The immunology underlying CNS autoantibody diseases

Jonathan Cleaver*,[1,2] Bryan Ceronie*,[1,2] Christine Strippel,[1,2] Adam Handel[1,2], and Sarosh R Irani[1,2,3]

1. Oxford Autoimmune Neurology Group, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
2. Department of Neurology, John Radcliffe Hospital, Oxford University Hospitals, Oxford, UK
3. Departments of Neurology and Neurosciences, Mayo Clinic, Jacksonville, Florida, USA

*These authors contributed equally.

Corresponding author:

Prof Sarosh R. Irani, Departments of Neurology and Neurosciences | 4500 San Pablo Road, Jacksonville, FL 32224, Mayo Clinic, Florida, USA. E-mail: irani.sarosh@mayo.edu

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Abstract

The past two decades have seen a considerable paradigm shift in the way autoimmune CNS disorders are considered, diagnosed, and treated; largely due to the discovery of novel neuroglial surface- and intracellular-autoantibodies. This successful immunobiological approach that has enabled *bona fide* CNS autoantibody-associated diseases to infiltrate the sphere of clinical neurology, facilitating advances in patient outcomes. This review focusses on the fundamental immunological concepts behind CNS autoantibody-associated diseases. First, we review the broad phenotypic profile of these conditions. Next, we explore the concept of immune checkpoints and relate these to the corresponding B cell lineage. Thirdly, the sources of CNS autoantibody production are discussed while subsequently reviewing triggers of immune tolerance failure, including neoplasms, infections and iatrogenic therapies. Penultimately, the role of T cells in CNS autoantibody diseases, followed by leucocyte trafficking into the CNS, is reviewed. Finally, biological insights from responses to targeted immunotherapies in different CNS autoantibody-associated diseases are summarised. The continued and rapid expansion of the CNS autoantibody-associated field holds promise for further improved diagnostic and therapeutic paradigms, ultimately leading to further improvements in patient outcomes.

Introduction

The description of central nervous system (CNS) autoimmune disorders has increased considerably over the past two decades, largely due to the discovery of autoantibodies targeting neuroglial surface and intracellular antigens.[1–3] This paradigm shift has defined over 25 novel, potentially immune-responsive, encephalitis syndromes.[4] Immunotherapies often improve patient outcomes, yet most patients show residual deficits and several treatment-resistant subgroups remain a clinical challenge.[5–7] A reductionist approach to explore the immunology underlying these diseases allows understanding of key immunopathogenic mechanisms, and hence a better appreciation of potential therapeutic strategies. This is especially so in the autoantibody-mediated CNS diseases, where transfer of the autoantibodies is proven to be sufficient for induction of a disease in experimental animals which mimics the patient's condition.

Herein, this review focuses on the immunology underlying CNS autoantibody-associated diseases. First, we review the broad phenotypic profile of these conditions. Next, we explore immune checkpoints within the bone marrow, periphery and secondary lymphoid structures; relating each checkpoint to the corresponding B cell lineage. Thirdly, the sources of autoantibody production are discussed with focus on germinal centre reactions and long-lived plasma cells. Fourthly, we highlight different triggers of immune tolerance failure including neoplasms, infections and iatrogenic therapies. Penultimately, the role of T cells in CNS autoantibody diseases is discussed followed by review of humoral and cell-mediated trafficking into the CNS. Finally, we summarise biological insights from targeted immunotherapies in different CNS autoantibody-associated diseases. Overall, this review highlights important discoveries in CNS autoantibody-associated diseases, details emerging immunobiological paradigms and showcases novel future research directions.

Clinical spectrum

Prior to reviewing the immunological processes fundamental to pathogenesis of CNS autoantibody diseases, we review the phenotypic clinical spectrum. Characteristic phenotypic and paraclinical features facilitate clinician-driven probabilistic reasoning to decipher the most likely causative autoantibodies (Figure 1).

Clinical presentations from encephalitic or demyelinating processes with individual autoantibody phenotypes can vary widely. Classical phenotypic examples include: multi-domain neuropsychiatric manifestations in young females with N-methyl-D-aspartate (NMDA) receptor-antibody encephalitis;[8] faciobrachial dystonic seizures (FBDS) in older males with leucine-rich glioma-inactivated protein 1 (LGI1)-antibody encephalitis;[1,9,10] neuromyotonia, dysautonomia and encephalopathy associated with contactin-associated protein-like 2 (CASPR2)-antibody disease;[1] and opticospinal syndromes mediated by pathogenic aquaporin-4 antibodies in neuromyelitis optica spectrum disorder (NMOSD).[11] In addition, the phenotypes associated with cell surface directed autoantibodies continue to expand – and recent findings have identified further clinic-serological observations including forms of acute disseminated encephalomyelitis (ADEM) in association with myelin oligodendrocyte glycoprotein (MOG) antibodies, and a very close link between neuroinflammation and neurodegeneration in association with immunoglobulin-like cell adhesion molecule 5 (Iglon5)-antibodies.

