Immunotherapy in autoimmune encephalitis

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ABSTRACT

Purpose of review: Autoimmune encephalitis (AE) refers to immune-mediated neurological syndromes characterised by the detection of pathogenic autoantibodies in serum and/or cerebrospinal fluid which target extracellular epitopes of neuroglial antigens. There is increasing evidence these autoantibodies directly modulate function of their antigens *in vivo*. Early treatment with immunotherapy improves outcomes. Yet, these patients commonly exhibit chronic disability. Importantly, optimal therapeutic strategies at onset and during escalation remain poorly understood. In this review of a rapidly emerging field, we evaluate recent studies on larger cohorts, registries, and meta-analyses to highlight existing evidence for contemporary therapeutic approaches in AE.

Recent findings: We highlight acute and long-term treatments used in specific AE syndromes, exemplify how understanding disease pathogenesis can inform precision therapy and outline challenges of defining disability outcomes in AE.

Summary: Early first-line immunotherapies, including corticosteroids and plasma exchange, improve outcomes, with emerging evidence showing second-line immunotherapies (especially rituximab) reduce relapse rates. Optimal timing of immunotherapy escalation remains unclear. Routine reporting of outcome measures which incorporate cognitive impairment, fatigue, pain, and mental health will permit more accurate quantification of residual disability and comprehensive comparisons between international multicentre cohorts, and enable future meta-analyses with the aim of developing evidence-based therapeutic guidelines.

INTRODUCTION

Autoimmune encephalitis (AE) typically presents with a subacute onset of neurological and psychiatric features. Many AE syndromes are associated with pathogenic autoantibodies which target the extracellular domains of specific neuroglial antigenic targets [1]. Hence, these autoantibodies can gain access to their target antigens and have been demonstrated to exert pathogenic effects *in vitro* and *in vivo*. In patients with these likely pathogenic neuroglial-surface directed autoantibodies, early diagnosis and administration of immunotherapies can improve outcomes and reduce the risk of relapses [2,3]. This review will focus on summarising clinical features (Table 1), and synthesising data which describes the therapeutic challenges, treatment regimes, and outcomes in these patients.

'Limbic encephalitis' in association with systemic malignancy was first described more than five decades ago [4]. Hu-antibodies were the first paraneoplastic neuronal antibody identified in patients with this form of encephalitis [5]. The list of paraneoplastic neuronal antibodies subsequently expanded to numerous intracellular antigens, typically nuclear or cytoplasmic proteins. These antibodies are often named after their target antigen (e.g. Ma) or the initials of the first patient with the condition, for example Ri and Yo [6]. In these paraneoplastic conditions, the tumours express the autoantigen to which the antibodies are directed. However, the antibodies themselves are not considered pathogenic as they do not access their targets *in vivo.* Rather, they are disease biomarkers, and their associated paraneoplastic neurological sequelae are thought to be largely T-cell mediated. These syndromes usually show a poor prognosis as patients are generally not immunotherapy-responsive and their outcome is often driven by the underlying malignancy [7].

In 2004, a new era began. Voltage-gated potassium channel (VGKC)-antibodies were identified in patients with an immunotherapy-responsive form of encephalitis [8]. In 2007, young women with AE and associated ovarian teratomas were identified as having antibodies targeting the extracellular domain of the N-methyl-D-aspartate receptor (NMDAR) [9]. In both series, patients presented over a few days to weeks with varying degrees of amnesia, seizures, and psychiatric disturbances. Immunotherapy, plus teratoma resection in the case of those with NMDAR-antibodies, resulted in significant improvements. In patients with VGKC-

antibodies, subsequent refinement of antibody targets identified the extracellular domain of contactin-associated protein-like 2 (CASPR2) and the secreted neuronal protein leucine-rich glioma-inactivated 1 (LGI1) as the key antigens [10]. This was a critical observation as VGKC antibody positivity without LGI1 and CASPR2 reactivities is now known to be clinically irrelevant [11].

A critical aspect aiding the identification and characterisation of subsequent AE syndromes has been the refinement of tissue immunohistochemistry and live cell-based assays (CBA) to detect these autoantibodies, in both serum and CSF [2,3]. Tissue immunohistochemistry detects the binding of antibodies to intracellular and extracellular determinants in rodent brain sections, and can permit recognition of the precise antigenic target when the observed binding pattern is sufficiently characteristic. Live CBAs employ human embryonic kidney (HEK293) cells to overexpress their target antigen at the plasma membrane. By maintaining the conformational tertiary structure of target proteins prior to application of fixative, and therefore only exposing the native extracellular domains to these antibodies, live CBAs allow the reliable detection of clinically relevant antibodies. This stands in marked contrast to commercial assays where the cell membranes are fixed or permeabilised, with disruption of the native antigen conformation. These biochemical differences are likely to account for the reduced sensitivity and specificity observed with commercial tests in the setting of AE [12,13].

Largely by utilising these assays, the last decade has witnessed the discovery of numerous likely pathogenic autoantibodies implicated in AE (Table 1). Recent expert consensus has generated diagnostic criteria to enable the earlier recognition and treatment of AE, and also highlight the need for managing patients with the clinical syndrome of AE without as yet identified autoantibodies (‘seronegative’ AE) [14].

The incidence of AE is increasing and in 2018 was comparable to that of infectious encephalitis, in a US study [15]. The marked increase in incidence of AE corresponds with a static infectious encephalitis incidence [16]. Reasons for this relative and absolute growth are likely to include growing clinician awareness of the expanding clinical spectrum of AE, leading to increased detection of seropositive and

seronegative cases, and the ongoing discovery of autoantibodies associated with these syndromes. Furthermore, prior cohorts and diagnostic criteria often relied on the presence of CSF pleocytosis and MRI abnormalities, now increasingly recognised as absent during in some AE syndromes, such as LGI1- and CASPR2-antibody encephalitis, particularly early on in the disease course.

