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Autoimmune encephalitis

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Abstract

Autoimmune encephalitis (AE) is a treatable neuro-inflammatory disorder increasing in incidence. AE can be associated with malignancy (paraneoplastic), but in many patients no tumour is present. The disease presentation of AE can be heterogeneous, depending on the type of antibody involved. AE is often caused by neuronal antibodies that bind to extracellular autoantigens(i.e. NMDAR, LGI1). Binding of these antibodies causes dysfunction of synaptic receptors, which leads to neurological symptoms. In these patients treatment with immunosuppressive therapies, is believed to decrease inflammation and deplete antibodies, and is essential for recovery. AE can also occur in patients with antibodies against intracellular antigens (i.e. Hu, Ri), in the setting of malignancy tumour treatment is essential for stabilization or improvement. Most frequent symptoms occurring are cognitive problems, behavioural changes and seizures. Rapid recognition of the syndromes is essential as earlier treatment of AE leads to better outcomes. For a definite diagnosis, identification of an autoantibody is a perquisite. However, some patients have seronegative AE. Most patients are severely affected during the acute disease, but long-term functional recovery is often good, particularly for patients without cancer. However, residual anxiety, fatigue and cognitive problems can have major impact on quality of life. Research focuses on improving our understanding of pathophysiological processes, establishing patient-tailored outcome measures, optimizing treatment prediction models and studying different therapeutic regimens, all aiming to improve treatment and long-term outcomes.

[H1] Introduction

Autoimmune encephalitis (AE) is a neuro-inflammatory disease that causes progressive inflammation of the brain. AE is often characterized by the presence of neuronal antibodies, for example anti-N-Methyl-D-Aspartate Receptor (anti-NMDAR), anti-leucine-rich glioma-inactivated 1 (anti-LGI1), anti-Glutamic Acid Decarboxylase 65 (anti-GAD65) anti anti-Hu. AE can be paraneoplastic paraneoplastic, but in many AE patients no tumour is present. Other less frequent provoking factors are recent herpes simplex virus 1 (HSV1) encephalitis[1] and the use of immune checkpoint inhibitors in the treatment of cancer.[2]

Studies have identified >15 neuronal antibodies and their related syndromes have been described in detail.[2] The description of clinical syndromes has improved awareness, reflected by an increase in the prevalence of AE. Mostly AE manifests as limbic encephalitis,s

but can affect all regions of the brain. Initially AE was considered only in the diagnostic work-up of severely ill patients with a subacute onset of cognitive problems, often combined with psychiatric symptoms and refractory seizures or status epilepticus. Today, it is known that not all patients develop a severe limbic or pan-encephalitis, but that patients can also have prolonged disease courses with less prominent symptoms. An example is anti-LGI1 encephalitis; most patients gradually develop focal seizures or (combined with) facio-brachial dystonic seizures (FBDS), followed by cognitive impairment and focal to bilateral tonic-clonic seizures.

Prior research has also focused on earlier recognition of symptoms, making diagnosis more uniform. One of the main forward steps has been the diagnostic guidelines published in 2016.[3] In antibody-negative patients the established criteria to diagnose ‘probable seronegative AE’ have been very useful.[4] In addition, the criteria for ‘probable anti-NMDAR encephalitis’ have facilitated earlier immunotherapy in those with high suspicion of this form of AE. Other factors that aim to improve earlier and better AE diagnosis are the availability of different diagnostic prediction tools, including the PNS-CARE score,[5] and optimization and better interpretation of different laboratory techniques. Altogether, the field of AE still suffers from both underdiagnosis and misdiagnosis. With increased knowledge and awareness it should be feasible to decrease both in the near future.

Concerning AE treatment, the first randomized trial evaluating immunotherapy effect has been published[6] and several are recruiting or are in development. These trials, as well as other types of research to asses treatment effects, will make a significant contribution to standardization of treatment regimens. These steps are essential to aim for precision medicine in the future, comparing different treatments using patient-specific characteristics from multiple countries and cohorts, necessary in rare diseases like AE. Further, all efforts share of the goal of accelerating functional recovery in patients, and improve long-term cognitive outcomes.

In this review we describe the pathophysiological mechanisms, the diagnostic process, treatment prognosis, quality of life and future perspectives of AE focusing on the adult patient.

[H1] Epidemiology

[H2] Definition and incidence

AE is an umbrella term including specific biomarker-defined variants with clear published case definitions (e.g. anti-NMDAR encephalitis) and variants of exclusion (probable seronegative AE [for definition see paragraph “diagnosis”]). AE comprises both patients with an autoimmune etiology and a paraneoplastic etiology. It is a rare disease with an estimated cumulative incidence of 0.5-1/100.000 persons/year (Table 1) in adults and between 1.0 and 1.3/100.000/year in children (mainly driven by the higher incidence of anti-NMDAR encephalitis and acute disseminated encephalomyelitis [ADEM]. Described incidence vary because of evolving disease concepts,[3] selection bias in available cohorts, and incomplete case registrations.
Although prior cohort studies describing overall incidence initially included ADEM (often associated with myelin oligodendrocyte glycoprotein [MOG] antibodies),[3] generally ADEM, glial autoimmune syndromes (i.e. other MOG antibody associated diseases [MOGAD],[7] or neuromyelitis optica spectrum disease [NMOSD][9]) are considered acute demyelinating syndromes (ADS), and not AE. Other neuronal antibody associated syndromes, like stiff person syndrome are not included in AE incidence calculations but can have phenotypic and serologic overlap with AE.[10] AE sequelae which follow up to 25% of young patients after HSV1 encephalitis are part of the AE spectrum.[11] Encephalitis syndromes with an infectious, metabolic or toxic cause and encephalitis associated with systemic conditions are not included in the definition of AE.[3]

The introduction of immune therapies (collectively referred to as immune-checkpoint inhibitors) in oncology has led to various immune related adverse event (IrAE). Between 1-3% of patients suffer from these complications.[12,13] of whom less than half have AE (with or without detectable autoantibodies). Since these therapies are being approved in more and more tumor entities, the incidence of IrAE is likely to increase and will become a larger part of the total amount of AE cases.

Considering the rarity of AE, incidence rates are mostly derived from large cohorts recruited by expert centers specialized in autoantibody testing **(Table 1).** Often, there is considerable selection bias, and coverage is mostly incomplete. Population-based cohorts in small countries or regions are limited by the final case numbers in rare disease. Unfortunately, national health-care databases are currently not well suited to evaluate the incidence of AE; the ICD-10 classification does not specifically categorize AE, and the more comprehensive OrphaNet coding is not universally applied in most countries. Despite these methodological differences, values across studies show very good concordance **(Table 1).**

[H2] Demographics

The sex and age spectrum varies considerably within AE variants **(Figure 1).** Strong female (e.g. adult onset teratoma-associated anti-NMDAR encephalitis)[14] and male predominance (e.g. anti-CASPR2 autoimmunity and in anti-LGI1 autoimmunity 60% are male)[1516] occur, yet in other variants both sexes are affected in roughly equal proportions (Figure 1A). AE occurs in children, adolescents and adults of all ages, yet each age group has specific “spectra” of causative AE variants **(Figure 1).** Most pediatric patients with antibody-positive AE have NMDAR or MOG antibodies.[11,17,18] Elderly adults rarely have ADEM with MOG antibodies, while CASPR2 antibodies mainly occurs in male patients >65 years of age. Older adults – often with a history of smoking – often have underlying small cell lung cancer (SCLC).[5] Of note, some AE variants have a bimodal age distribution with important differences in tumor associations. The rare anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (anti-AMPAR) encephalitis can be seen in young and middle-aged adults with thymoma, but more frequently idiopathic, while older patients often have breast or lung cancer.[19]

[H2] Risk factors

The main reported risk factors in certain AE variants are 1) underlying tumors of neuroectodermal or neuroendocrine origin or lymphoma (paraneoplastic), 2) presence of certain hetero- or homozygous HLA-haplotypes,[20-22] 3) prior use of immune checkpoint inhibitors, 4) recent episodes of viral encephalitis. More specific, in 25% of patients with recent HSV1 anti-NMDAR encephalitis occurs with an interval of 3-8 weeks, and AE has also been described after Japanese Encephalitis.[23] There appears to be a seasonal variance in NMDAR with a summer and autumn predominance of clinical onset, yet the responsible risk factors are unknown.

[H3] Genetic risk factors

In some AE variants, a strong genetic predisposition exists. 85%-90% of anti-LGI1 encephalitis patients carry HLA-DRB1*07:01,[20,21,24] and homozygosity confers a doubling of risk.[25] Yet around 12%-27% of the healthy population carries this HLA haplotype.[21,24] What constitutes the probable “second” factor is currently unknown; cross-reacting microbial peptides in susceptible individuals are just one hypothesis. Not all AE variants have an HLA-based predisposition. More than 50% of anti-NMDA receptor encephalitis cases[14] and almost all MOG-encephalitis cases[26] occur in children and young adults without any of these trigger factors and without strong HLA associations.[24,27]

[H2] Geographical heterogenicity

Most available epidemiological studies include anti-NMDA receptor encephalitis patients. For this disease, reported incidence ranged from 0.09 to 0.26/100.000/year and tended to be considerably higher in different regions: in countries with Black, Asian or Hispanic individuals incidences is 4 to 7-fold higher than in regions with mainly White individuals.[14,28] In New Zealand, incidence is higher among Pacific islander or Maori children.[29] Interestingly, in China anti-NMDAR encephalitis is more frequently seen in male patients while it has a strong female predominance elsewhere, shows a milder disease course, less ICU admission, is less frequently associated with ovarian teratomas and has a different HLA association.[30-32]

For another common variant, anti-LGI1 encephalitis, the incidence is described as around half the rate of anti-NMDAR encephalitis (0 6-1.4/million), and rarely affects black patients.[33] But a study (mainly including white patients) reports an incidence comparable to anti-NMDAR

encephalitis.[34] Interestingly, the incidence rate of anti-LGI1 encephalitis is considerably lower in Japan, and mainly paraneoplastic, likely as the HLA (DRB1*07:01) seen in 85-90% of idiopathic cases[20-22] hardly occurs in this country.[35]

[H1] Mechanisms/pathophysiology

Generally, AE is caused by misguided adaptive, antigen-specific immune reactions targeting the central nervous system (CNS). This general concept can be dissected into four stepwise, partially overlapping, and interacting pathogenic processes (Figure 2): (1) One or a combination of co-occurring trigger factors results in a breach of immunological tolerance. (2) The autoantigen-specific immune reaction is initiated, and antigen-specific lymphocytes are propagated to the target tissue. (3) Specific autoantigen-targeted immune reactions occur in the CNS. (4) Synaptic function is affected, leading to network disruptions. The type of target antigen, function, anatomical, and subcellular localization determine the phenomenology. Understanding these mechanisms, and their relative dominance in each syndrome, provides a rationale to tailor treatments. Broadly, diseases mediated via CD8+ T cell tissue injury, particularly associated with antibodies to intracellular epitopes, require different therapeutic considerations to those where the autoantibodies target extracellular epitopes and are considered pathogenic.[36] Within this latter group, the precise mechanisms by which the autoantibodies cause disease offer further nuances in terms of likely effective therapies. For example, AQP4-antibodies readily fix complement on the surface of astrocytes, causing downstream cellular lysis: complement blocking therapies have proven successful in AQP4-positive patient clinical trials. By contrast, NMDAR-antibodies are reported to act predominantly by acutely reducing channel function and internalization,[37] with limited evidence supporting involvement of complement.[38] Correspondingly, mouse models and retrospective human data have shown that drugs which modulate channel function and B cell depletion are effective therapies,[14,39] whereas complement inhibition has not been trialed. In diseases where protein-protein interactions are likely dominant mechanisms of these autoantibodies (e.g. those targeting LGI1 and CASPR2),[40-43] therapies which target these interacting domains or their downstream effects (e.g. AMPAR expression) may be effective interventions. More broadly, these autoantibody mediated syndromes may be effectively treated with drugs which deplete IgG or tackle the underlying active B and plasma cell responses: these modalities are the subject of ongoing clinical trials in the field.[44]

[H2] Breach of tolerance and autoimmunity development

The best-studied trigger factors for AE are - often small and occult - tumors with ectopic expression of neuronal/synaptic autoantigens.[5] One common tumor entity is SCLC.[45] In this situation, immune reactions against tumor-specific antigens are part of the natural “anti-tumor” response. However, some of these antigens are ectopically expressed neuronal “self” antigens (onconeural antigens, e.g., HuD in anti-Hu syndrome). These “onconeural” immune reactions are beneficial for tumor defense but detrimental to the central, and sometimes peripheral, nervous system. Onconeural autoimmunity only very rarely occurs without underlying tumors.[46] Indeed, tumor removal, to eliminate the ongoing presentation of self-antigen, is still the most potent therapeutic intervention, confirming the dominant effect of this factor. Not all associated tumors necessarily have to be malignant. Up to 35% of patients with anti-NMDAR encephalitis have underlying benign cystic ovarian teratomas.[14] These teratomas express NMDA receptors and show a dense infiltration of T-, B-lymphocytes, and plasma cells, and the intratumoral B cells show NMDAR-reactivities,[47,48] indicating ongoing anti-tumor immune responses which lead to the development of NMDA receptor-specific autoimmunity.[49]

It remains poorly understood why some patients with tumors develop paraneoplastic neurological syndromes and some don’t. Host-specific (hereditary and acquired) and tumor-specific factors have been hypothesized. The former includes a weak association with specific HLA haplotypes[50] and peculiarities of central and peripheral tolerization of onconeural autoantigens in the thymus.[51] Tumor-specific factors are expression levels or mutations of onconeural antigens[52] and modulation of tumor-immune interactions[53] with the presence or absence of tertiary lymphoid-like structures in the tumor tissue.[54] Indeed, similar tumors display a strong inter-individual heterogeneity of the inflammatory response observed within the tumor (immunotypes) [55]. Both host and tumor factors interact in a cancer-immunity cycle,[55] resulting in a more or less T-cell-promoting inflammatory tumor microenvironment. Differences in this interaction between patients could explain why some develop paraneoplastic neurological syndromes and others do not. However, the specific mechanisms shaping the anti-tumor immunity leading to paraneoplastic immune complications are only marginally understood.

