a cross-sectional analysis of cognitive deficits in 30 cases of anti-LGI1 encephalitis [43]. At a median of 23.3 post onset they found that delay in immunotherapy was significantly correlated to worse verbal and visuospatial episodic memory scores ($p = 0.02$, 0.03 respectively). MRS outcomes were not analyzed for this association. Two studies reported similar case series consisting of 103 and 10 cases of VGKC-complex associated faciobrachial dystonic seizures respectively. They found that delay in immunotherapy was significantly related to worse cognitive ($p = 0.02$) [17] and MRS scores ($p = 0.031$) [27] at 18–24 months. Titulaer et al. found that time to treatment was associated with both 24-month MRS scores ($p < 0.0001$) and failure of first line therapy ($p < 0.005$) in a large series of anti-NMDAR encephalitis cases [8]. One author reported two case series consisting of patients with autoimmune encephalitis. The findings included more seizure reduction in patients where treatment was commenced less than six months after symptoms ($p < 0.01$) [28], and greater improvement in the patients' major symptom when therapy was expedited ($p = 0.001$) [34].

3.5.12. ICU admission/mechanical ventilation

We found four papers that investigated ICU admission as a prognostic marker [8,19,35] and two of these found an association with poorer outcome [8,19].MRS was the outcome of interest in all but one publication [19]. Of note, the two studies that found an association focused on patients with anti-NMDAR encephalitis only. One publication found that admission to ICU was associated with both an unfavorable MRS at last follow-up and increased the likelihood of relapse within 2 years (multivariate analysis, $p < 0.0001$ for both) [8]. A prospective case series reported mortality rates amongst 96 patients with anti-NMDAR encephalitis and found on multivariate analysis that ICU admission was correlated with an increased risk of death ($p = 0.014$) [19].

A different series reviewed 161 patients with autoimmune limbic encephalitis [35]. While ICU admission was associated with an unfavorable MRS score in the univariate analysis (p 0.02), this association disappeared in the multivariate analysis (p = 0.383). Critical care also did not correspond with failure to improve MRS (p = 0.819). We note that there was a trend for higher rates of ICU admission among patients that received rituximab compared to those that did not (33.8% vs 18.5%). While this discrepancy was not significant, the authors did find that rituximab was associated with more MRS improvement (p = 0.011) and better outcomes among patients that did not respond to first line immunotherapy (p = 0.001).

Three studies examined the influence of mechanical ventilation on the outcome, all of which involved cases of anti-NMDAR encephalitis [19,24,47]. The outcomes examined were MRS and mortality. No correlation was found, although the quality was poor in all three.

4. Discussion

This review presents a qualitative analysis of prognostic factors in autoimmune encephalitis across a wide variety of different studies. Although the results were frequently conflicting, we were able to draw several important conclusions. Firstly, based on the quality and body of evidence in support, delay in immunotherapy commencement remains an important prognostic factor. Studies that did not show this relationship tended to be smaller and of lower quality. Within the constraints of this study, we also demonstrated a trend for both ICU admission and altered conscious state affecting medium-to-long term outcomes in anti-NMDAR encephalitis. Interestingly, we found that age, status epilepticus during admission or the diagnosis of an underlying neoplasm did not appear to demonstrate a strong relationship with patient outcomes. The same is true for early CSF and MRI abnormalities.

The results of our review indicate that patient demographics appear to have little association with outcome in many forms of autoimmune encephalitis. While this finding may have been unsurprising when considering sex, it is the weight of evidence against older age as a predictive factor that is most perplexing. There are several possible reasons why this association did not emerge. Firstly, age was assessed as either a continuous value or dichotomized into younger and older age groups. This may have a profound effect on statistical analysis depending on the age predilection for the studied antibody, the age cutoff used and how many cases are identified in either category. For example, two studies in the same population of patients found differing results. One study used an age cutoff of 45 years and found that worse MRS outcomes can be seen in older cases of anti-NMDAR encephalitis ($p < 0.026$) [51]. The other examined age both as a continuous variable and using a cutoff of 18 years, and found no correlation with between age and outcome in either circumstance [8]. Secondly, we found that the majority of relevant studies examined the functional outcome in the form of MRS. While an important outcome, especially amongst the elderly, it is possible that associations may exist with older age when outcomes such as death or cognition are considered. Thirdly, we postulate whether advanced age may contribute to worse outcomes only in paraneoplastic cases of autoimmune encephalitis. Certainly, we demonstrated that amongst cases with intracellular antibodies, malignant diagnoses were more common in the publication that did find an association compared with the studies that did not.