Cerebrospinal fluid (CSF) findings are often abnormal in neurological diseases associated with NMDA receptor-, gamma aminobutyric acid-$(GABA)_B$ receptor-, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-, myelin-oligodendrocyte glycoprotein (MOG)-, and glial fibrillary associated protein (GFAP)-antibodies - most commonly with a

lymphocytic pleocytosis [12]. Yet the absence of an inflammatory CSF profile is typical for several other CNS autoantibody diseases associated with LGI1-, CASPR2-, $GABA_A$-receptor-glycine receptor- and IgLON5-antibodies.[13,14] Moreover, more insidious forms of AE may not display classical imaging features of limbic encephalitis, particularly in association with LGI1-, CASPR2- and IgLON5-antibodies, highlighting the importance of clear phenotyping and reliable autoantibody assays.[13–15]

Why is knowledge of these clinical and paraclinical findings so important for patient care? The answer stems from the broad success of immunotherapies in patients with neuroglial surface autoantibodies (NSAbs); overall more so than in patients with autoantibodies targeting intracellular antigens. The prominence of syndrome-specific autoantibodies in addition to the consistent value of drugs which target the immune system support the fundamental importance of pathogenic immunobiological processes in disease causation and propagation. More specifically, the dysfunctional mechanisms for handling these autoreactivities are the likely basis for disease causation. It is this underlying immunology which forms the basis of our review, and we use clinical and laboratory observations from patients with neurological autoantibody-associated diseases to illustrate more precise examples of where and how this physiology is dysfunctional.