Further insights into underlying mechanisms stem from two clinical observations: post-infectious-encephalitis-CNS-autoimmunity and tumor-immune-therapy associated-AE. Up to

25% of patients with HSV1 encephalitis eventually develop symptomatic secondary autoimmune encephalitis targeting NMDA receptors and/or other neuronal antigens[23] and increased expression level of interferon type I-related genes. Viral replication in neurons generates pathogen-associated molecular patterns (PAMPs, e.g., double-stranded RNA), which activate pattern recognition “danger” receptors (PRRs, e.g., Toll-like receptor 4) and leads to the production of “antiviral” type I interferons.[23] These are potent activators of antigen-presentation and expression of T-cell costimulatory signals.[56] This suggests that combining neuronal tissue destruction (virus-mediated) with potent co-stimulatory T-cell signaling is sufficient for breaching endogenous tolerance to neuronal self-antigens. Yet not only co-stimulation but also absence of co-inhibition of T-cells can result in autoimmunization. With the advent of pharmacologic blockade of co-inhibitory signaling (immune checkpoints inhibitors) to enhance endogenous anti-tumor immunity, it became clear that autoimmunity is a common complication. Indeed, ~1% of patients develop AE.

More conventional B cell checkpoints, those which maintain central and peripheral tolerance,[58] have been investigated as points of failure in disease versus health.[43] By identifying CASPR2-reactive naïve B cells at equal proportions in health and disease, but CASPR2-reactive memory B cells only in disease, the authors conclude that permissive central tolerance operates in both states. But defective peripheral tolerance in patients permits licensing of pathogenic CASPR2-reactive antibodies. Similar future approaches aim to delineate key checkpoints which may control antigen-specific tolerance.

In most patients neither tumors nor preceding viral encephalitis can be identified as triggers (idiopathic AE).

[H2] Propagation autoimmune reaction and blood-brain barrier crossing

Following this initial “breach of tolerance,” systemic components of the immune system are needed to propagate the adaptive immune response observed in AE. There is evidence that regional secondary lymphoid organs (lymph nodes) might be involved.[47,59] Indeed, only within lymph nodes are the necessary constituents for propagation of CNS autoimmunity in close proximity: soluble autoantigen from the brain via g-lymphatic pathways, antigen-presenting dendritic cells, activated antigen-experienced T-lymphocytes and mature B-lymphocytes converge in lymphoid follicles/germinal centers. Germinal centers in lymph nodes in NMDA

receptor encephalitis[47,60] and AQP4 neuromyelitis optica[59] have been shown to contain affinity-matured B-lymphocytes, producing autoantibodies targeting the respective antigens. Similar constituents are present in tumor-draining lymph nodes (e.g., SCLC and mediastinal lymph nodes; teratoma and pelvic lymph nodes) where the presentation of the antigen to the immunological system occurs. This “spatial convergence” is able to promote the process of affinity maturation, inducing point mutations in hypervariable regions of the B-cell receptor (somatic hypermutation). The recombinant autoantibodies derived from patients with anti-LGI1[61] and anti-CASPR2 encephalitis[58,62,63] or clonally expanded intrathecal plasma cells from patients with anti-NMDA receptor encephalitis[64] show strong somatic hypermutation supporting this theory.[62-64] Most likely, the regional draining lymph nodes involved in teratoma-associated anti-NMDAR encephalitis are mediastinal and, cervical in bothnon-teratoma anti-NMDAR encephalitis and HSV1 encephalitis.

While the role of CD8 T-cells in AE with intracellular antigens is mostly undisputed, some evidence exists for the involvement (or absence) of CD4 T-lymphocytes in the propagation of the immune reaction in other AE variants. For anti-NMDA receptor encephalitis, a genome-wide association study identified an association to a gene involved in T-cell-independent B-cell-activation.[27] Yet in several “late-onset” AE variants (e.g., LGI1, CASPR2, IgLON5) there is a stronger case: Strong linkage of certain HLA class II haplotypes (see above) and the occurrence of IgG4-isotype autoantibodies strongly indicate CD4-T-cell help. Indeed, both IgG4 class switch and affinity maturation are CD4-T-cell dependent, and recent work provided some evidence of both together with clonally restricted CD4 (and also CD8) T-cells in the CSF of patients with anti-LGI1 and -CASPR2 encephalitis.[60,62] Thus, CD4-T-lymphocytes may play a role in promoting autoimmunity in some of these AE variants. Some evidence also points to a role of non-conventional T-cells, namely mucosa-associated invariant T-cells (MAIT), in propagating this immune response.[60]

The next step in the pathogenic chain of events is for autoantigen-specific lymphocytes to cross the blood-brain barrier, proliferate and survive in the CNS? A hallmark of AE is the predominant infiltration of B-cells and, to a lesser degree, T-lymphocytes surrounding the cerebral vessels in the Virchow-Robin spaces,[65] which also frequently contain plasmablasts[66] and plasma cells.[38] Fittingly, CXCL13, a strong B-cell attractant, can be found in the CSF of patients with acute

NMDAR encephalitis.[67] This CNS B-cell chemo-attraction's source has not been solved. It is tempting to speculate that the frequent (around 50%)[14] prodromal symptoms observed in anti-NMDAR and other AEs represent inflammatory episodes initiating this B-cell attraction and propagation of antibody-secreting B-cells into the CNS. However, ectopic, lymph-follicle-like structures (as observed in the meninges of patients with secondary progressive multiple sclerosis)[68] have not been demonstrated in AE patients. Nevertheless, it is plausible that the meninges - as an immunologically active organ barrier - play a role in shaping the immune response via their recently described capacity for negative selection of autoreactive B-cells,[69] which might be dysfunctional in AE.

[H2] Components of the immune reaction

One of the best-studied factors influencing pathogenicity, reversibility, and prognosis is the subcellular localization of the autoantigen:[70] intracellular versus cell-membrane-localized (neuronal surface). Intracellular “onconeural” autoantigens are mostly observed in patients with malignant neuroendocrine tumors. Hu-specific T-cells are present in the CSF of patients[71] and evidence from human histopathology points towards a cytotoxic T-cell mediated process.[72,73] Even though highly specific autoantibodies are present in high titers in serum and CSF,[74] they do not reach and bind their intracellular target antigen within intact cells or cause neuronal damage in vitro[75] or in vivo.[76] Yet they are extremely useful biomarkers. In contrast, patients with autoantigens localized on the neuronal surface (e.g., NMDA receptors, CASPR2, etc.) with or without underlying tumors often have better responses to therapy, outcome, and prognosis.[14,77] In these patients, neuropathological studies do not provide clear evidence of cytotoxic mechanisms.[65] Instead, the autoantibodies in vitro[78] and in vivo[79] bind their target antigen in intact cells and influence its function (see next section). The B-cell epitopes are highly conformational, and some variants with neuronal surface or extracellular autoantigens (LGI1,[80] CASPR2,[81,82] IgLON5[83]) show prominent IgG4 isotype autoantibodies. This peculiar antibody isotype is observed in situations of chronic antigen exposure, such as allergen tolerization,[84] are hardly able to activate complement and can be functionally monovalent,[85] reducing their cross-linking capacity. The immunologic cause and functional effects of this observation for pathogenicity are currently still unclear but recent investigations in myasthenia gravis suggest monovalency increases pathogenicity.[86] Finally, an evolving branch of research in AE and autoimmunity in general addresses the role of post-translational modifications (glycosylation,

etc.) of the constant region of the antibodies (Fc-terminus), which modify the crosstalk with different components of innate immunity such as antibody-dependent phagocytosis (by monocytes, neutrophils, or microglia), antibody-dependent cellular cytotoxicity (by natural killer cells), or antibody-dependent complement toxicity. In MOGAD, some evidence points towards a relevant role of the mechanism.[87]

[H2] Synaptic pathology and network effects

Behavioral, epileptic, and encephalopathic symptoms in AE are the result of synaptic, neuronal, and network dysfunction. AE associated with autoantibodies targeting intracellular antigens (e.g., anti-Hu syndrome) is caused by cytotoxic T-cell mediated destruction of synapses and neurons **(Figure 2)**. The discovery of neuronal surface autoantibodies has given rise to a new concept in neuroimmunology: autoantibodies that can directly and reversibly modulate synaptic function, thus leading to behavioral, cognitive, movement dysfunction and epileptic seizures. This concept is strikingly different from classical antibody-effector functions (complement, antibody-dependent cytotoxicity). The question of how these antibody effects are synapses conveyed has been addressed using several different in vitro and in vivo models and approaches **(Table 2 and supplementary Table 1)**. Some antibodies (e.g. NMDA receptor antibodies) have cross-linking abilities, causing multimeric "receptor-rafts," breakdown of signaling, trafficking, and intracellular scaffolding. Ultimately, internalization and degradation of these dysfunctional complexes lead to a net loss of surface receptor density. Another mechanism (e.g. in LGI1 antibodies) is steric interference with scaffolding proteins **(Figure 2).** This results in the breakdown of the synaptic architecture and (via diffusion out of the synapse) net loss of receptors and channels.[81] These mechanisms can co-occur: in anti-NMDA receptor encephalitis, cross-linking-mediated internalization of the NMDAR, interference with its surface dynamics,[88] and disruption of the cross-talk with other synaptic partners (ephrinB2-receptor, dopamine receptor) participate in the pathogenesis.[89,90] Similarly, autoantibodies against LGI1, which target distinct epitopes on the same molecule, may have different pathogenic role.[41] Direct effects on the electrophysiological properties of single receptors also play a role. Synaptic G-protein coupled receptors (e.g., $GABA_B$ receptor, mGluR5) are directly modulated by autoantibodies, and some evidence also points to changes in NMDA receptor electrophysiology.

Mechanistically understanding of synaptic dysfunction mediated by autoantibodies is important for translational therapeutic approaches. In vitro and in vivo experiments have shown that small molecules binding to receptors can change their tertiary conformation (positive allosteric modulators). This results in changes that improve synaptic function via changes in cell-surface dynamics of receptors and partial antagonism of antibody-mediated internalization, quickly counteracting the autoantibody effects, which current immunotherapies are unable to do.[88,90,91]

In summary, the specific autoantigen and its tissue and subcellular localization are major factors in the pathogenic mechanisms. They directly or indirectly influence the clinical phenotype, course, immunological triggers, chronicity, reversibility and prognosis, relapse propensity, and differential response to immunotherapy. This strongly supports the categorization of autoimmune encephalitis subtypes according to the target autoantigen, e.g. anti-NMDA receptor encephalitis. Ultimately, a thorough understanding of each of the pathogenic mechanisms underlying these diseases is not only essential for unraveling the physiopathology but also for the exploitation of process-specific markers and the development of “process-targeted” therapies.

[H1] Diagnosis, screening and prevention

[H2] Diagnostic criteria

AE is clinically diagnosed based on the recognition of core symptoms. These symptoms include memory deficits, psychiatric symptoms (psychosis, catatonia, behavioural changes), seizures, confusion, and altered consciousness.[3] The appearance of these can be acute, subacute, or more chronic and typically this depends on the associated autoantibodies.[3,92]

In 2016 a consensus guideline was published to accelerate and optimize the diagnosis and treatment of AE.[3] The diagnostic algorithm provided can be used as a three-layered filter. The first layer is possible AE or minimal requirements to suspect autoimmune encephalitis in the acute clinical setting. They include (1) acute or subacute onset (<3 months) of working memory deficits, altered mental state, or psychiatric symptoms, together with (2) at least one of the following criteria: i) new focal CNS symptom, ii) new-onset seizures, iii) cerebrospinal fluid (CSF) pleocytosis (>5/μL), or iv) brain MRI suggestive for encephalitis. (**Table 3**) Regardless of the level of evidence, it is crucial to exclude alternative diseases.[4] The second layer is probable

AE including probable anti-NMDAR encephalitis.[3] If these criteria are met, it is recommended to start (first-line) immunotherapy before diagnosis is confirmed with antibody testing. Recently, criteria for probable anti-LGI1 encephalitis have been suggested and validated.[4] (**Table 3**) The third filter is definite AE, consisting of a typical clinical syndrome according to the combined with positive antibody status.

[H2] Differential diagnoses

The differential diagnosis of AE is extensive and depends on clinical symptoms and results from ancillary testing. Distinguishing AE from infectious encephalitis can be challenging in the early stages, as clinical presentation and CSF findings can be similar. However, brain MRI can be helpful in such scenarios; for example, bilateral limbic T2/FLAIR hyperintensities are more common in AE compared with infectious encephalitis.[11] In every patient, comprehensive microbiological testing (blood and CSF) is required to exclude potential infectious causes and, in some, overlaps with rapidly progressive neurodegenerative conditions,[93] metabolic disorders and genetic mimics should be considered.[4] Notably, a multicenter study published in 2023,[94] described over a hundred patients misdiagnosed with AE; the most common alternative diagnoses were: functional neurological disorders, neurodegenerative diseases, primary psychiatric diseases, cognitive deficits from comorbidities, and cerebral neoplasms. Another study, describing over 200 patients suspected of AE, also showed that AE mimics are frequent.[4] Specificity of 'possible AE' is too low to allow it to be classified as a diagnosis (25%). Red flags and contributors that should raise suspicion for an alternative diagnosis are an insidious onset of symptoms, the absence of MRI or CSF findings suggestive for neuroinflammation, and overinterpretation of nonspecific antibody test results.[4,94,95]

However, within the 2016 guideline probable seronegative AE became a new entity.[3] This is a diagnosis per exclusion with well-defined criteria: 1) acute or subacute onset (< 3 months) of working memory deficits, altered mental state, or psychiatric symptoms, (2) absence of autoantibodies in serum and CSF, (3) at least two of the following criteria: i) mesiotemporal abnormalities on MRI [T2/FLAIR], ii) CSF abnormalities (pleocytosis, CSF-restricted oligoclonal bands [OCB] or raised immunoglobulin G [IgG] index), iii) pathologically confirmed AE.[96] These criteria have been applied successfully since,[97] and validated to be specific.[4] In the remaining patients, fulfilling criteria of possible AE, but without autoantibodies, it is important to

exclude other causes.[95] Specificity of ‘possible AE’ is too low to allow it to be classified as a diagnosis.[4]

One caveat is that several syndromes do not present subacu[98]te and take months to years to develop, therefore not fulfilling entry criteria for this diagnostic algorithm. This is mostly reflected in anti-IgLON5 and anti-CASPR2 diseases[92] and anti-GAD-associated syndromes. Additionally, especially in anti-LGI1 encephalitis, patients can also present with prominent seizures, but without fulminant encephalitis.Another caveat, is that the algorithm should not be applied to patients without clinical features of encephalopathy (working memory deficits, altered mental state, or psychiatric symptoms), for example, the algorithm should not be used in cases of cerebellar symptoms, brainstem encephalitis or myelopathy.