Regarding clinical factors, our results concerning autonomic dysfunction as a predictive factor of patient outcome were inconclusive. A major factor limiting this determination is the small number of studies. One study in this review did find that autonomic instability was associated with worse MRS scores among 32 patients with anti-NMDAR encephalitis, however these results were discarded from analysis as these patients were also reported in another study of the same category [39]. We also note that no study described whether autonomic instability was symptomatic, and the severity of autonomic dysfunction could still be of prognostic significance. All the studies that identified a correlation between impaired conscious state and poor outcome were performed solely in cases of anti-NMDAR encephalitis. There are potentially two factors that may contribute to ambiguity when assessing these results. Firstly, we found that altered consciousness was poorly defined, with only one study describing it as coma with a Glasgow Coma Score less than eight [19]. We recognize that impaired conscious state exists on a spectrum, with coma at one extreme and mild confusion at the other. It is possible that by following this definition, robust associations with long term outcome may emerge that might go otherwise unnoticed. Secondly, we have found through our own experience that coma in cases of autoimmune encephalitis may be due to seizure activity, increased intra-cranial pressure or the inflammation itself. Perhaps delineating the nature of the loss of consciousness is as important in prognosis as the symptom itself. On that note, within the limits of this review we also found no correlation between the presence of status epilepticus during admission and outcomes. Interestingly, only one of the studies evaluated seizure outcomes [18]. In our experience, we have found that it is the commencement of immune therapy that results in seizure remission in such patients, not the use of anti-epileptic agents. It is possible that status epilepticus, in fact, promotes clinicians to vigorously investigate patients, ultimately leading to earlier diagnoses and immune modulating treatment. To our knowledge, no study exists that compares time to diagnosis and immunotherapy commencement in cases with and without status epilepticus.

While we were expecting to find that underlying malignancy to lead to worse outcomes, our results suggested such an association was unconvincing. In fact, our data on anti-NMDAR encephalitis not only refuted this claim, but proposes that tumor diagnoses may be associated with lower rates of relapse in this cohort [8]. We feel that any association may be far more complicated than this. For instance, removing the source of the immune phenomenon likely plays a significant role in neurological outcomes, and in paraneoplastic cases that means complete removal of the underlying neoplasm. For certain types of malignancy, rates of cancer remission are much lower than others. This is an important consideration when discussing anti-NMDAR encephalitis, as ovarian teratoma is considered relatively treatable by surgical resection. We also acknowledge another phenomenon whereby the onset of paraneoplastic syndromes may unveil an underlying neoplasm of a relatively early stage, thereby increasing the success of oncological treatments. Functional assessment, both on presentation and at the disease nadir, was a relatively under-studied prognosis variable. One study found that while severe disability at the height of illness was associated with unfavorable MRS outcomes, rates of functional improvement were no different between the groups [35]. This might suggest that all patients, regardless of peak severity, are likely to experience a similar degree of functional improvement from this nadir. We also postulate that premorbid function may predict patient outcomes. While it may seem self-explanatory that the MRS is unlikely to improve beyond that patient's functional baseline, it is possible that a degree of disability before disease onset contributes to other outcomes such as mortality or cognition. No study in this review examined this variable.

Regarding variables identified by investigation findings, we were unable to discern any pattern of association between antibody titers and outcomes. We note that cases that evaluated this group were largely limited to autoimmune encephalitis with cell surface antibodies, and this highlights an important point. While future studies may be able to clarify if a correlation exists, its applicability may be limited by local laboratory practice. For example, reference laboratories may test for anti-NMDAR antibodies by immunofluorescence and titers cannot be determined. This also may explain the paucity of studies examining the effect of intracellular antibody titers. In addition, this variable will have no applicability in cases of antibody-negative autoimmune encephalitis. CSF and MRI abnormalities were variables that were extensively studied, but their association with prognosis was unconvincing. There was