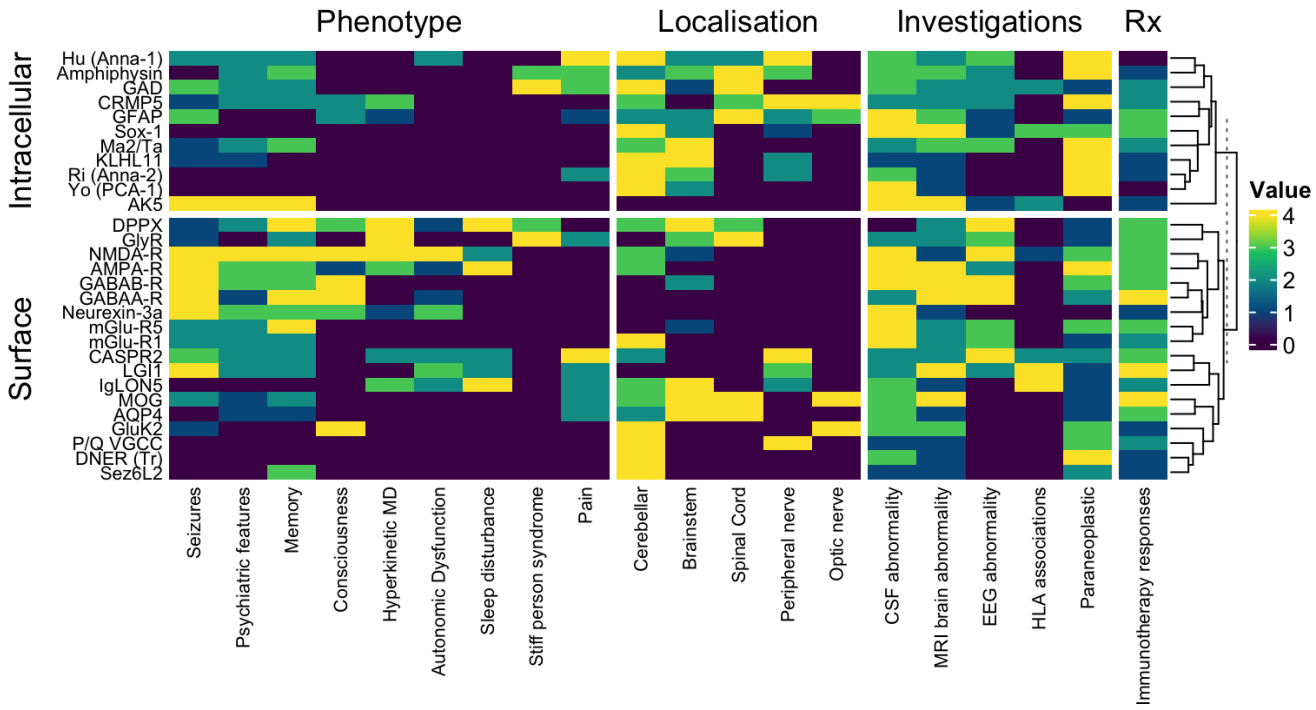


Figure 1 The clinical spectrum, investigations and treatment responses in CNS autoantibody diseases. *Annotations of clusters for the relative frequency of each clinical/paraclinical features and treatment responses. Semi-quantitative values (0-4) have been arbitrarily assigned by the authors. CSF = cerebrospinal fluid, EEG = electroencephalogram, HLA = human leucocyte antigen, Rx = treatment*

Immune tolerance

Neuroglial surface autoantibodies (NSAbs) are the secreted form of the B cell receptor (BCR), a membrane-bound immunoglobulin molecule expressed on the surface of functional B cells. To recognise the myriad antigenic targets that potential pathogens might display, this BCR is capable of enormous diversity. Through recombination of V, D and J gene segments during early B cell development, coupled with later somatic hypermutation, a vast number of unique BCR sequences can be generated. However, this diversity also creates the potential for BCRs to be able to recognise self-(auto)antigens, and hence target host tissues. Indeed, some reports suggest around up to 40% of circulating early B cells possess the ability to recognise self-antigens.[16,17]

The concept of immune tolerance describes the ability of the adaptive immune system to prevent the generation and escape of autoreactive cells through elimination or inactivation. Simultaneously, the system is aiming to preserve pathogen-specific leucocytes, and to maintain sufficient antigenic diversity to (self-) survey host cancer cells.[18] Tolerance breaches describe the process by which these mechanisms are impaired in autoimmunity.

In neurological autoimmunity, NSAbs are likely the products of impaired immune tolerance. During their development and maturation, B cells must successfully pass through a series of immune checkpoints.[16] These checkpoints function to permit the successful development of potentially beneficial B cells, while removing autoreactive cells. Breakdown of these checkpoints is thought to lead to autoimmunity.[19]

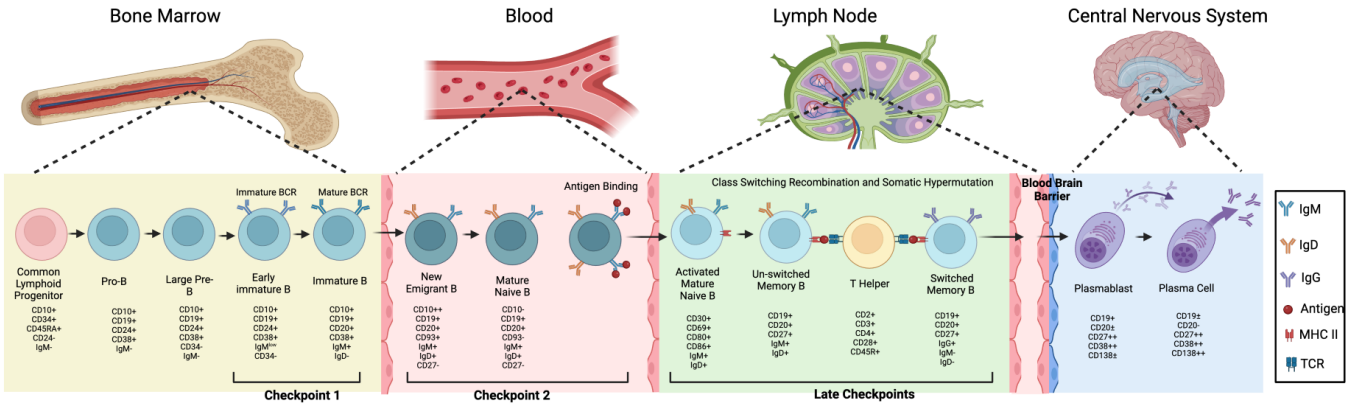


Figure 2 B cell ontogeny and development through immune checkpoints.

Checkpoint 1: in the bone marrow, early immature B cells acquire a functional BCR through expression of immunoglobulin heavy and light chains. If the BCR is not functional or overstimulated, it undergoes receptor editing, anergy or apoptosis. Checkpoint 2 occurs in the peripheral blood and spleen as new emigrant B cells mature into mature naïve B cells. If autoantigens are encountered, autoreactive B cells undergo apoptosis or become anergic. Mature naïve B cells that successfully pass through the checkpoint may encounter their cognate antigen, become activated and travel to the germinal centres of lymph nodes. Later checkpoints: during germinal centre reactions, B cells their encounter cognate antigen in conjunction with T cell stimulation and undergo differentiation into memory B cells. If autoreactive B cells encounter their cognate autoantigen, they may undergo apoptosis or anergy. Next, memory B cells can then mature into plasmablasts, exiting the germinal centre reaction and are able to traffic into the CNS. Plasmablasts and plasma cells no longer express their BCR as a surface receptor, which is instead secreted as a soluble antibody.