[H2] Ancillary testing

Neuroimaging with brain MRI can reveal specific features of limbic encephalitis, including bilateral medial temporal lobe T2 or FLAIR hyperintensities.[3,99] However, unilateral medial temporal lobe T2 or FLAIR hyperintensities can be seen as well, yet are considerably less specific. (**Figure 3**) In ADEM, but also in anti-gamma aminobutyric acid-A receptor (anti-$GABA_AR$) encephalitis, multifocal poorly demarcated large white matter lesions occur.[100] In MOGAD, AE signs of cortical encephalitis can be seen, with T2/FLAIR focal hyperintensity and swelling in cortical regions.[3] Nevertheless, a normal brain MRI does not exclude AE.

Conversely, some abnormal brain imaging findings can help to exclude other diagnosis, such as herpes encephalitis, glioma, lymphoma, Creutzfeldt-Jakob disease, and vasculitis, particularly MRI abnormalities extending beyond the mesiotemporal lobes, contrast enhancement, or diffusion restriction.[4,94,101] Longitudinal follow-up MRI assessments are clinically significant for confirming treatment responses, observing the resolution of previously observed T2/FLAIR lesions, capturing the progression of brain atrophy indicative of unfavorable clinical outcomes,[102] and detecting recurrent, or new, brain lesions.

CSF analysis frequently shows pleocytosis or increased total protein. Intrathecal antibody synthesis, characterized by an elevated CSF IgG index or OCB, is frequently associated with active immunopathogenesis within the CNS compartment.[103] Meanwhile, the prevalence of abnormal CSF findings varies depending on the associated autoantibodies; frequent in patients

with anti-NMDAR encephalitis[14] and rarer in those with LGI1, CASPR2 or IgLON5 antibodies.[16,92] Importantly, a normal routine CSF analysis is not uncommon in AE.[98] Electroencephalography (EEG) frequently shows slowing or epileptiform discharges. Extreme delta brushes are a distinctive pattern seen in anti-NMDAR encephalitis,[104] but only in a minority of mostly severely affected patients.[105]

Fluorodeoxyglucose positron emission tomography (FDG-PET) is not part of the routine diagnostic work-up of patients with possible AE in most patients. Although it is a sensitive tool, the specificity to distinguish from other neurological disorders is limited. It can be used in patients with rapid progressive dementia to distinguish between an autoimmune or neurodegenerative etiology. In anti-NMDAR encephalitis, FDG-PET can show frontal hypermetabolism and relative occipital hypometabolism.[106,107]

[H2] Antibody testing

Autoantibody testing plays a crucial role in establishing a definite AE diagnosis. Sometimes, these autoantibodies may represent the only paraclinical finding indicating neuroinflammation, especially for patients with LGI1, CASPR2 and IgLON5 antibodies.[16,92 108] The different available neuronal antibody tests include commercially available kits as well as in-house assays carried out only by experienced laboratories. The main techniques are tissue-based assays (TBA) [indirect immunohistochemistry or immunofluorescence on rodent brain tissue], immunoblots, cell-based assays (CBA), enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA) and live hippocampal neurons.

A comprehensive evaluation of both serum and cerebrospinal fluid (CSF) specimens is essential to increase diagnostic accuracy.[109] In most commercial antibody tests, specificity of CSF is higher compared to serum.[34] For anti-NMDAR encephalitis, CSF is also more sensitive and specific, [98,110,111] and the same applies to GFAP antibodies.[112] However, in testing for LGI1 antibodies, sensitivity using widely employed commercial test systems, is higher in serum compared to CSF.[15,113] It is important to realize that across the globe differing testing methods could be contributory, but that in some countries not all tests are available.

In interpreting test results, it is important to consider some issues. First, commercial kits, carry a high risk of false positive results, especially when testing serum only.[109,114] Therefore, antibody positivity should be confirmed by a second technique, preferably in a reference laboratory,

especially when the clinical presentation does not match the known phenotype.[95] Secondly, low titer test results obtained through ELISA (GAD65)[115] often lack clinical relevance.[116] It should also be noted that some patients may exhibit the concomitant presence of multiple antibodies, as demonstrated by double positivity for anti-NMDAR and MOG-IgG [117,118] or GFAP and NMDAR.[119]

[H2] Genetic testing

HLA analysis is not currently part of the routine diagnostic work-up of AE. However, associations have been described with specific HLA subtypes, and may be part of future management approaches. Examples include HLA-DRB1*07:01 in approximately 90% of patients with anti-LGI1 encephalitis,[20,21] DRB1*11:01 in 48%-94% of patients with anti-CASPR2 encephalitis,[22,120] DQB1*05:01 in approximately 85% of patients with anti-IgLON5 encephalitis,[121] and HLA-DQB1*02:01/HLA-DRB1*03:01 in 60-70% of patients with anti-Kelch-like protein 11 (KLHL11) encephalitis.[57]

[H2] Tumour screening

In general, in patients with suspected paraneoplastic etiology, tumor screening involves low-dose chest computed tomography (CT) and contrast-enhanced CT of the abdomen and pelvis, accompanied by mammography/breast ultrasound or MRI in females and testis ultrasound in males.[5,122] If screening is negative, usually positron emission tomography CT (PET-CT) is performed.[5,122] However, FDG-PET is not a sensitive tool to screen for mature teratomas.[122] Pelvic magnetic resonance imaging (preferentially 3T MRI with gadolinium), pelvic or transvaginal ultrasound are sensitive modalities for detecting small ovarian teratomas in anti-NMDAR encephalitis.[123] In the absence of an initial cancer diagnosis, repeated screening every 3-6 months for a period of at least 2 to 5 years[124] is advisable for patients with high PNS Care scores, reflecting high cancer risks.[5] This diagnostic score combines phenotype, antibody type and presence of a tumor (Table X).

[H1] Management

The comprehensive management of AE requires both the rational use of available pharmacotherapeutics and a multidisciplinary team-based approach to holistic care throughout

554 the often lengthy duration of the disease course. A comprehensive, multidisciplinary approach to
555 care is needed to optimize recovery from autoimmune encephalitis. Beyond neurologic care,
556 many other specialties serve an integral role in diagnosing and treating AE, including psychiatry,
557 critical care, pediatrics, oncology and rehabilitation medicine.[125]

558 Firstly, patients diagnosed with AE require rapid administration of empiric immunotherapies.[126]]
559 These should be initiated as soon as clinical suspicion permits a confident diagnosis, even
560 without the results of specialized neural autoantibody testing. This enables early immunotherapy,
561 a factor associated with improved neurologic outcomes in the two commonest forms of AE,
562 associated with LGI1- or NMDAR-antibodies.[3,4,14,33,127,128] Of course, this must be balanced
563 against the significant and established risks of mis- or over-diagnosis.[94] These risks include
564 infections and the opportunity to diagnose lymphomas or systemic inflammatory diseases.

565 Alongside immunotherapies, one important consideration is the effective and prompt treatment
566 of tumours, when present. This intervention can help to improve or to stabilize some patients.[129]
567 In addition to immunotherapies, other considerations include the use of symptomatic therapies
568 including anti-seizure medications (ASMs), sedation for behavioral features and drugs to treat
569 movement disorders. In general, these are far less effective than immunotherapies and are
570 required at large doses before clinical effects are observed. Also, in particular some ASMs
571 associate with significant allergic reactions or behavioral side effects.[22,130,131] Together, their
572 efficacy combined with adverse effects have a lower priority in AE.

573

574 **[H2] Immunotherapies - first line options**

575 Early in the disease, immunotherapies can be categorized into two broad categories: first line and
576 subsequent second line.

577

578 ***[H3] Corticosteroids:*** Corticosteroids are generally initiated as soon as AE is strongly suspected.
579 Corticosteroids exert broad anti-inflammatory effects, and are widely available.[132]
580 **(Supplementary Table 2)**. In patients with anti-LGI1 encephalitis in particular, seizure
581 reductions are seen with this intervention alone, typically over just days to weeks. However,

thereafter, these patients may be transitioned to oral prednisone/day to prevent the relapses observed with rapid corticosteroid tapering.[33] By contrast, in patients with anti-NMDAR encephalitis, around 50% of patients improve within four weeks, so immunotherapy escalation is warranted in many.[14,128,131] The value of steroid sparing agents is driven by very limited available data. In many cases – especially severe cases - steroids are often combined with IVIg and/or plasma exchange.

[H3] Plasma Exchange (PLEX): PLEX is thought to remove circulating antibodies, immune complexes, and cytokines.[133] The effect of PLEX can be apparent within just a few days. Although, it is challenging to attribute improvements to any individual agent. PLEX may be performed with central or peripheral venous access. The latter reduces the two main risks, significant hemorrhage and infection, and is more simple to administer in agitated or psychotic patients with AE.[134]

[H3] Intravenous Immunoglobulins (IVIg): IVIg is theorized to exert its effect via one of several immunomodulatory functions including neutralizing autoantibodies and/or cytokines, saturating neonatal Fc receptors to decrease antibody recycling, and inhibiting the complement cascade.[135] IVIg has been assessed in the only randomized controlled trial in AE. Although numbers were small and the effect was modest, IVIg did improve seizure and cognitive outcome by comparison to placebo.[6]

[H2] Further immunotherapies – second and third line, maintenance agents

After first-line agents, attention is given to how much of a clinical improvement has been observed. To date, no biomarkers exist to supplement the rational approach to this assessment. The degree of improvement, the known trajectory of the individual disease, and the consideration of relapse prevention guides the potential administration of second line agents. Typically, these have been used in cases considered refractory, or with unsatisfactory improvements, after first line agents, mostly those with anti-NMDAR encephalitis. Options include rituximab, cyclophosphamide and to a lesser extent tociluzimab, bortezomib, mycophenalate mofetil, azathioprine and maintenance IVIg.[126] In the authors' experiences, the vast majority of cases only receive either rituximab or cyclophosphamide.

Additionally, many novel, emerging medications have been studied in smaller numbers. These include complement inhibiting therapies, anti-CD38 monoclonals, BAFF/APRIL inhibitors,

calcineurin inhibitors, integrin inhibitors, and janus kinase (JAK) inhibitors. Below we discuss the experience with medications, mechanism of action are shown in **Figure 4**.

[H3] B-Cell Targeting Therapies*:* B-cells differentiate into antibody-secreting cells, present antigen to activate T-cells and secrete a variety of signaling molecules.[136] The ability to use monoclonal antibodies to deplete B-cells, by exploiting B-cell-restricted surface markers such as CD20 and CD19, provides an opportunity to potentially target all these roles, and offer options in a broad range of diseases. Although CD19 is expressed on a wider B-lineage, from pro-B-cell to some plasma cells, the direct role of CD19+CD20- antibody secreting cells in autoantibody-mediated diseases remains uncertain.[63,137] As CD20 therapies (i.e. Rituximab) do not reduce autoantibody levels substantially, it has been proposed that they work by termination of human germinal center reactions which appear important to the propagation of many of these diseases.[47,59] Each CD20 and CD19 depleter has distinctive target epitopes and binding affinity, with consequently differing mechanisms of B-cell depletion. These drugs also differ in immunogenicity, and frequency of infusion-related reactions,[138] but no head-to-head comparisons between these agents limits the ability to make specific recommendations. Yet, rituximab is currently the only medication in this class included in the WHO Model List of Essential Medicines, making it most accessible worldwide. Meta-analyses of patients with AE, NMOSD, and pediatric CNS inflammatory disorders show promising results for rituximab therapy.[139-142] In anti-NMDAR encephalitis, rituximab is associated with a reduction in modified Rankin Scale (mRS) and mortality, versus administration of no second line therapies.[14] The largest study of rituximab in AE has shown no clear benefit in the acute treatment of patients with anti-LGI1- and anti-GAD65 encephalitis,[77] although this study was not powered nor designed to identify an effect.

Inebilizumab is the only monoclonal antibody in the CD19 subclass studied in neurologic disease. Inebilizumab is FDA-approved for the treatment of NMOSD,[143] and an ongoing clinical trial in anti-NMDAR encephalitis (The ExTINGUISH Trial, NCT04372615) will inform its role in this AE. Its mechanism of action may be very similar to anti-CD20 therapies, although only small autoantibody reductions have been observed.[144]

Both rituximab and inebilizumab deplete peripheral B-cells for around 6-9 months. Regular dosing upon B cell reconstitution enhances compliance but increases infectious risks of infections and can render some patients hypogammaglobulinaemic. In particular, data from patients with MS suggests a particularly steep rise in infections after rituximab,[145] of relevance to the multiple later onset forms of AE, associated with antibodies to LGI1, CASPR2 and Iglon5.

In addition, cellular B cell depleting therapies are an emerging field. There are very few data in AE and related neurological diseases as yet,[146,147] but the striking and durable results in drug refractory lupus and systemic sclerosis cases has garnered enthusiasm for this approach.[148]

[H3] Inhibitors of DNA Synthesis: DNA synthesis Inhibition unselectively results in death of rapidly dividing cells. Many classical chemotherapeutic agents fall into this class. These medications are associated with toxicity at high doses, but at lower doses adverse effects are more limited.[126]

Cyclophosphamide is a cytotoxic alkylating agent with particular sensitivity to hematopoietic cells such as B and T-cells. Outside of oncology indications, this broad lymphocyte targeting, in addition to its crossing of the blood-brain barrier, has made it a valuable second-line treatment in autoimmune neurologic disorders. While affordable and with a relatively rapid onset, side effects include myelosuppression, bladder toxicity, gonadal toxicity, and subsequent malignancy. However, these are especially related to its chronic use, and cumulative doses much higher than those reached in acute AE treatment.[149]

Two other commonly used agents which interrupt DNA synthesis are azathioprine and mycophenolate mofetil. Both inhibit key pathways of cell division, purine metabolism and adenosine monophosphate dehydrogenase respectively, to which frequently dividing lymphocytes are especially sensitive. Azathioprine has been used as second-line immunotherapy in cases AE with different antibodies and MMF less frequently, but has been suggested to prevent relapses in patients with LGI1-antibody encephalitis.[150] However, a major drawback of either is that perceptible clinical benefit can take several months to achieve which, in these diseases, likely limits use exclusively to potential steroid sparing agents in reducing relapse rates, as these can be as high as 40% in some patient groups.

[H3] Cytokine Antagonists: Cytokines exert a wide variety of immunological effects, including the development and coordination of innate and adaptive immune responses.[151] Hence, cytokine antagonists are used to treat various systemic inflammatory and autoimmune conditions. The most relevant targeted cytokine in AE is IL-6.