The underlying immunobiology of AE and implications for treatment

There is increasingly strong evidence that most AE-associated autoantibodies are pathogenic. For example, antibodies from patients with NMDAR-antibody encephalitis react with the extracellular domain of the NR1 subunit of the NMDAR and result in a selective and reversible internalisation of cell-surface NMDARs [17]. Furthermore, mice infused with NMDAR-antibody encephalitis patients' CSF develop progressive memory deficits and depressive features which resolve after cessation of the infusion [18]. Serum IgG from LGI1-antibody encephalitis patients prevents binding of LGI1 to its receptors, ADAM22 (a disintegrin and metalloproteinase-22) and ADAM23; and can induce reversible defects in synaptic function and memory deficits in mice [19]. Patient-derived LGI1-directed monoclonal antibodies revealed that these effects were more nuanced: individual antibodies recognise specific LGI1 domains and those targeting the leucine-rich repeat domain could internalise the LGI1-ADAM22/23 complex in HEK293 cells and live hippocampal neurons, and induce memory impairment in rodents. In contrast, those targeting the epitempin domain were responsible for the blocking effects observed with unfractionated patient sera [20]. Human IgG from alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor (AMPAR)-antibody encephalitis patients also induced receptor internalisation and resulted in a reduction in synaptic AMPARs in passive-transfer rodent models, with long-term learning and memory deficits [21]. Taken together, these studies demonstrate that autoantibodies from patients with AE have pathogenic potential, and that methods to inhibit their effects may optimise management for these patients.

A second, related consideration in treating AE is which anatomical site(s) should be targeted. Evaluating serum and CSF antibody titres in individuals across multiple AE syndromes demonstrates that

autoantibodies are persistently present at higher levels in serum compared to CSF, thereby suggesting that the initial generation of autoantibodies is peripheral [1] (Figure 1A-B). Hence, therapeutic options targeting peripheral B-cell compartments or soluble circulating IgG have significant potential and proven efficacy. However, the presence of antigen-specific B-cells in the CSF of patients with AE highlight an intrathecal compartment which should also, and perhaps simultaneously, be considered, particularly in seemingly treatment-resistant patients [1,22].

Finally, the breakdown of immune tolerance in the periphery may inform ideal therapeutic targets. B-cells develop from the bone marrow, pass tolerance checkpoints, and may enter germinal centre reactions and/or form long-lived plasma cells in the bone marrow (Figure 2) [23]. During these developmental stages, surface markers on B cells significantly alter. Hence, the therapeutic value of understanding the relative contributions of these mechanisms becomes critical to the successful deletion of pathogenic autoreactive B-cells [1].

Overall, a detailed understanding of the mechanisms by which the autoantibodies are generated and perpetuated have important future implications for rationalising the choice of immunotherapy in AE. Currently available immunotherapeutic agents, their proposed mechanisms of action, and the developmental stages of B cells they may target are outlined in Table 2 and Figure 2. Some of the treatment options discussed in this review pertain to off label use not yet approved for this specific purpose.

N-methyl-D-aspartate receptor-antibody encephalitis

In NMDAR-antibody encephalitis, the best outcomes are seen in patients who received early immunotherapy and early tumour removal [24,25]. The latter observation may be best explained by the finding that these patients' ovarian teratomas contain B-cells with NMDAR reactivity [26]. In 2013, a retrospective study of 577 patients reported that first-line immunotherapy (corticosteroids, intravenous immunoglobulins and/or plasma exchange) with/without tumour removal resulted in improvement for 53% of patients at four weeks [27]. Outcomes continued to improve over 18 months, particularly in those who

received early administration of first-line therapy. As part of first-line immunotherapy, the addition of one-two courses of PLEX has been shown to result in greater clinical improvements in the first two months, although these differences are less apparent in the longer term [28]. Some of the most robust data comes from a recent meta-analysis evaluating immunotherapy in 1550 patients with NMDAR-antibody encephalitis [29]. In this study, a modified Rankin Score (mRS) ≤2 (often deemed a 'good' outcome) was associated with having received PLEX and/or corticosteroids and IVIg. Conversely, the absence of immunotherapy within 30 days of symptom onset was associated with an mRS≥3. In this study, 47 patients experienced a severe adverse event, which was commonly infectious sequelae in patients receiving PLEX.

In patients who failed first-line immunotherapies, second-line treatment (namely rituximab or cyclophosphamide) have been shown to result in superior outcomes [27]. Several datasets show beneficial effects of rituximab [29,30]. For example, rituximab-treated NMDAR-antibody encephalitis patients are more likely to achieve mRS ≤2 at long-term follow-up [30], despite this group being more severely affected at baseline. In the above meta-analyses, rituximab administration was also associated with particularly favourable outcomes after its early initiation and a significant reduction in relapse rates [29]. Overall, there is a 10-15% risk of relapse at 2 years, which is significantly lowered in those who receive second-line immunotherapies [27].

Tocilizumab, which blocks the IL-6 receptor, has been used as combination treatment with teratoma removal, corticosteroids, IVIg and rituximab in a large prospective cohort, demonstrating superior outcomes when compared to both the use of rituximab monotherapy, and to only first-line therapies. The main adverse event of concern was neutropaenia in 21% of patients [31]. Bortezomib, a drug which targets the proteosome and hence shows a theoretical predilection for plasma cells, has been reported to be efficacious in small case series of severe refractory cases [32,33], as has intrathecal methotrexate [34–36].

The 20-25% of NMDAR-antibody encephalitis patients with an mRS≥3 (mortality rate ~5%) represent a population with unmet needs [29]. It is a priority to develop clinical and laboratory biomarkers which may

identify these patients. While a valuable research tool, the prognostic NEOS (NMDAR-antibody encephalitis one-year functional status) score can only be applied at one month, thereby not guiding more proactive treatment escalation during early admissions [37]. It is also important to note that a role for chronic immunotherapy has not been adequately addressed by the literature; yet, patients with NMDAR-antibody encephalitis continue to show cognitive improvements several years after initiation of immunotherapies [38].