some ambiguity with regards to the influence of CSF abnormalities in anti-NMDAR encephalitis, but this may be due to how this variable was analyzed. For example, while one study did find a strong correlation between lower CSF white blood cell counts and better functional outcomes, the comparator group for this analysis was a cell count in excess of 50 cells/mm^3 [22]. However, most other studies simply define the CSF as being either inflammatory or non-inflammatory, thereby using a cutoff of 5 cells/mm^3. Therefore our review suggests that any correlation between abnormal CSF and outcomes may be limited to cases of anti-NMDAR encephalitis with marked CSF leukocytosis. Similar methodological considerations apply when examining CSF protein count. We also note, however, that the vast majority of publications on this subject reviewed MRS outcomes only, leaving other types of outcomes relatively under-studied. Regarding MRI variables, we again note a paucity of definitions of what is considered abnormal. Specifically, most of the included studies did not describe whether the abnormalities were likely due to encephalitis and not another unrelated condition. MRI interpretation is also observer-dependent, and subtle changes can easily be missed. While this problem is unavoidable, we suggest that it may be minimized by reviewing all scans with a dedicated MRI neuroradiologist or by automated analysis packages. Interestingly, one case series was able to identify several correlations between medial temporal lobe hypermetabolism on FDG-PET and their outcomes [52]. The absence of metabolic changes was correlated with both lower MRS scores ($p = 0.02$) and the achievement of MRS 0 ($p = 0.02$). In patients with lesions, unilateral lesions performed better in both these outcome measures when compared to bilateral lesions ($p < 0.001$ and $p = 0.001$ respectively). No such associations existed with regards to MRI changes and no neuroimaging findings were correlated with relapses, although only two patients had a relapse of the 13 that had any follow-up.

We observed some interesting results regarding the effect of patient treatments on outcomes. In particular, a number of studies refuted the general contention that early use of immunotherapy improves neurological outcomes. One of the important considerations when examining such a variable is that there are no evidence-based guidelines on the types of immune treatment. There are many retrospective studies that compare outcomes for patients administered corticosteroids and intravenous immunoglobulin, and most of these find no statistical difference. We note one study that found early immune treatment only correlated with better outcomes when a combined regimen was used [22]. The efficacy of immune treatment is likely also dependent on the current activity of the immune disease. Therefore illnesses that run a prolonged course may be less inclined to exhibit detrimental effects by treatment delays. We currently have no proven methods of actually quantifying disease activity, but research on serum, CSF and potentially radiological biomarkers may be promising [31,53]. It is possible that, depending on the disease, markedly delayed treatment has no disease modifying effects. This may explain some of the variance observed in studies that examined cases that received no treatment. We surmise that due to the breadth of publications in support of timely immune treatment, this also establishes a role for using immunotherapy to modulate ultimate prognosis. Interestingly, we found that while ICU admission was associated with poorer prognosis in the included studies, mechanical ventilation appears to have little impact on outcomes. Coupling this with our conclusions on status epilepticus, this may suggest that the indication for ICU admission may not be an essential consideration for prognostic purposes; a notion that is supported by one study [22]. Importantly, the data regarding critical care illness was limited beyond cases of anti-NMDAR encephalitis, and therefore the prognostic value of ICU admission and mechanical ventilation remains unclear in other antibody subsets. Using the information in the only study in this group that found no association with outcome, it is possible that the use of rituximab may mitigate the negative prognostic effects of critical illness [35].

A major limitation of this review was that only adult cases were included. This decision was based on the fact that certain forms of autoimmune encephalitis present with a distinct clinical picture in children versus adults, and hence combining the two populations would have led to a heterogeneous group of variables making analysis difficult. Our review is also limited by incorporating both cases with intracellular and cell surface antibodies. It has been established that the pathological mechanisms behind these diseases are quite different [54], and therefore prognostic factors may also vary between the groups. However, our review was designed to encompass autoimmune encephalitis as a whole, and incorporate the results of as many studies as possible. We also note that the number of identified cases with onconeuronal antibodies is quite small relative to the whole cohort, and therefore are unlikely to greatly affect our interpretation. Another limitation is related to the design, quality and size of the included studies themselves. In particular, we note observational and largely retrospective design of the included publications. This is likely because the rarity of autoimmune encephalitis necessitates such a design. These factors also contribute to limited numbers of identified cases and a short duration of follow-up in some of the publications. Certainly we expect that duration of follow-up will affect the proportion of patients in a cohort to have good or poor outcomes. We are also dependent on the rigor of case selection, which may be influenced by the availability antibody assays, as well as the accessibility of immunotherapy and the reproducibility of MRI interpretation. We also found that several studies only performed univariate analyses of predictor variables. Our review, therefore, inherits these methodological issues and restricts the power of our analysis.