IL-6 is a highly pleotropic pro-inflammatory cytokine which can promote B-cell survival, stimulate antibody production, support T-helper cell proliferation and, away from direct immune effects, decrease blood-brain barrier dysfunction.[152,153] IL-6R targeted monoclonal antibodies disrupting this pathway include tocilizumab and satralizumab. In retrospective series, the staged 'T-SIRT' approach (teratoma-steroids-IVIg- rituxi [145]mab-tociluzimab) has been reported to lower mRS in patients with anti-NMDAR encephalitis,[123] although many were treated very early with tocilizumab. In NMOSD, satralizumab has been shown to be effective in reducing relapses.[154,155] The CIELO clinical trial (NCT05503264) is currently recruiting to investigate the safety and efficacy of satralizumab in anti-NMDAR and anti-LGI1 AE.

[H3] Neonatal Fc Receptor Inhibiting Therapies: The neonatal Fc Receptor (FcRn) is expressed widely, including on endothelial cells and, at this site, extends the half-life of IgGs by endocytosing antibodies and preventing their degradation in circulation.[156] Blockade of FcRn results in a dramatic reduction of circulating IgG levels, often to 30% of baseline. Hence, unlike CD20/19-depleting targeting therapies, these drop IgG levels. However, akin to B cell depleters, they lack selectivity for the pathogenic autoantibodies.

Rozanolixizumab is a FcRn-directed monoclonal antibody now approved for the treatment of anti-AChR myasthenia gravis (MG) as well as anti-MuSK+ MG patients; randomized controlled trials are also studying its use for MOGAD.[157] [150]

[H3] Proteasome Inhibitors*:* Inhibitors of the proteasome subunits prevent protein degradation leading to the accumulation of toxic protein species, with subsequent cell death. As plasma cells have an especially high production of their key secreted proteins (antibodies), they are relatively susceptible to these drugs. There are case reports of patients with treatment-refractory anti-NMDAR encephalitis that suggest a possible benefit of bortezomib.[158-161] the Generate-Boost clinical trial (NCT03993262) is currently investigating its role in refractory AE.[162] However, its poor CNS penetration and lack of effect on CSF-enriched plasmablasts may limit this approach.[63,163]

[H1] Quality of life

Patients post-AE can experience a range of outcomes, with neural antibody type and underlying pathophysiology contributing to heterogeneity. Clinical relapses are seen in 12-35%,[164] and mortality can range between 5-40% depending on etiology and disease severity.[14,165,166] Disability is often measured using the mRS and long-term disability can be influenced by neural antibody type, immunosuppression, severity (including intensive care admission) and duration of follow up. In a large cohort of anti-NMDAR encephalitis patients followed for 24 months, 81% had a good mRS (0-2).[14] AE associated with high-risk paraneoplastic antibodies often have worse outcomes in terms of disability and mortality.[57,167]

The contemporary recognition of AE means there is a limited longitudinal data and AE-specific outcome measures. The mRS may fail to capture AE-specific longitudinal symptoms.[168] Patients post-AE often experience cognitive dysfunction, fatigue, sleep and mood disorders[169] that may not appear for months to years.[48,170-172] The clinical assessment scale in AE (CASE) was designed to more accurately grade disease severity in AE. It is a composite score including; seizures, memory dysfunction, psychiatric symptoms, level of consciousness, language problems, movement disorders, gait instability and ataxia, brainstem dysfunction, and weakness. This score correlates well with mRS, however as it was developed in a cohort enriched with anti-NMDAR encephalitis patients, it may not fully capture symptoms in other encephalitis cohorts.[173,174] Further, due to its aggregate structure, it may not capture detailed cognitive and mood symptoms (ceiling effect). It may be most useful in acute and subacute setting.

Cognitive impairment can be objectively evaluated with screening tools and neuropsychological testing. After anti-NMDAR encephalitis several cognitive domains can be affected..[175-179] The frequency depends on age, neuronal antibody, comorbidities and test batteries employed Psychiatric symptoms such as psychosis and mania are frequent in the acute phase of anti-NMDAR encephalitis.[78,180] Long-term psychological symptoms are frequent including depression and anxiety and may impact upon quality of life and contribute to other symptoms such as cognition.[169] In anti-LGI1 encephalitis, cognitive deficits have also been observed frequently after the acute disease, and also REM sleep behavior disorders.[181]

Seizures are frequent at the onset of AE, but the incidence of long-term epilepsy is more limited. In patients with AE and intracellular antibodies structural brain damage is common and the risk of developing epilepsy is higher compared to patients with cell-surface antibodies.[131,182,183 182,184], The risk of developing epilepsy after anti-LGI1 encephalitis varies between 3% and 25% [131,185-189] There are caveats interpreting these data, like the inclusion of relapses, selection bias for refractory cases and underdiagnosis of subclinical seizures, but in the authors' experience the most accurate frequency is below 10%.

Global function and quality life can be impacted by AE. In a longitudinal study of anti-NMDAR encephalitis patients, 50% were unable to return to work or use transport or travel in their communities, with nearly half unable to manage their finances.[190,191] Among a cohort of Anti-LGI1 encephalitis patients, only 15% returned to their premorbid role and many reported fatigue as a residual symptom.[172] Indeed, in this condition, residual fatigue is the main predictor of quality of life,[192,193] also captured in the recently developed LGI1-specific patient-reported outcome measure (LANTERN).[ref 181] Also, both pain and fatigue featured as prominent features in patients with anti-CASPR2 diseases, and were in fact predictors of quality of life outcomes and relapses.[194] Hence, these non-conventional features may hold both diagnostic and prognostic value.

[H1] Outlook

To date, AE is a well-described, treatable neuro-inflammatory condition. The incidence of AE has increased due to better recognition of symptoms and signs, and due to the optimization of laboratory techniques. Good international collaboration, essential in "rare" diseases, has contributed to these improvements. Important achievements are the diagnostic guidelines published in 2016 and 2021.[3,5] These guidelines contain well-defined criteria that help in clinicians: 1) when to include AE in the differential diagnosis in the acute setting (possible AE), 2) when to start immunotherapy before antibody results return (probable AE), 3) when to make a definite diagnosis (definite AE), and 4) how to rate and identify paraneoplastic syndromes and associated tumours. Next to better recognition of AE, more attention has been paid to diagnostic pitfalls.[95] Prior studies have focused on describing characteristics that occur more in AE than in alternative diagnoses and vice versa and also on optimizing antibody assays. Examples are clinical prediction tools to use in patients with prominent seizures or focal epilepsy (i.e. APE2

score,[195] ACES score[196]), description of typical and atypical MRI findings, the rise in biomarker research (i.e. neurofilament light chain levels in patients with psychiatric symptoms.[197])

With gathered knowledge we are able to identify the right patients that require immunotherapy. However, an important question to be answered next is: what treatment needs an individual patient with AE to reach optimal outcome. In other words, patient-tailored treatment, depending on specific patient characteristics and disease signs.

Therefore, the focus of current research is aimed to study antibody effects, optimizing AE outcome measures and prediction tools, comparing different treatment protocols and studying effects and side-effects of new treatments. The vast and rapid expansion of platforms to investigate expression and effects of single cells in tissue, CSF and blood of AE patients before and after treatment will allow us to improve our understanding of pathophysiological mechanisms in AE. The large amount of data generated will necessitate active collaboration between different researchers across the globe to provide sufficient statistical power for these analyses. Despite the continued discovery of antibodies present in patients with AE, the latest discoveries have proven more difficult to reach the mainstream diagnostic process or failed confirmation beyond the initial publications. There is therefore a rationale to try to identify novel ways of antibody discovery relevant to clinical practice.

Concerning treatment, therapeutic approach to AE remains largely empiric. Research efforts should focus on identifying factors to stratify patients and undertake trials of rationale immunotherapy. In AE types, like anti-NMDAR or anti-LGI1 encephalitis, randomized controlled clinical trials are underway to provide evidence to support treatment decisions in the future. The challenge in these diseases is recruiting enough patients to complete a meaningful clinical trial; the success of these trials and others will depend on neurologists and patients around the world recognizing that evidence-based treatment guidance necessitates participation and inclusion in randomized controlled trials (RCTs). On the other hand, the current complexity of trials, the outrageous costs and time efforts limit progress in the field of medicine, even more in rare diseases like AE. There will therefore be a need for creative solutions to compare treatment strategies in patients. This will still need robustness to ascertain the effects and safety of therapies, but will also touch upon the flexibility of medicine agencies to allow other evidence beyond RCTs.

In addition to immunotherapeutics, there is a great need for treatments addressing symptoms in both the acute phase and in the long-term chronic phase beyond the AE. This includes among others fatigue, pain, social isolation, persistent cognitive deficits, epilepsy, depression, and anxiety in order to maximize clinical recovery. Many of these appear as key

There is increasing interest in the multitude of sequelae other than relapses only. It is therefore useful to allow for a multidisciplinary approach, including rehabilitation medicine, mental health care, social workers and other specialist, asking both patients and caregivers for other symptoms, considering a more extensive checklist and allowing for a holistic treatment. To determine what treatment is best creating a robust, and pragmatic AE outcome measurement tool is essential encompassing the full trajectory of illness (acute, post-acute and chronic). Research is needed to develop and validate AE-specific longitudinal outcome measures including; standardized neuropsychological test batteries, mood (particularly anxiety and depression) scales and patient reported outcome measures.

802 **Table 1: Reported incidence rates for common autoimmune encephalitis variants**

AE	Population		Type of cohort	Region	Publication	Estimated incidence rate n/100.000/year (95%-CI)
Anti-NMDA receptor encephalitis	All age groups	1995-2016	Regional, population-based	North USA	Dubey et al. Ann Neurol 2018[198]	0.03*
		2013-2018	Regional, Referral-center-based	Trento and Treviso, Italy	Zuliani et al. J Neuroimm 2021[199]	0.04 (0.01-0.13)
		2005-2006	Hospital-based	England	Granerod et al. Lancet Infect Dis 2010[200]	0.09
		2016-2018	National, referral laboratory-based^	France	Hebert et al. Neurology N2 2020[201]	0.09 (0.04-0.16)^
		2007-2019	National, laboratory-/referral-based	Netherlands	Bastiaansen et al. Neurology N2 2022[166]	0.1§ (0.062-0.159)
		2009-2018&	National, population-based	Denmark	Nissen et al. J Neurol 2022[202]	0.17&
		2011-2022	Regional	Southern California	Alsalek et al. Neurology N2 2024[28]	Black: 0.29 (0.13-0.46) Hispanic: 0.22 (0.15-0.28) Asian/Pacific Island 0.20 (0.08-0.33) White 0.04 (0.01-0.07)
		2015-2019	Regional, hospital-based	Saba, Malaysia	Wong et al. J Neuroimm. 2021[203]	Overall 0.23 **Adult:** Austronesian: 0.26 Chinese: 0.13 **Pediatric:** Austronesian:0.36 Chinese: 0.26
	Pediatric patients	2011-2017	National, population-based	Denmark	Boesen et al. Eur J Paediatr Neurol. 2019[204]	0,07
		2010-2011	National, survey-surveillance study	United Kingdom	Wright et al. Arch Dis Child 2015[205]	0.09 (95% CI 0.06-0.11)
		2008-2015	National, hospital-based	New Zealand	Jones et al. Dev Med Child Neurol 2017[29]	Non-Maori 0.02 (95% CI 0.0-0.1) Māori: 0.34 (05% CI 0.14-0.7) Pacific descent: 1.0 (95% CI 0.4-2.0)
		2009-2015	Regional, hospital-based	Hong Kong	Ho et al. Brain Dev 2008[206]	0.22 (95% CI 0.12-0.36)
Anti-LGI1 encephalitis	Adults$	2016-2018	National, referral laboratory-based^	France	Hebert et al. Neurology N2 2020[201]	0.06 (0.02-0.13)^
		2007-2015	National, referral laboratory-based	The Netherlands	van Sonderen et al. Neurology 2016[15]	0.08
		2013-2018	Regional, Referral-center-based	Trento and Treviso, Itlay	Zuliani et al. J Neuroimm 2021[199]	0.1 (0.05-0.23)
		2009-2018	National, hospital-based	New Zealand	Liem et al. J Clin Neurosci 2023[207]	0.14

AE (overall)[#]	**All age groups**	2016-2021	National, referral laboratory-based	The Netherlands	Kerstens et al, in prep 2024[34]	0.56 (0.52-0.61)
		2016-2018	National, referral laboratory-based	France	Hébert et al, Neurol N2 2020[201]	0.32 (0.29-0.34)
		1995-2015	Regional, laboratory-based	Minnesota, United States	Dubey et al, Ann Neurol 2018[198]	0.8
		2009-2017	Regional, laboratory-based	Northeastern Italy	Vogrig et al, J Neurol 2020[208]	0.89
		1987-2018	Regional, laboratory-based	Minnesota, United States	Shah et al, Neurol N2 2022[209]	0.6
	Pediatric patients	2015-2018	National, referral laboratory-based	The Netherlands	de Bruijn et al. Neurology N2 2020[17]	0.15 (0.1-0.24)

*Incidence rate based on entire observational interval from 1995 to 2016. Authors indicate an increase in antibody-positive AE in the interval 2006-2015 compared to 1995-2005 likely due to increased awareness from 0.1 to 0.6. However, incidence rate changes for anti-NMDAR encephalitis in particular, are not provided. The indicated incidence rate is likely underestimated. [&]incidence rate in the final year of observation 2018 is indicated. Prior years saw increasing incidence rate. [§]Across entire recruitment interval. Incidence rate peak in 2017: 0.15 (0.099-0.22). [^]Incidence rate based on the region with the best estimated completeness of coverage in France Rhône-Ain-Isère region. [$]Adults were defined as age>15years in Liem et al.[207] °Including 4/7 patients with MOGAD with ADEM presentation. ¨80% of the affected population were children. Estimated incidence rate in adults 0.05. [#]Including antibody-positive AE (and paraneoplastic) and seronegative AE, excluding ADEM.

Abbreviations: AE = autoimmune encephalitis, NMDAR= N-Methyl-D-Aspartate-Receptor, LGI1= Leucine-rich glioma-inactivated 1, ADEM = acute disseminated encephalomyelitis.