Leucine-rich glioma-inactivated 1-antibody encephalitis

The first report of a large cohort of confirmed LGI1-antibody encephalitis cases was published in 2010: their mRS reduced significantly after immunotherapy administration [10]. In subsequent cohorts, cessation of faciobrachial dystonic seizures (FBDS), a pathognomonic seizure semiology in these patients, was observed in only 10% of patients on anti-seizure medications; by comparison to 51% at 30 days and 88% at 90 days after addition of immunotherapies [39,40]; anti-seizure medications are also more poorly tolerated [39–41]. Delays in immunotherapy reduced the likelihood of FBDS cessation, while expedited immunotherapy and the absence of cognitive impairment predicted favourable 24-month outcomes.

To help begin to address *which* immunotherapies are optimal, a recent retrospective observational study compared corticosteroids to IVIg. It found the former superior in achieving resolution of FBDS in conjunction with short-term improvements in mRS and cognitive measures; however, two-year outcomes were similar between the groups [42]. To date, the only randomised controlled trial in AE has been undertaken in LGI1- (14/17 patients) and CASPR2-antibody (3/17 patients) encephalitis. It compared IVIg to placebo and, despite early termination due to slow enrolment, IVIg was observed to associate with a significant 50% reduction in seizure frequency after five weeks. This may be the only definitive evidence that some immunotherapies are superior to placebo.

Although B cell depletion with rituximab may seem in intuitive second-line therapy in these diseases, a study of 61 LGI1-antibody encephalitis patients [30] revealed no significant differences in relapse rate or

proportion with mRS≤2 at last follow-up in a comparison of rituximab-treated and non-rituximab treated groups. However, other smaller studies suggest greater benefits with administration of rituximab in these patients [43–45]. These discrepancies warrant further investigation.

Overall, recently reported large cohorts reveal the following percentages of patients are taking the following immunotherapies: 70-75% corticosteroids, 35-40% IVIg, 10-15% PLEX and 20% with chronic immunosuppression [39,41,46,47]. The evidence for this practice will benefit from interrogation in future work.

In LGI1-antibody encephalitis, delays in immunotherapy have also been associated with poorer longer-term cognitive outcomes and hippocampal atrophy [39,47]. Outcomes of patients with AE in 2019 reported, at a median follow-up of 27 months, that while at least half the patients achieved seizure freedom after immunotherapy, 22% of LGI1-antibody encephalitis patients had a poor outcome (mRS 3-6) [41]. Similar proportions of chronically affected patients have been observed in other studies [39,48,49], with a recent paper showing ~80% of LGI1-antibody encephalitis patients achieve an mRS≤2, and ~40% still showed short term memory impairment at 2-year follow-up, suggesting ongoing cognitive impairment is common [42].

One longer-term outcome seems less of an issue: while seizures occur commonly and very frequently at onset in this form of AE, the rate of a ‘tendency to ongoing seizures’ (i.e. epilepsy) are surprisingly low (10-20%) [41,50–52]. In general, seizures in LGI1-antibody encephalitis are thought to represent acute symptomatic seizures rather than a persisting epileptogenic focus [53]; this calls into question the prolonged use of anti-seizure medications in these patients.

Contactin-associated protein-like 2 antibody encephalitis

CASPR2-antibody encephalitis is responsive to first-line immunotherapy in up to 80-90% of cases [10,54]; however, the small proportion of patients with CNS disease (both encephalitis and Morvan’s syndrome) in

association with tumours, appear to fare worse [10,49,54,55]. While CASPR2-antibody encephalitis rarely affects children compared to adults, case reports and case series of paediatric CASPR2-antibody encephalitis have been reported. In one study, patients as young as 18 months experienced remission following immunotherapy [56]. The recovery was generally favourable but behavioural abnormalities persisted in a proportion, albeit after a short median follow-up duration.

In terms of second-line immunotherapy response, from a cohort of 25 patients with CASPR2-antibody encephalitis [30], there was no significant difference between relapse rates nor participants achieving a mRS <3 when comparing rituximab and non-rituximab treated subgroups. Yet again, in this disease, long-term outcomes are far from ideal: relapsing disease occurs in ~25%; independent living (mRS≤2) in 70-75%; significant dependence (mRS 3-5) in ~15%; and mortality in 10-15% [49,54].

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)

MOGAD is predominately a demyelinating disorder that typically presents with acute disseminated encephalomyelitis (ADEM) in children, and bilateral optic neuritis and/or transverse myelitis in both children and adults [57,58]. More recently, emerging clinical phenotypes include presentations with seizures and cortical encephalitis [59–62]. In addition, there is a recognised overlap with AE syndromes, in particular, NMDAR-antibody encephalitis [63,64], with ~5% of all patients with NMDAR-antibody encephalitis having concurrent neuroglial autoantibodies, of which MOG-antibodies are the most common [63]. These patients may have clinical phenotypes of demyelination typically associated with MOG-antibodies, and AE typically associated with NMDAR-antibodies, that can occur either simultaneously or separated in time [65].

In children presenting with encephalitis other than ADEM, MOG-antibodies were more commonly identified than all other neuroglial antibodies combined [64]. 87% of MOG-antibody ADEM patients had an mRS≤1 at follow-up; however, 36% of non-ADEM MOG-antibody encephalitis patients had an mRS of 2-6, with 23% having cortical atrophy at follow-up [64]. Uncommonly, children younger than 7 years of age with

relapsing ADEM have been identified as having a ‘leukodystrophy-like’ MRI pattern of confluent symmetrical lesions associated with relapsing disease despite escalation of immunotherapy, and significant residual disability [66].