Our review highlights the need for future studies, in particular evaluating the role of antibody titers, autonomic dysfunction and underlying malignancy in certain antibody subtypes. We are also unaware of any study that correlates altered consciousness or the need for ICU admission with a delay in diagnosis, and subsequently immunotherapy. This would be an interesting topic, unifying our focus towards this single important modifiable factor in altering a patient's outcome. With increasing case identification, this may be the attention of large prospective cohort studies. Furthermore, this area is in need of randomized controlled trials comparing types of immunotherapy in order to generate guidelines for treatment. We suggest that future studies also focus on the evaluation of biomarkers as potential predictors of outcome.

5. Conclusion

We evaluated the current evidence of outcome predictors in patients with autoimmune encephalitis. Results of these studies were often conflicting and the definitions of outcome measures varied greatly, limiting the comparability of the studies. However, delay in the commencement of immunotherapy is clearly an important prognostic factor. This highlights the need for increased awareness, vigilance and early diagnosis. This review also highlights the desperate need for a unified minimum dataset on the one hand, and long-term seen-from-onset prospective studies on the other. Without a more systematic approach, the generation of evidence-based treatment guidelines remains elusive. The predictive value of onset and serial CSF parameters and the evolution of MRI abnormalities on determining the long-term outcome warrants further evaluation.

Funding

This review received no financial support.

Conflicts of interest

The authors declare no conflicts of interest.