816 **Table 2. The spectrum of antibodies in autoimmune encephalitis**

	Neurologic phenotypes	**Systemic tumor**	**Antibody assay**[*,#]
Hu	Limbic encephalitis, encephalomyelitis, sensory polyneuropathy	85%, SCLC, neuroendocrine tumors	IB-IF
Yo	Paraneoplastic cerebellar degeneration	>90%, ovary, breast	IB-IF
Ma1	Limbic encephalitis, brainstem encephalitis, cerebellar degeneration	>75%, testicular (Ma2, young); lung, breast, gastrointestinal (Ma1, older age)	IB-IF
Ma2	Brainstem encephalitis, limbic encephalitis		IB-IF
CRMP5 (CV2)	Encephalomyelitis, sensorimotor polyneuropathy	>80%, SCLC, thymoma	IB-IF
Amphiphysin	Stiff-person syndrome, Limbic encephalitis, myelitis, polyneuropathy, PERM	80%, breast, SCLC, stomach	IB-IF
Ri	Opsoclonus-myoclonus, brainstem encephalitis	>70%, breast, lung, ovary	IB-IF
Tr (DNER)	Cerebellar dysfunction	>70% Hodgkin lymphoma	IB-IF/ CBA[$]
Kelch-like 11 (KLHL11)	Brainstem encephalitis, cerebellar ataxia, hearing loss, limbic encephalitis	~70% germ cell tumor	CBA
NMDAR	Psychosis, memory loss, language dysfunction, dyskinesia, autonomic dysfunction, central hypoventilation, sleep alterations (insomnia in acute stage; hypersomnia in post-acute stage)	~40% teratoma in female, mainly 12-45; ~25% carcinomas in patients >45y	CBA (CSF>serum)
LGI1	Limbic encephalitis Facio-brachial dystonic seizures (FBDS)^	<5%, thymoma	CBA (serum>CSF)
CASPR2	Encephalitis, Morvan syndrome	~50% in Morvan syndrome(, ~25% in other phenotypes, thymoma	CBA (CSF+serum)
$GABA_B$ receptor	Limbic encephalitis, prominent seizures	>50%, SCLC	CBA (CSF>serum)
$GABA_A$ receptor	Encephalitis with prominent seizures, status epilepticus ; very rare stiff-person syndrome	<10%, Hodgkin lymphoma, thymoma	CBA (CSF>serum)

AMPAR (GluR1/2)	Limbic encephalitis	~65%, lung, breast, thymoma	CBA (CSF>serum)
Glycine receptor (GlyR)	PERM (progressive encephalomyelitis with rigidity and myoclonus), Stiff-person syndrome	<10%, thymoma, Hodgkin lymphoma	CBA (S+CSF)
mGluR5	Encephalitis, confusion, psychiatric and memory deficits	~50%, Hodgkin lymphoma	CBA (CSF>serum)
DPPX	Encephalitis with hyperekplexia, rare PERM-like symptoms; prodromal weight loss and diarrhea	<10%, B cell lymphoma	CBA (CSF>serum)
AK5	Limbic encephalitis	No associated tumor	CBA serum = CSF
IgLON5	Parasomnia, sleep apnea, Bulbar, PSP-like	Tumours rare, HLA-DRB1*10:01	CBA (serum>CSF)
GFAP	Meningoencephalitis	<10%[†]	CBA (CSF>serum)
GAD65	Limbic encephalitis, refractory epilepsy, stiff-person syndrome, cerebellar ataxia	<5%	ELISA (serum, concentration >10.000IU/L ; CSF >100IU/L) CBA, RIA
MOG	Cortical encephalitis, optic neuritis, ADEM, myelitis.	Rare	flowcytometry (serum)

[*] If commercially available, characteristics of commercial test provided. [$] Tr on IF-IB, DNER on CBA. [†] Excluding GFAP post- check-point inhibitors. ^sudden, brief, unilateral dystonic posture primarily affecting the arm and often the ipsilateral face[130] (a combination of peripheral nerve hyperexcitability, autonomic dysfunction, and neuropsychiatric symptoms. [#] If available, use a conformational technique (usually tissue based assay in antibodies against extracellular antigens).

Abbreviations: SCLC = small cell lung carcinoma, PERM = progressive encephalopathy with rigidity and myoclonus, PSP = progressive supranuclear palsy, ADEM = acute disseminated encephalomyelitis, IB = immunoblot, IF= immunofluorescence, CBA = cell based assay, ELISA = enzyme-linked immunosorbent assay, RIA = radio-immuno assay, HSV = herpes simplex virus.

Table 3. Diagnostic criteria of autoimmune encephalitis

Possible autoimmune encephalitis	**Probable anti-NMDA receptor encephalitis**	**Probable anti-LGI1 encephalitis**	**autoantibody-negative autoimmune encephalitis**
Diagnosis can be made when all of the following criteria have been met:			
Subacute onset (< 3 months) of working memory deficits (short-term memory loss), altered mental status*, or psychiatric symptoms.	Rapid onset of at least four of the six major groups of symptoms: - Abnormal behaviour or cognitive dysfunction - Speech dysfunction (pressured speech, verbal reduction, mutism) - Seizures - Movement disorder, dyskinesias, or rigidity, abnormal posture - Decreased level of consciousness - Autonomic dysfunction or central hypoventilation	Subacute onset (<3 months) of both: -Memory deficits, and -Typical facio-brachial dystonic seizures or 5 or more (subtle) stereotypical focal seizures a day	Subacute onset (< 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms.
At least one of the following: -New focal CNS findings -Seizures not explained by a previously known seizure disorder -CSF pleocytosis - MRI features suggestive of encephalitis†	At least one of the following: -Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic ctivity, or extreme delta rush) -CSF with pleocytosis or oligoclonal bands		Absence of well characterised autoantibodies in serum and CSF, and at least two of the following criteria: -MRI abnormalities suggestive of autoimmune encephalitis* - CSF with pleocytosis or oligoclonal bands -Brain biopsy showing inflammatory infiltrates and excluding other disorders
Reasonable exclusion of alternative causes#			

* Altered mental status defined as decreased or altered level of consciousness, lethargy, or personality change.
† Brain MRI hyperintens signal on T2-weighted fluid-attenuated inversion recovery sequences highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving grey matter, white matter, or both compatible with demyelination or inflammation.
# CNS infections, septic encephalopathy, metabolic encephalopathy, drug toxicity, cerebrovascular diseases, neoplastic disorders, Creutzfeldt-Jakob disease, epileptic disorders, rheumatological disorders, mitochondrial diseases. Additionally in children: Kleine-Levin, Reye syndrome, inborn errors of metabolism.

Figure legends

Figure 1. **Demographics of AE variants.** (A) Percentage of females, (B) age distribution for anti-NMDAR encephalitis, and (C) age distribution of anti-LGI1 encephalitis.[34,201] The figures show the differences in age and gender in AE. As illustrated anti-NMDAR encephalitis occurs mostly in young females, anti-LGI1 encephalitis mostly in middle aged patients, and slightly more in males than in females.[34]

Figure 2. Visual summary of the pathogenic steps occurring in AE. A Initial breach of tolerance caused by different and sometimes interacting triggers. Currently, these factors encompass ectopic expression of autoantigen on tumors, viral encephalitis mediated brain tissue destruction leading to expression of autoantigen together with pro-inflammatory signals, genetic predisposition mainly caused by certain human leukocyte antigen (HLA) haplotypes and dysfunction of immune checkpoints (iatrogenic through anti-tumor medication, acquired in lymphoma or hereditary immune check-point dysfunction). **B** Propagation of the cellular immune reaction in the systemic compartment and development of clonally expanded antigen-specific T-, B- and plasma cells. Intrinsic autoantigen-specific factors (subcellular localization, tissue-expression, shedding), the type and inflammatory context (tumor, virus) of interaction and host-specific factors (HLA- and T-cell receptor repertoire) determine this autoantigen-specific immune response. In most situations, this process initially occurs in the systemic immune compartment (most likely the lymph nodes close to the trigger, such as tumor-draining lymph nodes, or cervical lymph nodes for herpes simplex encephalitis). Eventually, auto-antigen-specific lymphocytes cross the blood-brain barrier and establish themselves intrathecally. **C** The dominant effector mechanisms on the target tissue can be broadly categorized into antibody-

mediated humoral versus cellular-mediated cytotoxic (with several further distinctions) mechanisms. These categories associate with inherent differences in cytotoxicity, reversibility, and response to some immunotherapies. **D** The final step is the direct effect on neuronal/synaptic function via antibody-mediated cross-linking and internalization (upper panel), steric interference with protein-protein interactions (middle panel), interference with the surface dynamics of targeted receptors (e.g., NMDAR, not shown), disruption of intracellular scaffolding proteins or cytoskeleton (e.g., IgLON5, not shown), or direct T-cell mediated cytotoxicity (lower panel). This causes synaptic dysfunction, compensatory mechanisms, network disruption and ultimately neurologic symptoms. These are often reminiscent of symptoms observed in patients treated with pharmacologic antagonists of the specific synaptic protein. CSF cerebrospinal fluid HLA Human leukocyte antigen = MHC Major histocompatibility complex. *Created with BioRender.com*

Figure 3A Typical MRI scans of patients with autoimmune encephalitis

The most typical MRI pattern is a bilateral hyperintens signal on T2/FLAIR images in both mesial temporal lobes, defined as limbic encephalitis (A), another less common finding is unilateral hyperintensity of the mesial temporal lobe on T2/FLAIR images (B). In anti-GABAaR encephalitis multifocal poorly demarcated large white matter lesions occur as seen on this FLAIR sequence. (C). In anti-GFAP astrocytopathy a typical MRI feature is contrast-enhanced T1-weighted linear/radial perivascular enhancement (D). [4,101]

Figure 4. Schematic overview of different second line immunotherapies

References

1 Leypoldt, F. *et al.* Herpes simplex virus-1 encephalitis can trigger anti-NMDA receptor encephalitis: case report. *Neurology* **81**, 1637-1639, doi:10.1212/WNL.0b013e3182a9f531 (2013).

2 Abboud, H. *et al.* Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. *J Neurol Neurosurg Psychiatry* **92**, 757-768, doi:10.1136/jnnp-2020-325300 (2021).

3 Graus, F. *et al.* A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* **15**, 391-404, doi:10.1016/S1474-4422(15)00401-9 (2016).

4 Van Steenhoven, R. W. *et al.* Mimics of Autoimmune Encephalitis: Validation of the 2016 Clinical Autoimmune Encephalitis Criteria. *Neurol Neuroimmunol Neuroinflamm* **10**, doi:10.1212/NXI.0000000000200148 (2023).

5 Graus, F. *et al.* Updated Diagnostic Criteria for Paraneoplastic Neurologic Syndromes. *Neurol Neuroimmunol Neuroinflamm* **8**, doi:10.1212/NXI.0000000000001014 (2021).

6 Dubey, D. *et al.* Randomized Placebo-Controlled Trial of Intravenous Immunoglobulin in Autoimmune LGI1/CASPR2 Epilepsy. *Ann Neurol* **87**, 313-323, doi:10.1002/ana.25655 (2020).

7 Banwell, B. *et al.* Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. *Lancet Neurol* **22**, 268-282, doi:10.1016/S1474-4422(22)00431-8 (2023).

8 Fang, B. *et al.* Autoimmune Glial Fibrillary Acidic Protein Astrocytopathy: A Novel Meningoencephalomyelitis. *JAMA Neurol* **73**, 1297-1307, doi:10.1001/jamaneurol.2016.2549 (2016).

9 Wingerchuk, D. M. *et al.* International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* **85**, 177-189, doi:10.1212/WNL.0000000000001729 (2015).

10 Muniz-Castrillo, S. *et al.* Novelties in Autoimmune and Paraneoplastic Cerebellar Ataxias: Twenty Years of Progresses. *Cerebellum* **21**, 573-591, doi:10.1007/s12311-021-01363-3 (2022).

11 Armangue, T. *et al.* Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. *Lancet Neurol* **17**, 760-772, doi:10.1016/S1474-4422(18)30244-8 (2018).

12 Dubey, D. *et al.* Severe Neurological Toxicity of Immune Checkpoint Inhibitors: Growing Spectrum. *Ann Neurol* **87**, 659-669, doi:10.1002/ana.25708 (2020).

13 Farina, A. *et al.* Neurological adverse events of immune checkpoint inhibitors and the development of paraneoplastic neurological syndromes. *Lancet Neurol* **23**, 81-94, doi:10.1016/S1474-4422(23)00369-1 (2024).

14 Titulaer, M. J. *et al.* Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol* **12**, 157-165, doi:10.1016/S1474-4422(12)70310-1 (2013).

15 van Sonderen, A. *et al.* Anti-LGI1 encephalitis: Clinical syndrome and long-term follow-up. *Neurology* **87**, 1449-1456, doi:10.1212/WNL.0000000000003173 (2016).

16 van Sonderen, A. *et al.* The clinical spectrum of Caspr2 antibody-associated disease. *Neurology* **87**, 521-528, doi:10.1212/WNL.0000000000002917 (2016).

17 de Bruijn, M. *et al.* Pediatric autoimmune encephalitis: Recognition and diagnosis. *Neurol Neuroimmunol Neuroinflamm* **7**, doi:10.1212/NXI.0000000000000682 (2020).

18 Chen, L. W. *et al.* Antibody Investigations in 2,750 Children With Suspected Autoimmune Encephalitis. *Neurol Neuroimmunol Neuroinflamm* **11**, doi:10.1212/NXI.0000000000200182 (2024).