In general, the response to first-line immunotherapy in demyelinating phenotypes in patients with MOGAD is favourable, with up to half the patients having a monophasic disease course [58]. However, while patients are exquisitely steroid-responsive, relapses frequently occur in the context of rapidly weaning steroid regimes, reduced prednisone doses, and within two months of steroid cessation [58]. Similar observations in a subgroup of patients with seizures in the context of MOGAD and cortical encephalitis [67] suggest that drugs which could mimic the mechanisms of action of steroids, but avoid their notorious side effect profile, may prove valuable in this condition.

IgLON5-antibody encephalitis

The first case series of eight patients with IgLON5-antibody encephalitis reported a limited response to therapy, with only one patient showing a response, and a 60% mortality-rate after a median follow-up of 54 months [68]. This may relate to the observed, likely irreversible and potentially progressive, tau deposition in the brains of patients with IgLON5-antibody encephalitis [68]. However, more recent cohorts report a more optimistic median mRS at last follow-up of 2.5 (median follow-up 15 months), along with examples of more favourable responses to immunotherapy [69–72]. A systematic review including 18 studies with 46 patients showed a 43% response rate to immunotherapy initially and 33% at last follow-up [73]. They identified combination therapy with second-line agents, the presence of cognitive impairment, atypical phenotypes, CSF inflammation, and HLA-DQB1*05:01 without HLA-DRB1*10:01, as being associated with an increased likelihood of a favourable immunotherapeutic response. However, the associated movement disorder has been reported with only ~13% sustained improvement after immunotherapies [74].

In summary, this condition presents an especially intriguing convergence of immunity and neurodegeneration with a consistent HLA association and unique tauopathy. Recent studies have identified that IgLON5-autoantibodies may induce neurodegeneration of human and rodent neurons *in vitro* resulting in tau accumulation or disruption of cytoskeletal organisation to provide a mechanistic link for the directionality of the association between autoimmunity and neurodegeneration [75,76].

The value of outcome measures and reaching consensus

The mRS is currently the most widely used tool to assess short- and long-term outcomes in AE. Yet, the mRS shows significant limitations in this field, primarily because this motor-function focussed scale was originally designed for use post-stroke [77]. It is not a valid tool for capturing common debilitating residual symptoms of AE including fatigue, neuropsychological deficits, cognitive impairment and pain. For example, a recent cohort of NMDAR-antibody encephalitis patients identified 80% had at least moderate severity cognitive deficits, despite a median mRS of 1 at 2 years [38]. These patients continued to improve for between two and four years of follow-up, highlighting the importance of longer-term longitudinal studies which would benefit from more sensitive measures than the mRS. Furthermore, the trend for mRS≤2 to be described as a 'good' outcome was recently questioned [78,79], with studies demonstrating poor patient reported outcomes and psychosocial functioning in NMDAR-antibody encephalitis patients despite 95% with low mRS ratings. Further, in patients with LGI1-antibody encephalitis, many patients in the 'good' mRS group experienced persistent fatigue, cognitive deficits, and could not return to employment [80].

The Clinical Assessment Scale in Encephalitis (CASE) score incorporates nine symptom domains of AE into a score out of 27 [81]. It fulfils reliability and validity criteria [82], and goes some way towards a clinical severity score which is specific to AE. However, it appears to lend itself principally to measuring change in NMDAR-antibody encephalitis and may not as accurately capture outcomes in LGI1-antibody encephalitis.

Neuropathic pain was identified in ~50% of CASPR2- and ~20% of LGI1-antibody encephalitis patients in a 2021 cohort study, using the DN4 (Douleur Neuropathique 4) pain scale [83]. However, pain is largely excluded by commonly used outcome measures such as the mRS, and should be taken into consideration in the clinical care of patients with these AE syndromes, and in cohort phenotyping for research studies.

Finally, future studies should employ patient reported outcome instruments to provide greater granularity related to quality of life as a critical outcome measure of long-term function in AE. This was exemplified by the use of the Patient-Reported Outcomes Measurement Information System-pain interference (PROMIS-PI) scales and the EQ-5D-5L to weight the effect of immunotherapy on pain, self-care, fatigue, anxiety, depression and other factors important to patients with LGI1- and CASPR2- antibodies, that are not included in currently used outcome measures. This study also identified 82% of immunotherapy trials in LGI1-antibody encephalitis patients resulted in improvement of pain, compared to only 38% of trials in CASPR2-antibody encephalitis patients suggesting persistence of pain may be a major factor in the poor longer-term outcomes observed in many CASPR2-antibody encephalitis patients. By comparison, this data may be obscured in the reported outcomes of 70-80% of patients with these two subtypes of AE who are reported as having an mRS of ≤2 at long-term follow-up [39,48,49,54].

With rare diseases, there is a clear need for multicentre international collaboration to generate the power to identify significant differences. The generation of robust data from meta-analyses [29], development of internationally applicable therapeutic guidelines [84] and complementary parallel advances in the biology, all represent exciting ways to progress the field.

CONCLUSIONS

There remain multiple therapeutic challenges in caring for patients with AE. A fundamental one is the variable geographical access to cell based assay diagnostics and the necessary positive controls, which are both critical for accurate diagnosis. Also, several retrospective studies have examined the value of first-line immunotherapies in the acute setting; however, there is a paucity of randomised or prospective data.

Nevertheless, a recurring and prominent theme is the importance of a rapid diagnosis to expedite first-line immunotherapies. Therefore, it may appear intuitive that a delay to second and third-line therapies, in those who require these, may also be deleterious; yet, the optimal timing of escalation to second-line therapies, such as rituximab or cyclophosphamide remains unclear. This metric appears to show significant variability across studies and, yet, is central to improving outcomes and minimising relapse risks in many patients. Despite overall optimism with the use of immunotherapies, the risks of unnecessary exposures to their potential consequences need to be balanced against the persistent deficits at long-term follow up in patients who respond only partially to first-line immunotherapies. These include long-term complications of immunotherapy, including the metabolic and bone health impact of corticosteroids; or the hypogammaglobulinaemia and infection risk induced by rituximab. The independent value of steroid sparing agents, such as mycophenolate and azathioprine, in AE remain to be clarified in inducing and maintaining disease remission. While AE syndromes have a known relapse risk, these patients are generally not considered for life-long immunosuppression, in contrast to other antibody-mediated neurological disorders with more certain likelihoods of relapses, such as NMOSD. In terms of deciding who to administer which immunotherapies, the field would greatly benefit from clinical, radiological and/or serological biomarkers which help select patients at disease onset in whom to escalate immunotherapy. In addition, standardisation of nomenclatures and outcome measures in cohorts of patients with AE is an imperative (as outlined in Table 3). Finally, with the alignment of clinical assessment, therapeutic regimens, and outcome reporting, and the provision of case-level data as supplementary material, the power of meta-analyses can be leveraged and with it, a new era in the management of these potentially devastating diseases.