References

[1] A. Didelot, J. Honnorat, Autoimmune limbic encephalitis, Future Neurol. 6 (2011) 97–111.
[2] L. Bataller, K.A. Kleopa, G.F. Wu, J.E. Rossi, M.R. Rosenfeld, J. Dalmau, Autoimmune limbic encephalitis in 39 patients: immunophenotypes and outcomes, J. Neurol. Neurosurg. Psychiatry 78 (2007) 381–385.
[3] J. Dalmau, A.J. Gleichman, E.G. Hughes, J.E. Rossi, X. Peng, M. Lai, S.K. Dessain, M.R. Rosenfeld, R. Balice-Gordon, D.R. Lynch, Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies, Lancet Neurol. 7 (2008) 1091–1098.
[4] S. Aurangzeb, M. Symmonds, R.K. Knight, R. Kennett, T. Wehner, S.R. Irani, LGI1-antibody encephalitis is characterised by frequent, multifocal clinical and subclinical seizures, Seizure 50 (2017) 14–17.
[5] J.I. Byun, S.T. Lee, J. Moon, K.H. Jung, J.W. Shin, J.S. Sunwoo, J.A. Lim, Y.W. Shin, T.J. Kim, K.J. Lee, K.I. Park, K.Y. Jung, S.K. Lee, K. Chu, Cardiac sympathetic dysfunction in anti-NMDA receptor encephalitis, Auton. Neurosci. 193 (2015) 142–146.
[6] U. Seneviratne, M. Cook, W. D'Souza, The prognosis of idiopathic generalized epilepsy, Epilepsia 53 (2012) 2079–2090.
[7] A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gotzsche, J.P. Ioannidis, M. Clarke, P.J. Devereaux, J. Kleijnen, D. Moher, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration, PLoS Med. 6 (2009) e1000100.
[8] M.J. Titulaer, L. McCracken, I. Gabilondo, T. Armangue, C. Glaser, T. Iizuka, L.S. Honig, S.M. Benseler, I. Kawachi, E. Martinez-Hernandez, E. Aguilar, N. Gresa-Arribas, N. Ryan-Florance, A. Torrents, A. Saiz, M.R. Rosenfeld, R. Balice-Gordon, F. Graus, J. Dalmau, Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study, Lancet Neurol. 12 (2013) 157–165.
[9] B.C. Duan, W.C. Weng, K.L. Lin, L.C. Wong, S.T. Li, M.H. Hsu, J.J. Lin, P.C. Fan, M.I. Lin, N.C. Chiu, Y.C. Lin, H.S. Wang, K.L. Hung, W.T. Lee, Variations of movement disorders in anti-N-methyl-D-aspartate receptor encephalitis: a nationwide study in Taiwan, Medicine (Baltim.) 95 (2016) e4365.
[10] S.B. Wells G, D. O'Connell, J. Peterson, V. Welch, M. Losos, P. Tugwell, The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, Accessed at, July 2018. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
[11] R. Herzog, M.J. Alvarez-Pasquin, C. Diaz, J.L. Del Barrio, J.M. Estrada, A. Gil, Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review, BMC Publ. Health 13 (2013) 154.
[12] G.B. Moga, D. Schopflocher, C. Harstall, Development of a Quality Appraisal Tool for Case Series Studies Using a Modified Delphi Technique, (2012) Accessed at https://www.ihe.ca/publications/development-of-a-quality-appraisal-tool-for-case-series-studies-using-a-modified-delphi-technique July 2018.
[13] J. Broadley, U. Seneviratne, P. Beech, K. Buzzard, H. Butzkueven, T. O'Brien, M. Monif, Prognosis in Autoimmune Encephalitis: Database, Data in Brief, (2018).
[14] R. Wang, H.Z. Guan, H.T. Ren, W. Wang, Z. Hong, D. Zhou, CSF findings in patients with anti-N-methyl-D-aspartate receptor-encephalitis, Seizure 29 (2015) 137–142.
[15] Y. Zhang, G. Liu, M.D. Jiang, L.P. Li, Y.Y. Su, Analysis of electroencephalogram characteristics of anti-NMDA receptor encephalitis patients in China, Clin. Neurophysiol. 128 (2017) 1227–1233.
[16] M.P. Malter, C. Helmstaedter, H. Urbach, A. Vincent, C.G. Bien, Antibodies to glutamic acid decarboxylase define a form of limbic encephalitis, Ann. Neurol. 67 (2010) 470–478.
[17] S.R. Irani, C.J. Stagg, J.M. Schott, C.R. Rosenthal, S.A. Schneider, P. Pettingill, R. Pettingill, P. Waters, A. Thomas, N.L. Voets, M.J. Cardoso, D.M. Cash, E.N. Manning, B. Lang, S.J. Smith, A. Vincent, M.R. Johnson, Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype, Brain 136 (2013) 3151–3162.