19 Hoftberger, R. *et al.* Encephalitis and AMPA receptor antibodies: Novel findings in a case series of 22 patients. *Neurology* **84**, 2403-2412, doi:10.1212/WNL.0000000000001682 (2015).
20 Kim, T. J. *et al.* Anti-LGI1 encephalitis is associated with unique HLA subtypes. *Ann Neurol* **81**, 183-192, doi:10.1002/ana.24860 (2017).
21 van Sonderen, A. *et al.* Anti-LGI1 encephalitis is strongly associated with HLA-DR7 and HLA-DRB4. *Ann Neurol* **81**, 193-198, doi:10.1002/ana.24858 (2017).
22 Binks, S. *et al.* Distinct HLA associations of LGI1 and CASPR2-antibody diseases. *Brain* **141**, 2263-2271, doi:10.1093/brain/awy109 (2018).
23 Armangue, T. *et al.* Neurologic complications in herpes simplex encephalitis: clinical, immunological and genetic studies. *Brain* **146**, 4306-4319, doi:10.1093/brain/awad238 (2023).
24 Mueller, S. H. *et al.* Genetic predisposition in anti-LGI1 and anti-NMDA receptor encephalitis. *Ann Neurol* **83**, 863-869, doi:10.1002/ana.25216 (2018).
25 Peris Sempere, V. *et al.* Human Leukocyte Antigen Association Study Reveals DRB1*04:02 Effects Additional to DRB1*07:01 in Anti-LGI1 Encephalitis. *Neurol Neuroimmunol Neuroinflamm* **9**, doi:10.1212/NXI.0000000000001140 (2022).
26 Hor, J. Y. & Fujihara, K. Epidemiology of myelin oligodendrocyte glycoprotein antibody-associated disease: a review of prevalence and incidence worldwide. *Front Neurol* **14**, 1260358, doi:10.3389/fneur.2023.1260358 (2023).
27 Tietz, A. K. *et al.* Genome-wide Association Study Identifies 2 New Loci Associated With Anti-NMDAR Encephalitis. *Neurol Neuroimmunol Neuroinflamm* **8**, doi:10.1212/NXI.0000000000001085 (2021).
28 Alsalek, S. *et al.* Racial and Ethnic Disparities in the Incidence of Anti-NMDA Receptor Encephalitis. *Neurol Neuroimmunol Neuroinflamm* **11**, e200255, doi:10.1212/NXI.0000000000200255 (2024).
29 Jones, H. F. *et al.* Anti-N-methyl-d-aspartate receptor encephalitis in Maori and Pacific Island children in New Zealand. *Dev Med Child Neurol* **59**, 719-724, doi:10.1111/dmcn.13420 (2017).
30 Gong, X. *et al.* Efficacy and tolerability of intravenous immunoglobulin versus intravenous methylprednisolone treatment in anti-N-methyl-d-aspartate receptor encephalitis. *Eur J Neurol* **29**, 1117-1127, doi:10.1111/ene.15214 (2022).
31 Zhang, H. *et al.* Long-Term Prognosis of Patients With Anti-N-Methyl-D-Aspartate Receptor Encephalitis Who Underwent Teratoma Removal: An Observational Study. *Front Neurol* **13**, 874867, doi:10.3389/fneur.2022.874867 (2022).
32 Liu, X. *et al.* Genome-Wide Association Study Identifies IFIH1 and HLA-DQB1*05:02 Loci Associated With Anti-NMDAR Encephalitis. *Neurol Neuroimmunol Neuroinflamm* **11**, e200221, doi:10.1212/NXI.0000000000200221 (2024).
33 Thompson, J. *et al.* The importance of early immunotherapy in patients with faciobrachial dystonic seizures. *Brain* **141**, 348-356, doi:10.1093/brain/awx323 (2018).
34 J, k. Autoimmune encephalitis: a nationwide study describing epidemiology and antibody testing pitfalls. *Neurol Neuroimmunol Neuroinflamm* (2024).
35 Oyama, M. *et al.* Association Between HLA Alleles and Autoantibodies in Dermatomyositis Defined by Sarcoplasmic Expression of Myxovirus Resistance Protein A. *J Rheumatol* **50**, 1159-1164, doi:10.3899/jrheum.2022-1321 (2023).
36 Segal, Y. *et al.* Toward curing neurological autoimmune disorders: Biomarkers, immunological mechanisms, and therapeutic targets. *Neuron*, doi:10.1016/j.neuron.2024.12.006 (2025).
37 Michalski, K. *et al.* Structural and functional mechanisms of anti-NMDAR autoimmune encephalitis. *Nature Structural & Molecular Biology* **31**, 1975-1986, doi:10.1038/s41594-024-01386-4 (2024).

38 Martinez-Hernandez, E. *et al.* Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis. *Neurology* **77**, 589-593, doi:10.1212/WNL.0b013e318228c136 (2011).
39 Maudes, E. *et al.* Neuro-immunobiology and treatment assessment in a mouse model of anti-NMDAR encephalitis. *Brain*, doi:10.1093/brain/awae410 (2024).
40 Patterson, K. R., Dalmau, J. & Lancaster, E. Mechanisms of Caspr2 antibodies in autoimmune encephalitis and neuromyotonia. *Ann Neurol* **83**, 40-51, doi:10.1002/ana.25120 (2018).
41 Ramberger, M. *et al.* Distinctive binding properties of human monoclonal LGI1 autoantibodies determine pathogenic mechanisms. *Brain* **143**, 1731-1745, doi:10.1093/brain/awaa104 (2020).
42 Petit-Pedrol, M. *et al.* LGI1 antibodies alter Kv1.1 and AMPA receptors changing synaptic excitability, plasticity and memory. *Brain* **141**, 3144-3159, doi:10.1093/brain/awy253 (2018).
43 Sun, B. *et al.* Permissive central tolerance plus defective peripheral checkpoints license pathogenic memory B cells in CASPR2-antibody encephalitis. *Sci Adv* **11**, eadr9986, doi:10.1126/sciadv.adr9986 (2025).
44 Abboud, H. *et al.* The Clinical Trial Landscape in Autoimmune Encephalitis: Challenges and Opportunities. *Neurology* **104**, e213487 (2025).
45 Seute, T., Leffers, P., ten Velde, G. P. & Twijnstra, A. Neurologic disorders in 432 consecutive patients with small cell lung carcinoma. *Cancer* **100**, 801-806, doi:10.1002/cncr.20043 (2004).
46 Villagran-Garcia, M. *et al.* Revisiting anti-Hu paraneoplastic autoimmunity: phenotypic characterization and cancer diagnosis. *Brain Commun* **5**, fcad247, doi:10.1093/braincomms/fcad247 (2023).
47 Al-Diwani, A. *et al.* Cervical lymph nodes and ovarian teratomas as germinal centres in NMDA receptor-antibody encephalitis. *Brain* **145**, 2742-2754, doi:10.1093/brain/awac088 (2022).
48 Yeshokumar, A. K. *et al.* Neurobehavioral outcomes in autoimmune encephalitis. *J Neuroimmunol* **312**, 8-14, doi:10.1016/j.jneuroim.2017.08.010 (2017).
49 Chefdeville, A. *et al.* Immunopathological characterization of ovarian teratomas associated with anti-N-methyl-D-aspartate receptor encephalitis. *Acta Neuropathol Commun* **7**, 38, doi:10.1186/s40478-019-0693-7 (2019).
50 de Graaf, M. T. *et al.* HLA-DQ2+ individuals are susceptible to Hu-Ab associated paraneoplastic neurological syndromes. *J Neuroimmunol* **226**, 147-149, doi:10.1016/j.jneuroim.2010.05.035 (2010).
51 Camdessanche, J. P. *et al.* Expression of the onconeural CV2/CRMP5 antigen in thymus and thymoma. *J Neuroimmunol* **174**, 168-173, doi:10.1016/j.jneuroim.2006.01.018 (2006).
52 Small, M. *et al.* Genetic alterations and tumor immune attack in Yo paraneoplastic cerebellar degeneration. *Acta Neuropathol* **135**, 569-579, doi:10.1007/s00401-017-1802-y (2018).
53 Vialatte de Pemille, C. *et al.* Transcriptomic immune profiling of ovarian cancers in paraneoplastic cerebellar degeneration associated with anti-Yo antibodies. *Br J Cancer* **119**, 105-113, doi:10.1038/s41416-018-0125-7 (2018).
54 Sautes-Fridman, C., Petitprez, F., Calderaro, J. & Fridman, W. H. Tertiary lymphoid structures in the era of cancer immunotherapy. *Nat Rev Cancer* **19**, 307-325, doi:10.1038/s41568-019-0144-6 (2019).
55 Mellman, I., Chen, D. S., Powles, T. & Turley, S. J. The cancer-immunity cycle: Indication, genotype, and immunotype. *Immunity* **56**, 2188-2205, doi:10.1016/j.immuni.2023.09.011 (2023).
56 Cao, L. L. & Kagan, J. C. Targeting innate immune pathways for cancer immunotherapy. *Immunity* **56**, 2206-2217, doi:10.1016/j.immuni.2023.07.018 (2023).

57 Dubey, D. *et al.* Expanded Clinical Phenotype, Oncological Associations, and Immunopathologic Insights of Paraneoplastic Kelch-like Protein-11 Encephalitis. *JAMA Neurol* **77**, 1420-1429, doi:10.1001/jamaneurol.2020.2231 (2020).
58 Meffre, E. & O'Connor, K. C. Impaired B-cell tolerance checkpoints promote the development of autoimmune diseases and pathogenic autoantibodies. *Immunol Rev* **292**, 90-101, doi:10.1111/imr.12821 (2019).
59 Damato, V. *et al.* Rituximab abrogates aquaporin-4-specific germinal center activity in patients with neuromyelitis optica spectrum disorders. *Proc Natl Acad Sci U S A* **119**, e2121804119, doi:10.1073/pnas.2121804119 (2022).
60 Esser, D. *et al.* Activated alphabeta T- and reduced mucosa-associated invariant T cells in LGI1- and CASPR2-encephalitis. *Brain*, doi:10.1093/brain/awaf096 (2025).
61 Kornau, H. C. *et al.* Human Cerebrospinal Fluid Monoclonal LGI1 Autoantibodies Increase Neuronal Excitability. *Ann Neurol* **87**, 405-418, doi:10.1002/ana.25666 (2020).
62 Esser, D. CSF plasma cell expansion in LGI1-/CASPR2-autoimmune encephalitis is associated with loss of regulatory MAIT cells. *biorxiv*, doi:https://doi.org/10.1101/2023.12.21.572754 (2023).
63 Theorell, J. *et al.* Ultrahigh frequencies of peripherally matured LGI1- and CASPR2-reactive B cells characterize the cerebrospinal fluid in autoimmune encephalitis. *Proc Natl Acad Sci U S A* **121**, e2311049121, doi:10.1073/pnas.2311049121 (2024).
64 Malviya, M. *et al.* NMDAR encephalitis: passive transfer from man to mouse by a recombinant antibody. *Ann Clin Transl Neurol* **4**, 768-783, doi:10.1002/acn3.444 (2017).
65 Zrzavy, T. *et al.* Neuropathological Variability within a Spectrum of NMDAR-Encephalitis. *Ann Neurol* **90**, 725-737, doi:10.1002/ana.26223 (2021).
66 Hara, A. *et al.* Circulating plasmablasts and follicular helper T-cell subsets are associated with antibody-positive autoimmune epilepsy. *Front Immunol* **13**, 1048428, doi:10.3389/fimmu.2022.1048428 (2022).
67 Leypoldt, F. *et al.* Investigations on CXCL13 in anti-N-methyl-D-aspartate receptor encephalitis: a potential biomarker of treatment response. *JAMA Neurol* **72**, 180-186, doi:10.1001/jamaneurol.2014.2956 (2015).
68 Magliozzi, R. *et al.* Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology. *Brain* **130**, 1089-1104, doi:10.1093/brain/awm038 (2007).
69 Wang, Y. *et al.* Early developing B cells undergo negative selection by central nervous system-specific antigens in the meninges. *Immunity* **54**, 2784-2794 e2786, doi:10.1016/j.immuni.2021.09.016 (2021).
70 Dalmau, J. & Graus, F. Antibody-Mediated Encephalitis. *N Engl J Med* **378**, 840-851, doi:10.1056/NEJMra1708712 (2018).
71 Roberts, W. K. *et al.* Patients with lung cancer and paraneoplastic Hu syndrome harbor HuD-specific type 2 CD8+ T cells. *J Clin Invest* **119**, 2042-2051, doi:10.1172/JCI36131 (2009).
72 Voltz, R., Dalmau, J., Posner, J. B. & Rosenfeld, M. R. T-cell receptor analysis in anti-Hu associated paraneoplastic encephalomyelitis. *Neurology* **51**, 1146-1150, doi:10.1212/wnl.51.4.1146 (1998).
73 Bernal, F. *et al.* Immunohistochemical analysis of anti-Hu-associated paraneoplastic encephalomyelitis. *Acta Neuropathol* **103**, 509-515, doi:10.1007/s00401-001-0498-0 (2002).
74 Vega, F. *et al.* Intrathecal synthesis of the anti-Hu antibody in patients with paraneoplastic encephalomyelitis or sensory neuronopathy: clinical-immunologic correlation. *Neurology* **44**, 2145-2147, doi:10.1212/wnl.44.11.2145 (1994).
75 Tanaka, K., Ding, X. & Tanaka, M. Effects of antineuronal antibodies from patients with paraneoplastic neurological syndrome on primary-cultured neurons. *J Neurol Sci* **217**, 25-30, doi:10.1016/j.jns.2003.08.006 (2004).

76 Sillevis Smitt, P. A., Manley, G. T. & Posner, J. B. Immunization with the paraneoplastic encephalomyelitis antigen HuD does not cause neurologic disease in mice. *Neurology* **45**, 1873-1878, doi:10.1212/wnl.45.10.1873 (1995).
77 Thaler, F. S. *et al.* Rituximab Treatment and Long-term Outcome of Patients With Autoimmune Encephalitis: Real-world Evidence From the GENERATE Registry. *Neurol Neuroimmunol Neuroinflamm* **8**, doi:10.1212/NXI.0000000000001088 (2021).
78 Dalmau, J. *et al.* Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* **7**, 1091-1098, doi:10.1016/S1474-4422(08)70224-2 (2008).
79 Planaguma, J. *et al.* Human N-methyl D-aspartate receptor antibodies alter memory and behaviour in mice. *Brain* **138**, 94-109, doi:10.1093/brain/awu310 (2015).
80 Lai, M. *et al.* Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. *Lancet Neurol* **9**, 776-785, doi:10.1016/S1474-4422(10)70137-X (2010).
81 Lancaster, E. *et al.* Investigations of caspr2, an autoantigen of encephalitis and neuromyotonia. *Ann Neurol* **69**, 303-311, doi:10.1002/ana.22297 (2011).
82 Irani, S. R. *et al.* Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. *Brain* **133**, 2734-2748, doi:10.1093/brain/awq213 (2010).
83 Sabater, L. *et al.* A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. *Lancet Neurol* **13**, 575-586, doi:10.1016/S1474-4422(14)70051-1 (2014).
84 Koneczny, I. *et al.* Common Denominators in the Immunobiology of IgG4 Autoimmune Diseases: What Do Glomerulonephritis, Pemphigus Vulgaris, Myasthenia Gravis, Thrombotic Thrombocytopenic Purpura and Autoimmune Encephalitis Have in Common? *Front Immunol* **11**, 605214, doi:10.3389/fimmu.2020.605214 (2020).
85 van der Neut Kolfschoten, M. *et al.* Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange. *Science* **317**, 1554-1557, doi:10.1126/science.1144603 (2007).
86 Huijbers, M. G. *et al.* MuSK myasthenia gravis monoclonal antibodies: Valency dictates pathogenicity. *Neurol Neuroimmunol Neuroinflamm* **6**, e547, doi:10.1212/NXI.0000000000000547 (2019).
87 Spatola, M. *et al.* Humoral signatures of MOG-antibody-associated disease track with age and disease activity. *Cell Rep Med* **4**, 100913, doi:10.1016/j.xcrm.2022.100913 (2023).
88 Maudes, E., Jamet, Z., Marmolejo, L., Dalmau, J. O. & Groc, L. Positive Allosteric Modulation of NMDARs Prevents the Altered Surface Dynamics Caused by Patients' Antibodies. *Neurol Neuroimmunol Neuroinflamm* **11**, e200261, doi:10.1212/NXI.0000000000200261 (2024).
89 Planaguma, J. *et al.* Ephrin-B2 prevents N-methyl-D-aspartate receptor antibody effects on memory and neuroplasticity. *Ann Neurol* **80**, 388-400, doi:10.1002/ana.24721 (2016).
90 Carceles-Cordon, M. *et al.* NMDAR Antibodies Alter Dopamine Receptors and Cause Psychotic Behavior in Mice. *Ann Neurol* **88**, 603-613, doi:10.1002/ana.25829 (2020).
91 Ceanga, M. *et al.* Human NMDAR autoantibodies disrupt excitatory-inhibitory balance, leading to hippocampal network hypersynchrony. *Cell Rep* **42**, 113166, doi:10.1016/j.celrep.2023.113166 (2023).
92 Benoit, J. *et al.* Early-Stage Contactin-Associated Protein-like 2 Limbic Encephalitis: Clues for Diagnosis. *Neurol Neuroimmunol Neuroinflamm* **10**, doi:10.1212/NXI.0000000000200041 (2023).