KEY POINTS

- Pathogenic autoantibodies targeting the extracellular domains of neuroglial antigens can each result in distinctive autoimmune encephalitis syndromes which can manifest with seizures, cognitive impairment, psychiatric disturbances, and movement disorders.
- Early immunotherapy with first-line treatments, including corticosteroids and plasma exchange, improves outcomes, with emerging evidence from larger cohorts showing second-line

immunotherapies (especially rituximab) can reduce relapse rates in AE. The optimal timing of immunotherapy escalation remains unclear.

- Defining residual disability with currently utilised outcome measures is insufficient to quantify and monitor the efficacy of specific immunotherapeutic agents on fatigue, pain, mood, cognitive impairment and quality of life.
- We identify commonly used data collection points which are currently in use, and propose further outcome measures to more accurately identify and track treatment response of cognitive impairment, fatigue, and pain, which may heavily impact quality of life. The routine use of these scales will permit more accurate quantification of residual disability and comprehensive comparisons between international multicentre cohorts, and enable future systematic reviews and meta-analyses with the aim of developing robust therapeutic guidelines.

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Conflicts of interests

SR serves as a consultant on an advisory board for UCB and Limbic Neurology, and has been an invited speaker for Biogen, Excemed, and Limbic Neurology.

SRI is a coapplicant and receives royalties on patent application PCT/GB2009/051441 entitled Neurological Autoimmune Disorders and has received honoraria / research support from UCB, Immunovant, MedImmun, Roche, Cerebral therapeutics, Medlink Neurology, CSL Behring, UCB and ONO Pharma.

Table *1*: Characterisation of the more prevalent autoimmune encephalitis syndromes associated with likely pathogenic autoantibodies.

Abbreviations: *ADEM – Acute disseminated encephalomyelitis; AMPAR – Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2 – Contactin-associated protein-like 2; DPPX – Dipeptidyl-peptidase-like protein-6; D2R – Dopamine 2 receptor; EDSS – Expanded disability status scale; FBDS – Faciobrachial dystonic seizure; GABA – Gamma-amino butyric acid; GAD65 – Glutamic acid decarboxylase (65 kDa isoform); GFAP – Glial fibrillary acidic protein; GluD2 – Glutamate receptor delta2; GluK2 – Glutamate kainite receptor subunit 2; GlyR – Glycine receptor; ITx – Immunotherapy; Kv – Voltage-gated potassium channel; LE – Limbic Encephalitis;LGI1 – Leucine-rich glioma-inactivated 1; LOC – Level of consciousness; mGluR – Metabotropic glutamate receptor ; MOGAD – Myelin Oligodendrocyte Glycoprotein-associated disease; NAD – No abnormalities detected; NMDAR – N-Methyl-D-Aspartate; OCB – Positive CSF-restricted oligoclonal bands; SCLC – Small cell lung cancer; SEZ6L2 – Seizure-related 6 homolog like 2; T2H – T2 hyperintensities on MRI; y/o – Years old.*

Modified from Ramanathan et al (J Neurol 2019) and Uy et al (Pract Neurol 2021)

Antigen-predominate IgG subclass	Antigenic target	Demographics	Clinical presentation	Tumour association	Investigations	Immunotherapy response	Clinical outcomes
NMDAR-IgG1 [17,24,27,29,85–87]	Extracellular domain of the NR1 subunit of NMDAR;	*Incidence*: 0.1/100,000 person-years; *Sex (F:M)*: 3:1; *Age of Onset (median [range]):* 20 y/o [2 months old – 85 y/o]	Flu-like prodrome followed by subacute onset of seizures, psychiatric disturbances, movement disorders, dysautonomia, altered level of consciousness, central hypoventilation	20% have ovarian teratoma; 2% have extraovarian teratoma or another malignancy	*CSF*: ~20% NAD, ~80% lymphocytic pleocytosis, ~65% OCB; *MRI*: ~60% NAD; *EEG*: 5-10% extreme delta brush	55% improve in 4 weeks with first line ITx; 35% improve after second line ITx	80% mRS≤2 at 24 months; 5-15% mortality; relapse rate 10%-20% (lower in recent years); <5% risk of chronic epilepsy
LGI1-IgG4 [20,39,48]	LGI1 is secreted and interacts with disintegrin and metalloproteinase domain (ADAM) proteins – presynaptic ADAM23 and	*Incidence:* 0.08/100,000 person-years; *Sex (F:M)*: 1:2; *Age of Onset (median [range])*: 64 y/o [20 – 92 y/o]	Subacute onset of seizures (most characteristically FBDS), behavioural / personality changes, anterograde and retrograde amnesia, other cognitive	<10% with thymoma, other tumours rare	*CSF*: NAD in ~75%; *MRI*: ~40% NAD, ~50% mesial temporal T2H, ~10% basal ganglia T2H; *EEG*: ~50% NAD; *Other*: ~45% serum hyponatraemia; >90% carry HLA-DRB1*07:01	ITx (particularly steroids) prevent progression of FBDS to cognitive impairment; >90% are responsive to ITx	At 2 years, ~55% functionally independent; ~35% improved but dependent; ~10% severely disabled or dead (5%