MHC II = major histocompatibility class II, TCR = T cell receptor

In humans, B cell tolerance checkpoints are known to exist in the bone marrow, spleen, and in germinal centres (the latter is discussed in the *germinal centre* section).[17,20–22] B cell ontogeny begins with their differentiation from a common lymphoid progenitor in the bone marrow (Figure 2). In the bone marrow (BM), early immature B cells combine immunoglobulin heavy and light chains to express their first functional surface BCR, as an IgM molecule. If an early immature B cell successfully expresses a functional BCR, it may bind to cognate antigens. Central tolerance occurs when early immature B cells with surface-expressed IgM encounter a self-antigen within the bone marrow. Upon this encounter, they can be tolerised through apoptosis, receptor editing or anergy (functional inactivation of the BCR). Almost all antigens in the BM microenvironment are autoantigens, so successful binding at this stage will trigger tolerisation.[17,23] B cells that express functional, non-autoreactive BCRs undergo positive selection and successfully pass through this checkpoint: these can egress into the bloodstream as new emigrant B cells. This is relevant to human disease. For example, higher frequencies of self-reactive new emigrant B cells have been identified in patients with NMOSD, by comparison to healthy controls, suggesting central checkpoint dysfunction.[24,25]

Following entry into circulation, new emigrant B cells migrate to the spleen and must pass through an additional checkpoint. Here, successful escapees gain IgD expression in addition to IgM, and develop into mature naïve B cells. If autoreactive B cells encounter their cognate antigen at this point, they may undergo deletion or anergy.[26] This peripheral tolerance checkpoint is in part mediated by cytokines including interleukin-10 and B cell activating factor (BAFF), as well as Treg cells.[27–29] The number of mature circulating B cells is reported to be 50% lower than new emigrant B cells.[30] Yet, in systemic lupus erythematosus rates of

autoreactive mature naive B cells are elevated,[31] suggesting dysfunction at this checkpoint. B cells undergoing maturation and selection in the spleen can then exit into circulation without entering germinal centre reactions.

Germinal centres: in the periphery and CNS

Once in the peripheral circulation, mature naïve B cells may travel to secondary lymphoid organs, typically lymph nodes. In the germinal centres of these lymphoid organs, B cells may further encounter their cognate antigen. If accompanied by co-stimulation from cognate T cells, this can lead to the process of affinity maturation, which involves two key components. Firstly, somatic hypermutation (SHM) describes the insertion of mutations into the variable region of the immunoglobulin gene which allows B cells to potentially increase their binding affinity and specificity for an antigen.[32] Secondly, immunoglobulin class-switching recombination (CSR) describes the 'switch' from expression of IgD / IgM to IgG. During this process, and thereafter, traversing further checkpoints will allow B cells to mature into memory B cells. Finally, B cells may mature into antibody-secreting cells (ASCs) such as plasmablasts and plasma cells, where the BCR is no longer tethered to the membrane and instead is secreted as an antibody.[19]

Germinal centres (GCs)

In GCs, checkpoints can also eliminate autoreactive B cells, presumably when the target autoantigen is locally expressed.[22] The relative rarity of encountering neuroglial antigens in the periphery may be one explanation which facilitates CNS-reactive B cell evasion, and consequent autoimmunity.[33] Alternatively, diversification of BCRs through SHM may also inadvertently lead to class-switched memory B cells acquiring autoreactivity.[34] Memory B

and plasma cells isolated from patients with NMOSD,[24] LGI1-antibody encephalitis[35] and $GABA_A$ receptor-antibody encephalitis[36] demonstrate substantial somatic hypermutations, supporting the notion that GCs are pivotal sites for these autoimmunisations. Conversely, in NMDA receptor-antibody encephalitis, unmutated memory B cell and plasma cell populations have been described.[37–39] One approach to studying the effects of SHM is through the reversion of the somatically hypermutated BCR sequence to their germline genes. These unmutated common ancestors (UCAs), allow us to understand the consequences of SHM. In NMOSD, reverting mutated BCRs to their UCAs caused loss of binding to AQP4 but increased polyreactivity, suggesting GC reactions were crucial for disease pathogenesis.[24] Conversely, in NMDA receptor-antibody encephalitis, UCAs were capable of binding to their target receptor and exerted functional downstream effects, suggesting a less critical role for GC reactions.[38]