93 Day, G. S. Rapidly Progressive Dementia. *Continuum (Minneap Minn)* **28**, 901-936, doi:10.1212/CON.0000000000001089 (2022).
94 Flanagan, E. P. *et al.* Autoimmune Encephalitis Misdiagnosis in Adults. *JAMA Neurol* **80**, 30-39, doi:10.1001/jamaneurol.2022.4251 (2023).
95 Dalmau, J. & Graus, F. Diagnostic criteria for autoimmune encephalitis: utility and pitfalls for antibody-negative disease. *Lancet Neurol* **22**, 529-540, doi:10.1016/S1474-4422(23)00083-2 (2023).
96 van Steenhoven, R. W. *et al.* Clinical impact and safety of brain biopsy in unexplained central nervous system disorders: a real-world cohort study. *Ann Clin Transl Neurol*, doi:10.1002/acn3.70000 (2025).
97 Lee, W. J. *et al.* Seronegative autoimmune encephalitis: clinical characteristics and factors associated with outcomes. *Brain* **145**, 3509-3521, doi:10.1093/brain/awac166 (2022).
98 Bastiaansen, A. E. M. *et al.* Autoimmune Encephalitis Resembling Dementia Syndromes. *Neurol Neuroimmunol Neuroinflamm* **8**, doi:10.1212/NXI.0000000000001039 (2021).
99 Hartung, T. J. *et al.* MRI findings in autoimmune encephalitis. *Rev Neurol (Paris)* **180**, 895-907, doi:10.1016/j.neurol.2024.08.006 (2024).
100 Spatola, M. *et al.* Investigations in GABA(A) receptor antibody-associated encephalitis. *Neurology* **88**, 1012-1020, doi:10.1212/WNL.0000000000003713 (2017).
101 Kelly, M. J. *et al.* Magnetic Resonance Imaging Characteristics of LGI1-Antibody and CASPR2-Antibody Encephalitis. *JAMA Neurol* **81**, 525-533, doi:10.1001/jamaneurol.2024.0126 (2024).
102 Lee, W. J., Lee, S. T., Kim, D. Y., Kim, S. & Chu, K. Disease progression and brain atrophy in NMDAR encephalitis: Associated factor & clinical implication. *Ann Clin Transl Neurol* **9**, 912-924, doi:10.1002/acn3.51604 (2022).
103 Gadoth, A. *et al.* Elevated LGI1-IgG CSF index predicts worse neurological outcome. *Ann Clin Transl Neurol* **5**, 646-650, doi:10.1002/acn3.561 (2018).
104 Schmitt, S. E. *et al.* Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology* **79**, 1094-1100, doi:10.1212/WNL.0b013e3182698cd8 (2012).
105 Sonderen, A. V. *et al.* Predictive value of electroencephalography in anti-NMDA receptor encephalitis. *J Neurol Neurosurg Psychiatry* **89**, 1101-1106, doi:10.1136/jnnp-2018-318376 (2018).
106 Leypoldt, F. *et al.* Fluorodeoxyglucose positron emission tomography in anti-N-methyl-D-aspartate receptor encephalitis: distinct pattern of disease. *J Neurol Neurosurg Psychiatry* **83**, 681-686, doi:10.1136/jnnp-2011-301969 (2012).
107 Probasco, J. C. *et al.* Decreased occipital lobe metabolism by FDG-PET/CT: An anti-NMDA receptor encephalitis biomarker. *Neurol Neuroimmunol Neuroinflamm* **5**, e413, doi:10.1212/NXI.0000000000000413 (2018).
108 Gaig, C. *et al.* Clinical manifestations of the anti-IgLON5 disease. *Neurology* **88**, 1736-1743, doi:10.1212/WNL.0000000000003887 (2017).
109 Dechelotte, B. *et al.* Diagnostic yield of commercial immunodots to diagnose paraneoplastic neurologic syndromes. *Neurol Neuroimmunol Neuroinflamm* **7**, doi:10.1212/NXI.0000000000000701 (2020).
110 Gresa-Arribas, N. *et al.* Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol* **13**, 167-177, doi:10.1016/S1474-4422(13)70282-5 (2014).
111 Guasp, M., Modena, Y., Armangue, T., Dalmau, J. & Graus, F. Clinical features of seronegative, but CSF antibody-positive, anti-NMDA receptor encephalitis. *Neurol Neuroimmunol Neuroinflamm* **7**, doi:10.1212/NXI.0000000000000659 (2020).

112 Flanagan, E. P. *et al.* Glial fibrillary acidic protein immunoglobulin G as biomarker of autoimmune astrocytopathy: Analysis of 102 patients. *Ann Neurol* **81**, 298-309, doi:10.1002/ana.24881 (2017).
113 McCracken, L. *et al.* Improving the antibody-based evaluation of autoimmune encephalitis. *Neurol Neuroimmunol Neuroinflamm* **4**, e404, doi:10.1212/NXI.0000000000000404 (2017).
114 Ruiz-Garcia, R., Martinez-Hernandez, E., Saiz, A., Dalmau, J. & Graus, F. The Diagnostic Value of Onconeural Antibodies Depends on How They Are Tested. *Front Immunol* **11**, 1482, doi:10.3389/fimmu.2020.01482 (2020).
115 Munoz-Lopetegi, A. *et al.* Neurologic syndromes related to anti-GAD65: Clinical and serologic response to treatment. *Neurol Neuroimmunol Neuroinflamm* **7**, doi:10.1212/NXI.0000000000000696 (2020).
116 Varley, J. A. *et al.* Absence of Neuronal Autoantibodies in Neuropsychiatric Systemic Lupus Erythematosus. *Ann Neurol* **88**, 1244-1250, doi:10.1002/ana.25908 (2020).
117 Titulaer, M. J. *et al.* Overlapping demyelinating syndromes and anti-N-methyl-D-aspartate receptor encephalitis. *Ann Neurol* **75**, 411-428, doi:10.1002/ana.24117 (2014).
118 Lee, W. J. *et al.* MOG antibody-associated encephalitis in adult: clinical phenotypes and outcomes. *J Neurol Neurosurg Psychiatry* **94**, 102-112, doi:10.1136/jnnp-2022-330074 (2023).
119 Gravier-Dumonceau, A. *et al.* Glial Fibrillary Acidic Protein Autoimmunity: A French Cohort Study. *Neurology* **98**, e653-e668, doi:10.1212/WNL.0000000000013087 (2022).
120 Muniz-Castrillo, S. *et al.* Anti-CASPR2 clinical phenotypes correlate with HLA and immunological features. *J Neurol Neurosurg Psychiatry* **91**, 1076-1084, doi:10.1136/jnnp-2020-323226 (2020).
121 Yogeshwar, S. M. *et al.* HLA-DQB1*05 subtypes and not DRB1*10:01 mediates risk in anti-IgLON5 disease. *Brain* **147**, 2579-2592, doi:10.1093/brain/awae048 (2024).
122 Titulaer, M. J. *et al.* Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. *Eur J Neurol* **18**, 19-e13, doi:10.1111/j.1468-1331.2010.03220.x (2011).
123 Lee, W. J. *et al.* Teratoma Removal, Steroid, IVIG, Rituximab and Tocilizumab (T-SIRT) in Anti-NMDAR Encephalitis. *Neurotherapeutics* **18**, 474-487, doi:10.1007/s13311-020-00921-7 (2021).
124 Villagran-Garcia, M. *et al.* Paraneoplastic neurological syndromes associated with renal or bladder cancer: case series and PRISMA-IPD systematic review. *J Neurol* **270**, 283-299, doi:10.1007/s00415-022-11356-9 (2023).
125 Abbatemarco, J. R. *et al.* Autoimmune Neurology: The Need for Comprehensive Care. *Neurol Neuroimmunol Neuroinflamm* **8**, doi:10.1212/NXI.0000000000001033 (2021).
126 Abboud, H. *et al.* Autoimmune encephalitis: proposed recommendations for symptomatic and long-term management. *J Neurol Neurosurg Psychiatry* **92**, 897-907, doi:10.1136/jnnp-2020-325302 (2021).
127 de Montmollin, E. *et al.* Anti-N-Methyl-d-Aspartate Receptor Encephalitis in Adult Patients Requiring Intensive Care. *Am J Respir Crit Care Med* **195**, 491-499, doi:10.1164/rccm.201603-0507OC (2017).
128 Nosadini, M. *et al.* Use and Safety of Immunotherapeutic Management of N-Methyl-d-Aspartate Receptor Antibody Encephalitis: A Meta-analysis. *JAMA Neurol* **78**, 1333-1344, doi:10.1001/jamaneurol.2021.3188 (2021).
129 Greenlee, J. E. *et al.* Paraneoplastic and Other Autoimmune Encephalitides: Antineuronal Antibodies, T Lymphocytes, and Questions of Pathogenesis. *Front Neurol* **12**, 744653, doi:10.3389/fneur.2021.744653 (2021).
130 Irani, S. R. *et al.* Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. *Ann Neurol* **69**, 892-900, doi:10.1002/ana.22307 (2011).
131 de Bruijn, M. *et al.* Evaluation of seizure treatment in anti-LGI1, anti-NMDAR, and anti-GABA(B)R encephalitis. *Neurology* **92**, e2185-e2196, doi:10.1212/WNL.0000000000007475 (2019).

132 Witt, K. A. & Sandoval, K. E. Steroids and the blood-brain barrier: therapeutic implications. *Adv Pharmacol* **71**, 361-390, doi:10.1016/bs.apha.2014.06.018 (2014).
133 Zanatta, E., Cozzi, M., Marson, P. & Cozzi, F. The role of plasma exchange in the management of autoimmune disorders. *Br J Haematol* **186**, 207-219, doi:10.1111/bjh.15903 (2019).
134 Klemencic Kozul, T., Yudina, A., Donovan, C., Pinto, A. & Osman, C. Cost-minimisation analysis of plasma exchange versus IVIg in the treatment of autoimmune neurological conditions. *BMC Health Serv Res* **22**, 904, doi:10.1186/s12913-022-08210-z (2022).
135 Chaigne, B. & Mouthon, L. Mechanisms of action of intravenous immunoglobulin. *Transfus Apher Sci* **56**, 45-49, doi:10.1016/j.transci.2016.12.017 (2017).
136 Forsthuber, T. G., Cimbora, D. M., Ratchford, J. N., Katz, E. & Stuve, O. B cell-based therapies in CNS autoimmunity: differentiating CD19 and CD20 as therapeutic targets. *Ther Adv Neurol Disord* **11**, 1756286418761697, doi:10.1177/1756286418761697 (2018).
137 Makuch, M. *et al.* N-methyl-D-aspartate receptor antibody production from germinal center reactions: Therapeutic implications. *Ann Neurol* **83**, 553-561, doi:10.1002/ana.25173 (2018).
138 Bar-Or, A., O'Brien, S. M., Sweeney, M. L., Fox, E. J. & Cohen, J. A. Clinical Perspectives on the Molecular and Pharmacological Attributes of Anti-CD20 Therapies for Multiple Sclerosis. *CNS Drugs* **35**, 985-997, doi:10.1007/s40263-021-00843-8 (2021).
139 Damato, V., Evoli, A. & Iorio, R. Efficacy and Safety of Rituximab Therapy in Neuromyelitis Optica Spectrum Disorders: A Systematic Review and Meta-analysis. *JAMA Neurol* **73**, 1342-1348, doi:10.1001/jamaneurol.2016.1637 (2016).
140 Kosmidis, M. L. & Dalakas, M. C. Practical considerations on the use of rituximab in autoimmune neurological disorders. *Ther Adv Neurol Disord* **3**, 93-105, doi:10.1177/1756285609356135 (2010).
141 Dale, R. C. *et al.* Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. *Neurology* **83**, 142-150, doi:10.1212/WNL.0000000000000570 (2014).
142 Nepal, G. *et al.* Efficacy and safety of rituximab in autoimmune encephalitis: A meta-analysis. *Acta Neurol Scand* **142**, 449-459, doi:10.1111/ane.13291 (2020).
143 Cree, B. A. C. *et al.* Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. *Lancet* **394**, 1352-1363, doi:10.1016/S0140-6736(19)31817-3 (2019).
144 Pittock, S. J. Association of B cell Subsets and Aquaporin-4 antibody titers with Disease Activity in Participants in the N-MOmentum trial Receiving Inebilizumab Treatment *Neurology* **100**, doi:https://doi.org/10.1212/WNL.0000000000202362 (2023).
145 Karlowicz, J. R. *et al.* Predictors of hospitalization due to infection in rituximab-treated MS patients. *Mult Scler Relat Disord* **71**, 104556, doi:10.1016/j.msard.2023.104556 (2023).
146 Faissner, S. *et al.* Successful use of anti-CD19 CAR T cells in severe treatment-refractory stiff-person syndrome. *Proceedings of the National Academy of Sciences* **121**, doi:10.1073/pnas.2403227121 (2024).
147 Qin, C. *et al.* Anti-BCMA CAR T-cell therapy CT103A in relapsed or refractory AQP4-IgG seropositive neuromyelitis optica spectrum disorders: phase 1 trial interim results. *Signal Transduct Target Ther* **8**, 5, doi:10.1038/s41392-022-01278-3 (2023).
148 Muller, F. *et al.* CD19 CAR T-Cell Therapy in Autoimmune Disease - A Case Series with Follow-up. *N Engl J Med* **390**, 687-700, doi:10.1056/NEJMoa2308917 (2024).
149 Smets, I. & Titulaer, M. J. Antibody Therapies in Autoimmune Encephalitis. *Neurotherapeutics* **19**, 823-831, doi:10.1007/s13311-021-01178-4 (2022).
150 Liu, M. *et al.* Mycophenolate mofetil reduces the risk of relapse in anti-leucine-rich glioma-inactivated protein 1 encephalitis: a prospective observational cohort study. *Neurol Sci*, doi:10.1007/s10072-023-06968-6 (2023).