	postsynaptic ADAM22.		impairments				mortality); relapse rate ~30%
CASPR2-IgG4 [10,49,54,56,83]	Cell adhesion molecule colocalises with Kv at the neural juxtaparanode in CNS and PNS, and expressed in synapses.	*Incidence:* Approximately 30% of LGI1-antibody encephalitis; *Sex (F:M)*: 1:9; *Age of Onset (median [range])*: 60 y/o [1.5 - 80y/o]	Subacute onset of peripheral nerve hyperexcitability with associated neuropathic pain (up to 60%), limbic encephalitis, dysautonomia, sleep disturbance and ataxia	~20% have a tumour (mainly thymoma), other malignancies less common	*CSF*: ~65% NAD, ~20% lymphocytic pleocytosis, ~25% OCB; *MRI*: ~70% NAD, ~25% mesial temporal T2H; *EEG*: 40% epileptiform; *EMG:* Myokymia and fasciculations. Up to 90% carry HLA*DRB1*11:01	80% have favourable responses to ITx – especially in absence of a tumour; 50% good/complete response to tumour therapy and ITx	10% mortality rate; 20-30% relapse rate
MOG-IgG1 [58,88–91]	Outer lamellae of CNS myelin and oligodendrocytes	*Incidence:* 0.1/100,000 person-years (AE presentation only); *Sex (F:M)*: 1:1; *Age of Onset (median [range])*: paediatric and adult bimodal distribution [1-75 y/o]	ADEM most common paediatric presentation. Bilateral and/or recurrent optic neuritis and transverse myelitis most common demyelinating presentations. Encephalitic presentations include cortical encephalitis, and overlap syndromes with AE (particularly NMDAR-antibody encephalitis)	Nil recognised	*CSF:* ~60% lymphocytic pleocytosis, ~10% OCB; *MRI*: ~25% NAD, ADEM - bilateral poorly demarcated subcortical lesions; encephalitic presentations may have leptomeningeal enhancement; *EEG*: Paediatric cohort 10% NAD, 20% epileptiform; 90% slowing	Steroid responsive but may relapse with rapid steroid weans / cessation.	Outcomes with demyelination tend to be favourable compared to AQP4-NMOSD, although may have up to 50-60% with some form of residual disability. Relapse rates vary from 30-60%.

IgLON5-IgG4 [68,73,74,92,93]	Member of the immunoglobulin superfamily and a cell adhesion molecule in neurons.	*Incidence:* very rare; *Sex (F:M)*: 1:1; *Age of Onset (median [range])*: 64 y/o [13 - 85 y/o]	Chronic, progressive sleep disorder with associated movement disorder with gait disturbance, bulbar dysfunction and cognitive impairment	Nil recognised	*CSF:* 30% lymphocytic pleocytosis, 50% increased protein, 10% OCB; *MRI*: 80% NAD; *EEG*: 90% NAD	40-45% may show some improvement but there is a lesser sustained response (30-35%); majority have a progressive disease course. Combination therapy may be more effective than monotherapy	At 3 years: 35% mRS 1-3; 5% mRS 4-5; 60% mortality rate
AMPAR-IgG1 [15,86,94–96]	Ionotropic glutamate receptor; GluR1/2 subunits. Critical in synaptic plasticity and excitatory transmission	*Incidence*: 0.03/100,000 person-years; *Sex (F:M)*: 2:1; *Age of Onset (median [range]):* 50-60 y/o [20-90 y/o]	Limbic encephalitis, seizures, cognitive impairment, amnesia, disordered sleep, movement disorders	50-70% have SCLC, breast, thymus, and ovarian cancers	CSF: may have lymphocytic pleocytosis and intrathecally restricted OCB; MRI: 25% NAD; frequently have uni-/bilateral medial temporal lobe T2H, may have long-term atrophy EEG: 30% epileptiform	Majority have a partial response to tumour management and immunotherapy. 15-50% relapse rate.	15% mortality - usually due to malignancy; In survivors, the median mRS=1; <5% risk of chronic epilepsy
$GABA_AR$-IgG1 [97–100]	Ionotropic receptor mediating fast inhibitory synaptic transmission; α1, b3, and γ2	*Sex (F:M)*: 1:1; *Age of Onset (median [range]):* 40 y/o (1-90 y/o)	Encephalitis with severe seizures (inclusive of status epilepticus, epilepsia partialis continua); cognitive dysfunction,	<20% with tumours, including thymoma, Non-Hodgkin's Lymphoma, SCLC and	CSF: 55-60% abnormal (lymphocytic pleocytosis, increased protein or OCB); MRI: 20% NAD, often have multiple "fluffy" cortico-	>80% may respond to ITx and/or tumour removal (full recovery in 30%)	~20% mortality (especially due to status epilepticus); ~10% relapse rate. 15% risk of chronic