In CNS diseases, one such set of germinal centres may reside in the deep cervical lymph nodes; the most direct proposed site of immunological drainage from the meningeal lymphatics. Indeed, pioneering work has shown that cervical lymph node aspirates from NMOSD and NMDA receptor-antibody encephalitis patients harbour plentiful autoantigen-reactive B cells and contain locally synthesised autoantigen-reactive antibodies.[40,41] These findings implicate local GCs as key sites of an ‘autoimmunisation’ in these diseases. Further, their study may yield key therapeutic observations. For example, a ‘clinical-serological paradox’ exists in NMOSD: after rituximab administration, pathogenic serum AQP4-IgGs often persist despite a highly-effective clinical response.[42] Yet, rituximab has been shown to effectively reduce AQP4-IgG levels in cervical lymph nodes, suggesting a potential compartmentalised mechanism to explain its clinical efficacy is the termination of a GC reaction.[40]

Another concept of particular pertinence in CNS diseases, is that the meninges can themselves act as 'ectopic' GCs, sometimes termed tertiary lymphoid structures (TLS). In multiple sclerosis, such histologically-apparent structures are reported to affinity mature B cells within the CNS. Hence, these TLS form important therapeutic targets to halt progression of pathogenic B cells. In CNS autoantibody-mediated diseases, the importance of CNS B cell maturation has been investigated using patient CSF.[43,44] Firstly, in patients with CASPR2- and LGI1-antibody disease, numerous B cells were observed and often participated in small clonal expansions.[43] Of these B cells, a remarkable ~75% were reactive to either LGI1 or CASPR2, more commonly those within larger clonal expansions. Next, these BCRs carried multiple mutations which correlated with overall binding strengths. However, within any one B cell clone, the binding strength of individual autoantigen-reactive BCRs showed very limited variation, and few intraclonal mutations were noted, a result which suggested a limited role for intrathecal TLS in maturation of the LGI1- and CASPR2-antibody response. In contrast, a comparison of the UCA with the founder intrathecal B cell revealed marked jumps in both mutational load and BCR binding strength to the autoantigen, suggesting most of the BCR maturation is achieved peripherally. Collectively, these observations implicate peripheral immunity, most likely in cervical lymph nodes, as a key site of autoantibody maturation and, hence, a core therapeutic target for preventing disease propagation.

Origins of autoantibody production

Using these immunological principles, the origins of peripheral autoantibody production can be broadly delineated into two principal mechanisms (Figure 3). These models are likely not mutually exclusive, collectively contributing to the reservoir of secreted autoantibodies.

Model one describes repeat autoantigen exposures trigger recurrent GC reactions.[19] Herein, repeated early GC reactions are responsible for the generation of autoantigen-reactive IgMs – the first immunoglobulins produced in a humoral response, and subsequently IgGs. The continual nature of these repeat autoantigen-specific challenges are proposed to create surges in the short-lived IgM autoreactive antibody pool,[45] likely secondary to new naïve B cells recurrently gaining access to GCs.[45]

Evidence in support of this 'recurrent autoimmunisation' model comes from direct and more indirect patient observations. For example, antigen-specific IgM autoantibodies have been detected in patients with NMOSD[46] and NMDA receptor-antibody encephalitis.[47,48] Despite debate over the direct pathogenicity of IgM autoantibodies, they have been associated with relapses in NMOSD and peak towards disease onset in NMDA receptor-antibody encephalitis. In the latter, they can persist for several months. Given IgM's half-life is around 5 days, this provides support for recurrent GC reactions perpetuating ongoing autoantibody production.[41] Indeed, a canonical marker of GC activity, the chemokine CXCL13, is elevated both in the CSF and lymph node aspirates of NMDA receptor-antibody encephalitis patients, and in the serum and CSF of patients with LGI1-antibody encephalitis.[41,49] Overall, these studies provide evidence for the role of recurrent or ongoing autoimmunisations in several CNS autoantibody diseases. Also, in both NMDAR-antibody encephalitis and NMOSD, patient PBMCs secrete the autoantibodies in proportion to the serum titres of individual patients. (pls add refs 25; 48) However, in MOGAD, circulating B cells from some patients with higher serum titres fail to secrete MOG-antibodies *in vitro,* observations which suggest a minor role for GC reactions in this disease.[50] [51]