151 Azodi, S. & Jacobson, S. Cytokine Therapies in Neurological Disease. *Neurotherapeutics* **13**, 555-561, doi:10.1007/s13311-016-0455-1 (2016).
152 Khan, A. W., Farooq, M., Hwang, M. J., Haseeb, M. & Choi, S. Autoimmune Neuroinflammatory Diseases: Role of Interleukins. *Int J Mol Sci* **24**, doi:10.3390/ijms24097960 (2023).
153 Erta, M., Quintana, A. & Hidalgo, J. Interleukin-6, a major cytokine in the central nervous system. *Int J Biol Sci* **8**, 1254-1266, doi:10.7150/ijbs.4679 (2012).
154 Kleiter, I. *et al.* Long-term Efficacy of Satralizumab in AQP4-IgG-Seropositive Neuromyelitis Optica Spectrum Disorder From SAkuraSky and SAkuraStar. *Neurol Neuroimmunol Neuroinflamm* **10**, doi:10.1212/NXI.0000000000200071 (2023).
155 Yamamura, T. *et al.* Trial of Satralizumab in Neuromyelitis Optica Spectrum Disorder. *N Engl J Med* **381**, 2114-2124, doi:10.1056/NEJMoa1901747 (2019).
156 Pyzik, M., Kozicky, L. K., Gandhi, A. K. & Blumberg, R. S. The therapeutic age of the neonatal Fc receptor. *Nat Rev Immunol* **23**, 415-432, doi:10.1038/s41577-022-00821-1 (2023).
157 Bril, V. *et al.* Efficacy and Safety of Rozanolixizumab in Moderate to Severe Generalized Myasthenia Gravis: A Phase 2 Randomized Control Trial. *Neurology* **96**, e853-e865, doi:10.1212/WNL.0000000000011108 (2021).
158 Karunaratne, K. *et al.* Bortezomib for anti-NMDAR encephalitis following daclizumab treatment in a patient with multiple sclerosis. *BMJ Neurol Open* **3**, e000096, doi:10.1136/bmjno-2020-000096 (2021).
159 Scheibe, F. *et al.* Bortezomib for treatment of therapy-refractory anti-NMDA receptor encephalitis. *Neurology* **88**, 366-370, doi:10.1212/WNL.0000000000003536 (2017).
160 Turnbull, M. T. *et al.* Early Bortezomib Therapy for Refractory Anti-NMDA Receptor Encephalitis. *Front Neurol* **11**, 188, doi:10.3389/fneur.2020.00188 (2020).
161 Simmons, M. L. & Perez, K. A. Bortezomib for treatment of anti-NMDA receptor encephalitis in a pediatric patient refractory to conventional therapy. *Am J Health Syst Pharm* **78**, 395-400, doi:10.1093/ajhp/zxaa415 (2021).
162 Wickel, J. *et al.* Generate-Boost: study protocol for a prospective, multicenter, randomized controlled, double-blinded phase II trial to evaluate efficacy and safety of bortezomib in patients with severe autoimmune encephalitis. *Trials* **21**, 625, doi:10.1186/s13063-020-04516-7 (2020).
163 Huehnchen, P. *et al.* Bortezomib at therapeutic doses poorly passes the blood-brain barrier and does not impair cognition. *Brain Commun* **2**, fcaa021, doi:10.1093/braincomms/fcaa021 (2020).
164 Mittal, M. K. *et al.* Autoimmune Encephalitis in the ICU: Analysis of Phenotypes, Serologic Findings, and Outcomes. *Neurocrit Care* **24**, 240-250, doi:10.1007/s12028-015-0196-8 (2016).
165 Schubert, J. *et al.* Management and prognostic markers in patients with autoimmune encephalitis requiring ICU treatment. *Neurol Neuroimmunol Neuroinflamm* **6**, e514, doi:10.1212/NXI.0000000000000514 (2019).
166 Bastiaansen, A. E. M. *et al.* Anti-NMDAR Encephalitis in the Netherlands, Focusing on Late-Onset Patients and Antibody Test Accuracy. *Neurol Neuroimmunol Neuroinflamm* **9**, doi:10.1212/NXI.0000000000001127 (2022).
167 Dalmau, J. *et al.* Clinical analysis of anti-Ma2-associated encephalitis. *Brain* **127**, 1831-1844, doi:10.1093/brain/awh203 (2004).
168 Banks, J. L. & Marotta, C. A. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke* **38**, 1091-1096, doi:10.1161/01.STR.0000258355.23810.c6 (2007).
169 Morgan, A. *et al.* Longitudinal Disability, Cognitive Impairment, and Mood Symptoms in Patients With Anti-NMDA Receptor Encephalitis. *Neurology* **102**, e208019, doi:10.1212/WNL.0000000000208019 (2024).

170 Munoz-Lopetegi, A., Graus, F., Dalmau, J. & Santamaria, J. Sleep disorders in autoimmune encephalitis. *Lancet Neurol* **19**, 1010-1022, doi:10.1016/S1474-4422(20)30341-0 (2020).
171 Diaz-Arias, L. A. *et al.* Fatigue in Survivors of Autoimmune Encephalitis. *Neurol Neuroimmunol Neuroinflamm* **8**, doi:10.1212/NXI.0000000000001064 (2021).
172 Binks, S. N. M. *et al.* Residual Fatigue and Cognitive Deficits in Patients After Leucine-Rich Glioma-Inactivated 1 Antibody Encephalitis. *JAMA Neurol* **78**, 617-619, doi:10.1001/jamaneurol.2021.0477 (2021).
173 Cai, M. T. *et al.* Validation of the Clinical Assessment Scale for Autoimmune Encephalitis: A Multicenter Study. *Neurol Ther* **10**, 985-1000, doi:10.1007/s40120-021-00278-9 (2021).
174 Aboseif, A. *et al.* Clinical Determinants of Longitudinal Disability in LGI-1-IgG Autoimmune Encephalitis. *Neurol Neuroimmunol Neuroinflamm* **11**, doi:10.1212/NXI.0000000000200178 (2024).
175 Galioto, R., Aboseif, A., Krishnan, K., Lace, J. & Kunchok, A. Cognitive outcomes in anti-LGI-1 encephalitis. *J Int Neuropsychol Soc* **29**, 541-550, doi:10.1017/S1355617722000509 (2023).
176 Finke, C. *et al.* Cognitive deficits following anti-NMDA receptor encephalitis. *J Neurol Neurosurg Psychiatry* **83**, 195-198, doi:10.1136/jnnp-2011-300411 (2012).
177 de Bruijn, M. *et al.* Long-term neuropsychological outcome following pediatric anti-NMDAR encephalitis. *Neurology* **90**, e1997-e2005, doi:10.1212/WNL.0000000000005605 (2018).
178 Heine, J. *et al.* Long-Term Cognitive Outcome in Anti-N-Methyl-D-Aspartate Receptor Encephalitis. *Ann Neurol* **90**, 949-961, doi:10.1002/ana.26241 (2021).
179 Guasp, M. *et al.* Clinical characterisation of patients in the post-acute stage of anti-NMDA receptor encephalitis: a prospective cohort study and comparison with patients with schizophrenia spectrum disorders. *Lancet Neurol* **21**, 899-910, doi:10.1016/S1474-4422(22)00299-X (2022).
180 Tellez-Martinez, A. *et al.* Suicidal Thoughts and Behaviors in Anti-NMDA Receptor Encephalitis: Psychopathological Features and Clinical Outcomes. *J Neuropsychiatry Clin Neurosci*, appineuropsych20220200, doi:10.1176/appi.neuropsych.20220200 (2023).
181 Munoz-Lopetegi, A. *et al.* Neurological, psychiatric, and sleep investigations after treatment of anti-leucine-rich glioma-inactivated protein 1 (LGI1) encephalitis in Spain: a prospective cohort study. *Lancet Neurol* **23**, 256-266, doi:10.1016/S1474-4422(23)00463-5 (2024).
182 Geis, C., Planaguma, J., Carreno, M., Graus, F. & Dalmau, J. Autoimmune seizures and epilepsy. *J Clin Invest* **129**, 926-940, doi:10.1172/JCI125178 (2019).
183 Rada, A. *et al.* Seizures associated with antibodies against cell surface antigens are acute symptomatic and not indicative of epilepsy: insights from long-term data. *J Neurol* **268**, 1059-1069, doi:10.1007/s00415-020-10250-6 (2021).
184 Smith, K. M. *et al.* Seizure characteristics and outcomes in patients with neurological conditions related to high-risk paraneoplastic antibodies. *Epilepsia* **64**, 2385-2398, doi:10.1111/epi.17695 (2023).
185 Shen, C. H. *et al.* Seizures and risk of epilepsy in anti-NMDAR, anti-LGI1, and anti-GABA(B) R encephalitis. *Ann Clin Transl Neurol* **7**, 1392-1399, doi:10.1002/acn3.51137 (2020).
186 Smith, K. M., Dubey, D., Liebo, G. B., Flanagan, E. P. & Britton, J. W. Clinical Course and Features of Seizures Associated With LGI1-Antibody Encephalitis. *Neurology* **97**, e1141-e1149, doi:10.1212/WNL.0000000000012465 (2021).
187 Thompson, J. *et al.* The importance of early immunotherapy in patients with faciobrachial dystonic seizures. *Brain* **141**, 348-356, doi:10.1093/brain/awx323 (2018).
188 Baumgartner, T. *et al.* Seizure underreporting in LGI1 and CASPR2 antibody encephalitis. *Epilepsia* **63**, e100-e105, doi:10.1111/epi.17338 (2022).

189 Feyissa, A. M., Chiriboga, A. S. L. & Britton, J. W. Antiepileptic drug therapy in patients with autoimmune epilepsy. *Neurology-Neuroimmunology & Neuroinflammation* **4**, doi:ARTN e353 10.1212/NXI.0000000000000353 (2017).
190 Heine, J. *et al.* Patient-Reported Outcome Measures in NMDA Receptor Encephalitis. *Neurol Neuroimmunol Neuroinflamm* **12**, e200343, doi:10.1212/NXI.0000000000200343 (2025).
191 Brenner, J. *et al.* Long-Term Cognitive, Functional, and Patient-Reported Outcomes in Patients With Anti-NMDAR Encephalitis. *Neurology* **103**, e210109, doi:10.1212/WNL.0000000000210109 (2024).
192 Binks, S. N. M. *et al.* Fatigue predicts quality of life after leucine-rich glioma-inactivated 1-antibody encephalitis. *Ann Clin Transl Neurol* **11**, 1053-1058, doi:10.1002/acn3.52006 (2024).
193 Kelly, M. J. *et al.* Capturing what matters: Patient-reported LGI1-ANTibody encephalitis outcome RatiNg scale (LANTERN). *Ann Clin Transl Neurol* **12**, 821-831, doi:10.1002/acn3.70006 (2025).
194 Ceronie, B. *et al.* Immunotherapy-Resistant Neuropathic Pain and Fatigue Predict Quality-of-Life in Contactin-Associated Protein-Like 2 Antibody Disease. *Ann Neurol*, doi:10.1002/ana.27177 (2025).
195 Dubey, D., Pittock, S. J. & McKeon, A. Antibody Prevalence in Epilepsy and Encephalopathy score: Increased specificity and applicability. *Epilepsia* **60**, 367-369, doi:10.1111/epi.14649 (2019).
196 de Bruijn, M. *et al.* Antibodies Contributing to Focal Epilepsy Signs and Symptoms Score. *Ann Neurol* **89**, 698-710, doi:10.1002/ana.26013 (2021).
197 Guasp, M. *et al.* Neurofilament Light Chain Levels in Anti-NMDAR Encephalitis and Primary Psychiatric Psychosis. *Neurology* **98**, e1489-e1498, doi:10.1212/WNL.0000000000200021 (2022).
198 Dubey, D. *et al.* Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. *Ann Neurol* **83**, 166-177, doi:10.1002/ana.25131 (2018).
199 Zuliani, L. *et al.* Epidemiology of neuronal surface antibody-mediated autoimmune encephalitis and antibody-based diagnostics. *J Neuroimmunol* **357**, 577598, doi:10.1016/j.jneuroim.2021.577598 (2021).
200 Granerod, J. *et al.* Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis* **10**, 835-844, doi:10.1016/S1473-3099(10)70222-X (2010).
201 Hebert, J. *et al.* Epidemiology of paraneoplastic neurologic syndromes and autoimmune encephalitides in France. *Neurol Neuroimmunol Neuroinflamm* **7**, doi:10.1212/NXI.0000000000000883 (2020).
202 Nissen, M. S. *et al.* NMDA-receptor encephalitis in Denmark from 2009 to 2019: a national cohort study. *J Neurol* **269**, 1618-1630, doi:10.1007/s00415-021-10738-9 (2022).
203 Wong, C. K. *et al.* High incidence of NMDAR encephalitis among Austronesians: A population-based study in Sabah, Malaysia. *J Neuroimmunol* **356**, 577584, doi:10.1016/j.jneuroim.2021.577584 (2021).
204 Boesen, M. S., Born, A. P., Lydolph, M. C., Blaabjerg, M. & Borresen, M. L. Pediatric autoimmune encephalitis in Denmark during 2011-17: A nationwide multicenter population-based cohort study. *Eur J Paediatr Neurol* **23**, 639-652, doi:10.1016/j.ejpn.2019.03.007 (2019).
205 Wright, S. *et al.* N-methyl-D-aspartate receptor antibody-mediated neurological disease: results of a UK-based surveillance study in children. *Arch Dis Child* **100**, 521-526, doi:10.1136/archdischild-2014-306795 (2015).
206 Ho, A. C. *et al.* Anti-N-methyl-d-aspartate receptor encephalitis in children: Incidence and experience in Hong Kong. *Brain Dev* **40**, 473-479, doi:10.1016/j.braindev.2018.02.005 (2018).
207 Liem, B. *et al.* Encephalitis in adults in the Auckland and Northland regions of New Zealand, 2009 to 2018. *J Clin Neurosci* **107**, 172-177, doi:10.1016/j.jocn.2022.10.024 (2023).

208 Vogrig, A. *et al.* Epidemiology of paraneoplastic neurological syndromes: a population-based study. *J Neurol* **267**, 26-35, doi:10.1007/s00415-019-09544-1 (2020).
209 Shah, S. *et al.* Population-Based Epidemiology Study of Paraneoplastic Neurologic Syndromes. *Neurol Neuroimmunol Neuroinflamm* **9**, doi:10.1212/NXI.0000000000001124 (2022).

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Conflict of interest