	subunits		movement disorders	rectal cancer	subcortical T2H; EEG: 75-80% epileptiform		epilepsy
$GABA_BR$-IgG1 [95,101–105]	Neuronal synaptic G protein-coupled receptor involved in inhibitory synaptic transmission	*Sex (F:M)*: 2:3; *Age of Onset (median [range]:* 60 y/o (15-80 y/o)	Limbic encephalitis with a prominent seizure phenotype (often temporal with secondary generalisation +/- status epilepticus)	50% have tumours (mainly SCLC)	*CSF*: 50-80% lymphocytic pleocytosis; *MRI*: 30% NAD; 40-50% mesial temporal lobe T2H (can be bilateral); *EEG*: 75% ictal abnormalities	60-70% of patients with seizures achieve seizure freedom after immunotherapy (and tumour removal where indicated)	Up to 40% mortality – usually due to malignancy; 10% relapse rate
DPPX-IgG1, IgG4 [106–108]	Extracellular subunit of Kv4.2; influences potassium channel gating in cerebellum, hippocampus, and myenteric plexus	*Sex (F:M)*: 1:2; *Age of Onset (median [range]):* 55 y/o [13-90 y/o]	Prodrome of diarrhoea and weight loss with chronic progressive cognitive impairment (with agitation and hallucinations), followed by seizures (20-25%), sleep dysfunction; tremor, myoclonus and hyperekplexia, bulbar dysfunction, autonomic dysfunction	B cell neoplasms in up to 10% (e.g., gastrointestinal follicular lymphoma, chronic lymphocytic leukaemia)	*CSF*: 30% abnormal (lymphocytic pleocytosis, increased protein or OCB); *MRI*: NAD or non-specific; *EEG*: 70% focal or diffuse slowing	60-70% respond at least partially to aggressive ITx	15-20% mortality; 20-30% relapse rate
mGluR1-IgG1 [104,109]	mGluRs are G-protein coupled synaptic glutamate receptors. Implicated in memory,	*Sex (F:M)*: 2:3; *Age of Onset (median [range]):* 55 y/o [6-65 y/o]	Subacute cerebellar ataxia, neuropsychiatric symptoms and seizures	Nil recognised	*CSF*: 75% abnormal (pleocytosis or OCB); *MRI*: Usually normal, sometimes cerebellar T2H and atrophy chronically; *EEG*: 62% interictal	Can improve early with ITx; however, relapses often occur on discontinuation	50% stabilise or mildly improve from nadir; 40% significant or complete improvement;

	learning, anxiety and nociception				abnormalities		10% mortality
mGluR5-IgG1 [86,104,110–112]	Important for synaptic depression in the hippocampus	*Sex (F:M)*: 2:3; *Age of Onset:* 20-30 y/o (6-75 y/o)	Subacute cognitive impairment (memory deficit, confusion, psychiatric symptoms)	~70% have Hodgkin lymphoma (Ophelia Syndrome)	*CSF*: Pleocytosis very common; 75% OCB; *MRI*: 55% NAD, mesial temporal and cortical diffusion restriction reported; *EEG*: 50-60% slowing, 20% epileptiform (esp. paediatric)	Broadly responsive to lymphoma treatment and ITx	At 4 years: 20% mRS>=2. <5% risk of epilepsy
GlyR-IgG1 [113–117]	Ionotropic receptor that facilitates inhibitory transmission in brainstem and spinal cord, α subunit	*Sex (F:M)*: 3:2; *Age of Onset (median [range]):* 45 [1-80 y/o]	Progressive encephalomyelitis with rigidity and myoclonus (PERM)	10-15% have tumours (mainly thymoma), also lymphoma, breast cancer	*CSF*: 25-40% pleocytosis, 20% OCB; *MRI*: 5% temporal T2H, 30% non-specific T2H, 20% myelitis; *EEG*: 60% slowing, 15% epileptiform; EMG: 60% continuous motor unit activity	40-45% full recovery, 20-35% partial recovery	15% relapse rate; 5-10% mortality
Neurexin-3α-IgG1 [86,118]	Presynaptic cell adhesion molecule important for synapse formation and development	*Sex (F:M)*: 3:1; *Age of Onset (median [range]):* 45 y/o [20-60 y/o]	Prodromal fever, headache, gastrointestinal symptoms; encephalopathy with agitation,80% have seizures, orofacial dyskinesias, central hypoventilation	Nil recognised	*CSF*: Pleocytosis frequently occurs; *MRI*: 20% mesial temporal T2H	75% ITx initially responsive	40% mortality; complete recovery rare
SEZ6L2-IgG4 [119,120]	Antigen found near AMPAR in the cerebellum	*Sex (F:M)*: 3:2; *Age of Onset (median [range]):* 60 y/o	Subacute ataxia, mild extrapyramidal	1/5 reported cases died of ovarian	*CSF*: 25% pleocytosis; *MRI*: Chronic cerebellar	Some response in few cases	At 3 years: Median mRS 4

	and hippocampus.	[50-70 y/o]	symptoms and memory and language deficits	cancer	atrophy in 1 reported case;		
D2R-IgG [121]	Postsynaptic receptor in striatum, important for dopaminergic transmission and motor control, extracellular domain of N-terminus	*Sex (F:M)*: 1:1; *Age of Onset (median [range]):* 6 y/o [1-15 y/o]	Parkinsonism, dystonia, chorea and hypersomnolence; neuropsychiatric features (OCD, psychosis and emotional lability are common) – 'basal ganglia encephalitis'	Nil recognised	*CSF*: 25% lymphocytic pleocytosis, 50% increased protein, 40% OCB; *MRI*: 50% bilateral basal ganglia T2H/ swelling/ enhancement, may have atrophy on follow up; *EEG*: 50% slowing (0 epileptiform)	ITx responsive	25% relapse rate
GluK2-IgG1[122]	Kainate tetrameric ionotroptic glutamate receptors regulate excitatory and inhibitory presynaptic transmitter release.	*Sex (F:M)*: 2:3; *Age of Onset:* 30 y/o (14-75 y/o)	Acute to subacute cerebellar ataxia and altered level of consciousness. 1/8 reported cases with seizures.	Nil recognised unless positive for AMPAR-Ab also (thymoma and SCLC reported)	*CSF*: 80-90% pleocytosis, 25-30% OCB; *MRI*: 50% cerebellar T2H, 25% obstructive hydrocephalus; *EEG*:	2/7 partial recovery; 1/7 full recovery	After 2.5 years: 40-45% mRS<=2 25-30% mortality (1/7 "cause unknown" death)