[18] J.I. Byun, S.T. Lee, K.H. Jung, J.S. Sunwoo, J. Moon, J.A. Lim, D.Y. Lee, Y.W. Shin, T.J. Kim, K.J. Lee, W.J. Lee, H.S. Lee, J. Jun, D.Y. Kim, M.Y. Kim, H. Kim, H.J. Kim, H.I. Suh, Y. Lee, D.W. Kim, J.H. Jeong, W.C. Choi, D.W. Bae, J.W. Shin, D. Jeon, K.I. Park, K.Y. Jung, K. Chu, S.K. Lee, Effect of immunotherapy on seizure outcome in patients with autoimmune encephalitis: a prospective observational registry study, PloS One 11 (2016) e0146455.
[19] X. Chi, W. Wang, C. Huang, M. Wu, L. Zhang, J. Li, D. Zhou, Risk factors for mortality in patients with anti-NMDA receptor encephalitis, Acta Neurol. Scand. 136 (2017) 298–304.
[20] J. Dalmau, F. Graus, A. Villarejo, J.B. Posner, D. Blumenthal, B. Thiessen, A. Saiz, P. Meneses, M.R. Rosenfeld, Clinical analysis of anti-Ma2-associated encephalitis, Brain 127 (2004) 1831–1844.
[21] H. Hemingway, Prognosis research: why is Dr. Lydgate still waiting? J. Clin. Epidemiol. 59 (2006) 1229–1238.
[22] E. de Montmollin, S. Demeret, N. Brule, M. Conrad, F. Dailler, N. Lerolle, J.C. Navellou, C. Schwebel, M. Alves, M. Cour, N. Engrand, J.M. Tonnelier, E. Maury, S. Ruckly, G. Picard, V. Rogemond, E. Magalhaes, T. Sharshar, J.F. Timsit, J. Honnorat, R. Sonneville, E.S.G.d. dagger, Anti-N-Methyl-d-Aspartate receptor encephalitis in adult patients requiring intensive care, Am. J. Respir. Crit. Care Med. 195 (2017) 491–499.
[23] B. von Rhein, J. Wagner, G. Widman, M.P. Malter, C.E. Elger, C. Helmstaedter, Suspected antibody negative autoimmune limbic encephalitis: outcome of immunotherapy, Acta Neurol. Scand. 135 (2017) 134–141.
[24] W. Wang, J.M. Li, F.Y. Hu, R. Wang, Z. Hong, L. He, D. Zhou, Anti-NMDA receptor encephalitis: clinical characteristics, predictors of outcome and the knowledge gap in southwest China, Eur. J. Neurol. 23 (2016) 621–629.
[25] X. Chen, F. Liu, J.M. Li, X.Q. Xie, Q. Wang, D. Zhou, H. Shang, Encephalitis with antibodies against the GABAB receptor: seizures as the most common presentation at admission, Neurol. Res. 39 (2017) 973–980.
[26] S. Litmeier, H. Pruss, E. Witsch, J. Witsch, Initial serum thyroid peroxidase antibodies and long-term outcomes in SREAT, Acta Neurol. Scand. 134 (2016) 452–457.
[27] J. Thompson, M. Bi, A.G. Murchison, M. Makuch, C.G. Bien, K. Chu, P. Farooque, J.M. Gelfand, M.D. Geschwind, L.J. Hirsch, E. Somerville, B. Lang, A. Vincent, M.I. Leite, P. Waters, S.R. Irani, G. Faciobrachial Dystonic Seizures Study, The importance of early immunotherapy in patients with faciobrachial dystonic seizures, Brain 141 (2018) 348–356.
[28] D. Dubey, J. Singh, J.W. Britton, S.J. Pittock, E.P. Flanagan, V.A. Lennon, J.M. Tillema, E. Wirrell, C. Shin, E. So, G.D. Cascino, D.M. Wingerchuk, M.T. Hoerth, J.J. Shih, K.C. Nickels, A. McKeon, Predictive models in the diagnosis and treatment of autoimmune epilepsy, Epilepsia 58 (2017) 1181–1189.
[29] W.J. Lee, S.T. Lee, J. Moon, J.S. Sunwoo, J.I. Byun, J.A. Lim, T.J. Kim, Y.W. Shin, K.J. Lee, J.S. Jun, H.S. Lee, S. Kim, K.I. Park, K.H. Jung, K.Y. Jung, M. Kim, S.K. Lee, K. Chu, Tocilizumab in autoimmune encephalitis refractory to rituximab: an institutional cohort study, Neurotherapeutics 13 (2016) 824–832.
[30] G. Harutyunyan, L. Hauer, M.W. Dunser, T. Moser, S. Pikija, M. Leitinger, H.F. Novak, W. Aichhorn, E. Trinka, J. Sellner, Risk factors for intensive care unit admission in patients with autoimmune encephalitis, Front. Immunol. 8 (2017) 835.
[31] R. Constantinescu, D. Krysl, F. Bergquist, K. Andren, C. Malmestrom, F. Asztely, M. Axelsson, E.B. Menachem, K. Blennow, L. Rosengren, H. Zetterberg, Cerebrospinal fluid markers of neuronal and glial cell damage to monitor disease activity and predict long-term outcome in patients with autoimmune encephalitis, Eur. J. Neurol. 23 (2016) 796–806.
[32] S.R. Irani, P. Pettingill, K.A. Kleopa, N. Schiza, P. Waters, C. Mazia, L. Zuliani, O. Watanabe, B. Lang, C. Buckley, A. Vincent, Morvan syndrome: clinical and serological observations in 29 cases, Ann. Neurol. 72 (2012) 241–255.