A second model of autoantibody production focusses on long-lived plasma cells (LLPCs). Classically, post-GC memory B cells have potential to differentiate into antibody-secreting short-lived plasma cells/plasmablasts, which have median survival of a few days.[52] To survive for longer periods, plasmablasts must exit germinal centres and migrate to take up residence in specialised niches, particularly in the bone marrow. Here, under the influence of survival signals, they are termed LLPCs and are capable of surviving for decades, secreting up to 90% of total IgG.[53,54]

Interestingly, a direct example of this was the observation that glutamic acid decarboxylase (GAD) autoantibody patient derived bone marrow mononuclear cells showed *in vitro* capacity to secrete GAD-antibodies in the context of peripheral B cell depletion.[55] Less directly, in NMOSD, patient-derived bone marrow ASCs expressed upregulated protein modification genes and downregulated cell adhesion and HLA genes, suggesting a long-lived phenotype, although no inferences on autoantigen-specificity could be made.[56] Other indirect evidence for the role of LLPCs in CNS autoantibody diseases comes from the use of autologous haematopoietic stem cell transplantation (AHSCT).[57] AHSCT has been used successfully in the treatment of NMOSD where 9 of 11 patients were relapse-free and became seronegative; the latter is a rare phenomenon in this condition with any other therapies.[58] However, recent follow-up of these patients identifies some with NMOSD relapses and a recurrence of AQP4-antibodies.[59] This observation may be consistent with further *de novo* autoimmunisations, independent of LLPCs. Further work on the bone marrow LLPC niche in CNS autoantibody diseases is a hugely intriguing but challenging area, due to difficulty both accessing the compartment and in successfully culturing LLPCs.

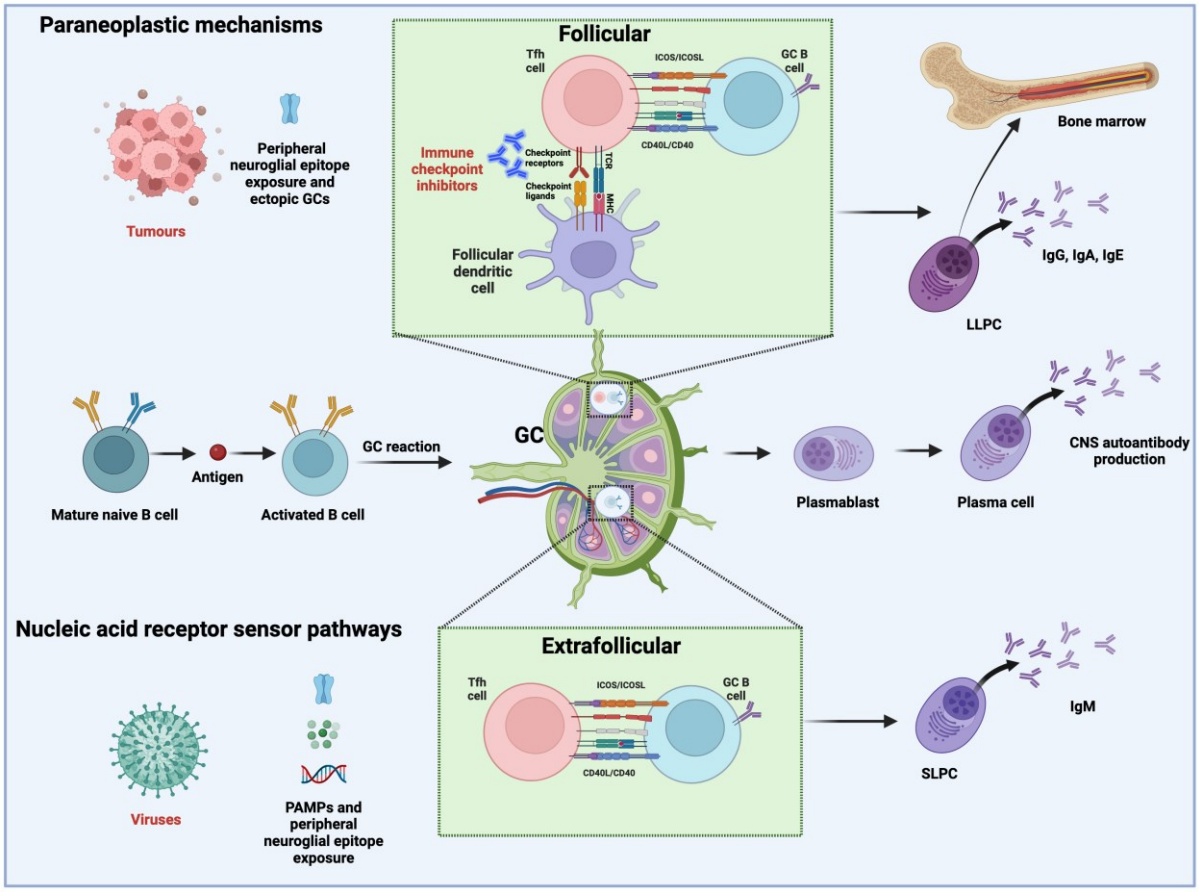


Figure 3 Sources of autoantibody production and triggers of tolerance failure

Germinal centre reactions are illustrated following antigen exposure with both follicular and extra-follicular reactions contributing to the subsequent autoantibody reservoir. Tumours, viruses and immune checkpoint inhibitors are highlighted with either bone fide or proposed mechanisms by which they breach immune tolerance.