Table 2: Mechanisms of action of immunotherapies

	Agent	Known specific mechanisms of action
First-line treatment	Corticosteroid [123,124]	• Impairs upstream B-cell receptor signalling and reduces the transcriptional output from genetic immunoglobulin loci • Affects T-cells via interference with transcription of their key growth factor (IL-2) • Impairs pro-inflammatory functions of monocytes and macrophages • Induces apoptosis of B-cell subsets, dependent on stage of differentiation
	Intravenous immunoglobulin [125,126]	• Inhibits Fc receptors required for immune cell activation once pathogenic antibodies have attached to their target • Inhibits FcRn which is responsible for recycling IgG and prolonging IgG half-life • Activates inhibitory Fc receptors to suppress production of inflammatory mediators • Neutralisation of circulating autoantibodies by anti-idiotypes
	Plasma exchange [127]	• Removes immune complexes, complement and cytokines, amongst other proteins
Second-line treatment	Rituximab [128]	• Depletes B-cells expressing CD20 • Does not target long-lived plasma cells • Both B cells in lymph nodes and the central nervous system may show resistance due to limited rituximab penetration
	Azathioprine [129]	• Cell division inhibitor which is converted to a purine analogue which competes with inosine monophosphate (IMP) to block the synthesis of guanosine monophosphate and thus DNA. • Generates a compound which binds to Rac1, which is required for CD28 co-stimulation
	Mycophenolate	• Cell division inhibitor via blocking the activity of IMP
	Methotrexate	• Cell division inhibitor via blocking the production of tetrahydrofolate, which is important for purine and pyrimidine synthesis and therefore DNA
	Cyclophosphamide [130]	• Cell division inhibitor which alkylates DNA, thereby increasing crosslinking and decreasing DNA synthesis • Good CNS penetration of non-polar active metabolites[130]
Third-line treatment	Tocilizumab [31]	• Inhibits membrane-bound and soluble IL6-R • IL-6 is an important cytokine for activation of lymphocytes by other immune cells from both the innate and adaptive immune systems • IL-6 promotes T-cell growth and differentiation, especially during acute phase responses
	Bortezomib [131]	• Proteosome inhibitor leading to the build-up of proapoptotic factors and cell death, especially in plasma cells due to their high protein turnover • Prior to cell death, it also causes dysfunction of the ubiquitin-proteasome pathway required for angiogenesis, cell-cell adhesion and proliferation

Table 3: Currently used and proposed standardised data collection in autoimmune encephalitis research cohorts. ***Abbreviations****: ACE-R - Addenbrooke's Cognitive Examination-Revised; BDI - Beck depression inventory; CTCAE - Common terminology criteria for adverse events; DN4 - Douleur Neuropathique 4; EQ-5D-5L - EuroQol-5 Dimensions-5 Levels; FSMC - Fatigue Scale for Motor and Cognitive Function; HADS - Hospital anxiety and depression score; MFIS - Modified fatigue impact scale; mRS - Modified Rankin score; PROMIS-PI - Patient-reported outcomes measurement information system - Pain interference; RBANS - Repeatable Battery for the Assessment of Neuropsychological Status; SARA - Scale for the assessment and rating of ataxia; VAS - Visual Analogue Scale*

Domain	*Components*	*Method(s) of assessment*
Clinical characterisation (Inclusive of the Clinical assessment scale in encephalitis (CASE) breakdown [81]) To be completed at disease onset and at relapse nadir	Consciousness	Glasgow Coma Score
	Central hypoventilation	Presence/absence
	Seizures	Seizure semiology and frequency (events/day)
	Movement disorder	Description of phenomenology (dystonia, dyskinesia, stereotypies, chorea etc)
	Cognitive impairment	Addenbrooke's Cognitive Examination-Revised (ACE-R)
	Psychiatric manifestations	Presence/ absence and description (e.g., catatonia, psychosis, mood, behaviour, etc)
	Sleep dysfunction	Presence/ absence and description (rapid eye movement sleep behaviour disorder, sleep wake reversal)
	Gait instability and ataxia	Presence/ absence; Scale for the assessment and rating of ataxia (SARA)
	Brainstem dysfunction	Presence/ absence
	Neuromyotonia/ PNH	Presence/ absence, neurophysiological results
	Pain	Douleur Neuropathique 4 (DN4)
Therapeutic interventions	Relapses	Number of relapses, time to first and subsequent relapses
	Time to therapy and therapy escalation	Time from disease onset to first-line immunotherapy, second-line immunotherapy, and third-line immunotherapy
	Treatment regimes	Dose, duration, weaning schedule
	Adverse effects	According to the Common terminology criteria for adverse events (CTCAE)
Outcome data To be calculated at disease onset, relapse nadirs, at 12 months post disease onset, and annually thereafter	Global measures of outcomes	Modified Rankin score, EuroQol-5 Dimensions-Visual Analogue Scale
	Cognitive	ACE-R, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Cognitive performance score (CPS), formal neuropsychometry
	Pain	Patient-reported outcomes measurement information system - Pain interference (PROMIS-PI) score
	Mood	Hospital anxiety and depression score (HADS), Beck depression inventory (BDI)
	Fatigue	Modified fatigue impact scale (MFIS), Fatigue Scale for Motor and Cognitive Function (FSMC)
	Quality of life	EuroQol-5 Dimensions-5 Levels

Figure Legend

Figure 1: Disease mechanisms in autoimmune encephalitis and immunotherapeutic targets

(A) Median serum and cerebrospinal fluid (CSF) antibody titres in patients summarised from multiple cohorts consistently demonstrate the principle that autoantibodies are present at higher titres in serum compared to the CSF across a number of autoimmune encephalitis syndromes [20,25,97,99,101,132–140]. (B) This data is represented as a ratio of serum:CSF titres in these specific AE syndromes.

Figure 2: Immunotherapeutic mechanisms in autoimmune encephalitis

Developmental lineage of B cells highlighting which subpopulations of B cells are targeted by first-, second- and third-line immunotherapeutic agents.

Abbreviations: *CD – Cluster of Differentiation; CSR – class switch recombination, IgG immunoglobulin G, IgM immunoglobulin M, IL – Interleukin; IL-6R – interleukin-6 receptor, FcRn – Neonatal fragment crystallisable region of IgG; IMP – Inosine monophosphate; GMP – Guanosine monophosphate; DHFR – Dihydrofolate reductase; mAb – Monoclonal antibody; SHM – somatic hypermutation*

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