[33] D. Dubey, N. Samudra, P. Gupta, M. Agostini, K. Ding, P.C. Van Ness, S. Vernino, R. Hays, Retrospective case series of the clinical features, management and outcomes of patients with autoimmune epilepsy, Seizure 29 (2015) 143–147.
[34] D. Dubey, A. Sawhney, B. Greenberg, A. Lowden, W. Warnack, P. Khemani, O. Stuve, S. Vernino, The spectrum of autoimmune encephalopathies, J. Neuroimmunol. 287 (2015) 93–97.
[35] W.J. Lee, S.T. Lee, J.I. Byun, J.S. Sunwoo, T.J. Kim, J.A. Lim, J. Moon, H.S. Lee, Y.W. Shin, K.J. Lee, S. Kim, K.H. Jung, K.Y. Jung, K. Chu, S.K. Lee, Rituximab treatment for autoimmune limbic encephalitis in an institutional cohort, Neurology 86 (2016) 1683–1691.
[36] I. Gabilondo, A. Saiz, L. Galan, V. Gonzalez, R. Jadraque, L. Sabater, A. Sans, A. Sempere, A. Vela, F. Villalobos, M. Vinals, P. Villoslada, F. Graus, Analysis of relapses in anti-NMDAR encephalitis, Neurology 77 (2011) 996–999.
[37] S.R. Irani, K. Bera, P. Waters, L. Zuliani, S. Maxwell, M.S. Zandi, M.A. Friese, I. Galea, D.M. Kullmann, D. Beeson, B. Lang, C.G. Bien, A. Vincent, N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes, Brain 133 (2010) 1655–1667.
[38] Y. Jang, S.T. Lee, T.J. Kim, J.S. Jun, J. Moon, K.H. Jung, K.I. Park, K. Chu, S.K. Lee, High albumin level is a predictor of favorable response to immunotherapy in autoimmune encephalitis, Sci. Rep. 8 (2018) 1012.
[39] J.A. Lim, S.T. Lee, K.H. Jung, S. Kim, J.W. Shin, J. Moon, J.I. Byun, T.J. Kim, Y.W. Shin, K.J. Lee, Y.S. Kim, K.I. Park, S.K. Lee, K. Chu, Anti-N-methyl-d-aspartate receptor encephalitis in Korea: clinical features, treatment, and outcome, J. Clin. Neurol. 10 (2014) 157–161.
[40] N. Gresa-Arribas, M.J. Titulaer, A. Torrents, E. Aguilar, L. McCracken, F. Leypoldt, A.J. Gleichman, R. Balice-Gordon, M.R. Rosenfeld, D. Lynch, F. Graus, J. Dalmau, Diagnosis and significance of antibody titres in anti-NMDA receptor encephalitis: a retrospective study, Lancet Neurol. 13 (2014) 167–177.
[41] C.R. Butler, T.D. Miller, M.S. Kaur, I.W. Baker, G.D. Boothroyd, N.A. Illman, C.R. Rosenthal, A. Vincent, C.J. Buckley, Persistent anterograde amnesia following limbic encephalitis associated with antibodies to the voltage-gated potassium channel complex, J. Neurol. Neurosurg. Psychiatry 85 (2014) 387–391.
[42] C. Finke, U.A. Kopp, A. Pajkert, J.R. Behrens, F. Leypoldt, J.T. Wuerfel, C.J. Ploner, H. Pruss, F. Paul, Structural hippocampal damage following anti-N-Methyl-D-Aspartate receptor encephalitis, Biol. Psychiatry 79 (2016) 727–734.
[43] C. Finke, H. Pruss, J. Heine, S. Reuter, U.A. Kopp, F. Wegner, F. Then Bergh, S. Koch, O. Jansen, T. Munte, G. Deuschl, K. Ruprecht, W. Stocker, K.P. Wandinger, F. Paul, T. Bartsch, Evaluation of cognitive deficits and structural hippocampal damage in encephalitis with leucine-rich, glioma-inactivated 1 antibodies, JAMA Neurol. 74 (2017) 50–59.
[44] H. Arino, T. Armangue, M. Petit-Pedrol, L. Sabater, E. Martinez-Hernandez, M. Hara, E. Lancaster, A. Saiz, J. Dalmau, F. Graus, Anti-LGI1-associated cognitive impairment: presentation and long-term outcome, Neurology 87 (2016) 759–765.
[45] E.P. Flanagan, A. McKeon, V.A. Lennon, B.F. Boeve, M.R. Trenerry, K.M. Tan, D.A. Drubach, K.A. Josephs, J.W. Britton, J.N. Mandrekar, V. Lowe, J.E. Parisi, S.J. Pittock, Autoimmune dementia: clinical course and predictors of immunotherapy response, Mayo Clin. Proc. 85 (2010) 881–897.
[46] M. Toledano, J.W. Britton, A. McKeon, C. Shin, V.A. Lennon, A.M. Quek, E. So, G.A. Worrell, G.D. Cascino, C.J. Klein, T.D. Lagerlund, E.C. Wirrell, K.C. Nickels, S.J. Pittock, Utility of an immunotherapy trial in evaluating patients with presumed autoimmune epilepsy, Neurology 82 (2014) 1578–1586.
[47] T. Iizuka, J. Kaneko, N. Tominaga, H. Someko, M. Nakamura, D. Ishima, E. Kitamura, R. Masuda, E. Oguni, T. Yanagisawa, N. Kanazawa, J. Dalmau,