GC = germinal centre; ICOS = inducible co-stimulator; ICOSL = inducible co-stimulator ligand; LLPC = long-lived plasma cell; PAMPs = pathogen-associated molecular patterns; SLPC = short-lived plasma cell; Tfh = T follicular helper

Triggers of tolerance failure

Paraneoplastic

NSAbs with high tumour prevalence include diseases associated with NMDA-,[41] $GABA_B$-,[61] and AMPA-receptor autoantibodies.[62] Recent studies have enhanced our understanding regarding the role of ovarian teratomas in NMDA receptor-antibody encephalitis.[41] Multiplex immunofluorescence has shown ectopic expression of the NR1 subunit of the NMDA receptor – the key immunodominant subunit for patient autoantibodies - together with several features consistent with prototypical GCs, notably ASCs, B cells including activated and GC populations, T-follicular helper cells, dendritic cells, high endothelial venules and lymphatics.[41,63] These observations provide structural evidence for a TLS within the ovarian teratomas. Moreover, functional data show that the patient teratomas harbour B cells with capacity to produce NR1-reactive antibodies, suggesting these are functioning sites of a NR1-directed immunisation.(ref makuch and al-diwani)

Small cell lung carcinomas associated with $GABA_B$ receptor- and AMPA receptor-autoantibodies are derived from neuroectoderm. Therefore, they may present peripheral sources of CNS antigens, triggering the immune responses to self.[61,64] Specifically, overexpression of the $GABA_B$ receptor accessory protein, KCTD16, has been observed in $GABA_B$ receptor-antibody encephalitis patient small cell lung cancers.[61,64] In contrast, T cell- and interferon-γ-related signatures have been observed in Hu-antibody associated tumours.[64] Moreover, in Yo-antibody syndromes, altered expression of the autoantigens (cerebellar degeneration protein (CDR)-2L and CDR2) have been observed.[65,66] These observations suggest characteristics within the tumour may precipitate the paraneoplastic neurological response.

An alternative mechanism may operate in patients with CASPR2- and LGI1-antibody disease,[67,68] where a malignant thymoma is a recognised association.[69] Given the striking HLA associations of both diseases,[70] and the fundamental importance of the thymus in T cell education, it seems plausible that thymic malignancies lead to aberrant CD4+ T cell clonal development which, in turn, fail to suppress autoreactive B cells.

Infections

Herpes simplex virus encephalitis (HSE) has long been observed to generate a secondary clinical response in a subset of patients, characterised by an encephalopathy without detectable herpes simplex virus (HSV) in the CSF. This clinical observation became biologically dissected as relapses associated with a variety of autoantibodies; most consistently those directed against the NMDA receptor.[71,72] Prospective data suggest that such AE can follow index HSE in around a quarter of cases, typically in younger patients.[73]

Despite this important observation, the fundamental mechanisms behind post-HSE AE remain unclear. Theories include molecular mimicry, non-specific B cell activation secondary to viral antigens and autoimmunisation from peripheral exposure to neuroglial antigens.[74] Indirect evidence supports the latter given the myriad neurotropic infections which can trigger NMDA receptor autoantibody production, and the multiple neuroglial antigenic targets associated with post-HSE autoantibodies, including unknown antigenic targets.[73,74]. One study used a mouse model to identify release of different neuroglial antigens eight weeks after HSV-1 CNS infection.[75] Recent evidence has also shown that when injected into mice, NMDA receptor proteins embedded within liposomal membranes generate a robust cell-mediated and humoral immune response supporting the autoimmunisation hypothesis.[76] the JEV sentences very long and confusing. Perhaps easier to omit?

Immune checkpoint inhibitors

Immune checkpoint inhibitor (ICI) treatments have transformed treatments of some cancers over the past decade. As indicated by their name, they facilitate evasion of immune checkpoints thereby enhancing the ability for the host immune system to recognise and target 'foreign' tumour cells.