K. Nishiyama, Association of progressive cerebellar atrophy with long-term outcome in patients with anti-N-Methyl-d-Aspartate receptor encephalitis, JAMA Neurol. 73 (2016) 706–713.
[48] E. Lancaster, M. Lai, X. Peng, E. Hughes, R. Constantinescu, J. Raizer, D. Friedman, M.B. Skeen, W. Grisold, A. Kimura, K. Ohta, T. Iizuka, M. Guzman, F. Graus, S.J. Moss, R. Balice-Gordon, J. Dalmau, Antibodies to the GABAB receptor in limbic encephalitis with seizures: case series and characterisation of the antigen, Lancet Neurol. 9 (2010) 67–76.
[49] F. Graus, M.J. Titulaer, R. Balu, S. Benseler, C.G. Bien, T. Cellucci, I. Cortese, R.C. Dale, J.M. Gelfand, M. Geschwind, C.A. Glaser, J. Honnorat, R. Hoftberger, T. Iizuka, S.R. Irani, E. Lancaster, F. Leypoldt, H. Pruss, A. Rae-Grant, M. Reindl, M.R. Rosenfeld, K. Rostasy, A. Saiz, A. Venkatesan, A. Vincent, K.P. Wandinger, P. Waters, J. Dalmau, A clinical approach to diagnosis of autoimmune encephalitis, Lancet Neurol. 15 (2016) 391–404.
[50] A.M. Quek, J.W. Britton, A. McKeon, E. So, V.A. Lennon, C. Shin, C. Klein, R.E. Watson Jr., A.L. Kotsenas, T.D. Lagerlund, G.D. Cascino, G.A. Worrell, E.C. Wirrell, K.C. Nickels, A.J. Aksamit, K.H. Noe, S.J. Pittock, Autoimmune epilepsy: clinical characteristics and response to immunotherapy, Arch. Neurol. 69 (2012) 582–593.
[51] M.J. Titulaer, L. McCracken, I. Gabilondo, T. Iizuka, I. Kawachi, L. Bataller, A. Torrents, M.R. Rosenfeld, R. Balice-Gordon, F. Graus, J. Dalmau, Late-onset anti-NMDA receptor encephalitis, Neurology 81 (2013) 1058–1063.
[52] Y.W. Shin, S.T. Lee, J.W. Shin, J. Moon, J.A. Lim, J.I. Byun, T.J. Kim, K.J. Lee, Y.S. Kim, K.I. Park, K.H. Jung, S.K. Lee, K. Chu, VGKC-complex/LGI1-antibody encephalitis: clinical manifestations and response to immunotherapy, J. Neuroimmunol. 265 (2013) 75–81.
[53] F. Leypoldt, R. Hoftberger, M.J. Titulaer, T. Armangue, N. Gresa-Arribas, H. Jahn, K. Rostasy, W. Schlumberger, T. Meyer, K.P. Wandinger, M.R. Rosenfeld, F. Graus, J. Dalmau, Investigations on CXCL13 in anti-N-methyl-D-aspartate receptor encephalitis: a potential biomarker of treatment response, JAMA Neurol. 72 (2015) 180–186.
[54] F. Graus, A. Saiz, J. Dalmau, Antibodies and neuronal autoimmune disorders of the CNS, J. Neurol. 257 (2010) 509–517.