Neurological immune-related adverse events (NirAEs) have been reported in 1-5% of ICI-treated patients, and many of these are likely immune-mediated.[78] Antigenic targets of autoantibodies associated with NirAEs are more often intracellular including GAD65, Ma2 (and others) and known surface targets including, aquaporin 4, $GABA_B$ and NMDA receptors.[79–81] Also, a series of observations have described as yet unknown autoantibodies in patients with NirAEs including those with peripheral nerve, neuromuscular and brainstem syndromes.[82,83]

Although ICIs upregulate T cells to promote an anti-tumour response, there is also a shift in the B cell repertoire. In fact, declines in circulating B cells, increases in plasmablasts and the emergence of a $CD21^{lo}$ B cell population have been reported.[84] Interestingly, these $CD21^{lo}$ cells are thought to represent a subtype of post-germinal centre B cells which can differentiate into LLPCs. Moreover, CXCL13 is increased in the plasma of patients following ICI therapy providing evidence for an upregulated germinal centre response.[84] It is this dynamic B cell-lineage shift which correlates with an increased frequency of severe adverse events. These iatrogenic observations highlight the research potential for autoantigen discovery and B cell immunology in the context of NirAEs.

Gut microbiome

The gut microbiome niche is an increasingly recognised organ in modulating immune responses. Indeed, dysbiosis is associated with various autoimmune diseases including rheumatoid arthritis, diabetes, inflammatory bowel disease and multiple sclerosis.[85–87] In the context of CNS autoantibody diseases, alterations in the gut microbiome have been particularly identified in NMOSD [88] and NMDA receptor antibody diseases.[89]

In NMOSD, intriguing homology has been identified between the *Clostridium perfringens* bacterium and residues 66-75 of aquaporin 4 (AQP4).[90] NMOSD patient T-helper 17 (Th17) cells exhibited a robust proliferative and pro-inflammatory response when stimulated by a variety of truncated AQP4 peptide sequences with the most immunogenic response precipitated by residues 63-76. Later analysis of the gut microbiome in patients with NMOSD revealed an over-abundance of *C.perfringens* versus healthy controls and MS disease controls, which was maintained when correcting for rituximab use in both MS and NMOSD patients.[88] Therefore, higher gut residence of *C.perfringens* in NMOSD has potential to elicit cross-reactivity to AQP4 self-antigen, suggesting molecular mimicry could, in part, play a role in disease pathogenesis.

The gut-microbiome-brain axis has also received interest in NMDA receptor-antibody encephalitis. Here, in the absence of clear triggers for tolerance failure, a variety of different bacterial signatures have been reported by comparison to healthy controls.[89] Also, an interspecies multi-sequence alignment reviewed homologies between the GAD protein, GABA-producing bacteria within the gut and GAD65 T cell receptor epitopes in patients with Type 1 diabetes (T1DM).[91] The authors identified similarities in the GAD sequences between GABA-producing bacteria and humans. Furthermore, there were bacterial GAD

sequence overlaps with known human GAD65 T cell receptor epitopes. In view of the observable reduction in GABA-producing gut bacteria in T1DM, the authors hypothesise that their death releases GAD65 mimetics precipitating antigen presentation to CD8+ T cells in local lymph nodes which are then able to access pancreatic lymphatic pathways and subsequently GAD65-expressing pancreatic beta cells. Although intriguing in autoimmune T1DM,[91] analysis of GAD antibody associated neurological diseases is necessary before conclusions can be extended to CNS diseases.

The role of T cells in CNS autoantibody diseases

T cells in the CNS

T cells seem to be essential for the health of the CNS, as a defence mechanism against pathogens and in maintaining CNS homeostasis. $CD8^+$ T cells are an important defence against viral infections: they patrol the CNS and recognise their cognate antigen in the context of MHC class I. $CD4^+$ T cells can be divided into several subtypes with varying functions.[19] Regulatory T cells (Tregs) have been implicated in maintaining brain health as well as playing a key role in neuroinflammatory diseases.[92] $CD4^+$ follicular helper T cells (Tfh) interact with B-cells in the germinal centres and recognise their cognate antigen in the context of MHC class II molecules, which in turn shape the B cell response and maturation. As all T cells recognise their antigen in the context of MHC, human leucocyte antigen (HLA) association can be seen as an indication of specific T cell involvement.

Tissue immunopathology

The classical paraneoplastic CNS autoantibody disorders with antibodies against intracellular, nuclear, or cytosolic targets (e.g. Hu-antibody encephalitis) are largely considered T cell-

mediated diseases. $CD8^+$ cytotoxic T cells are thought to inflict neuronal damage whereas the antibodies themselves are largely considered an epiphenomenon, by virtue of their inherently limited access to intracellular targets.[93] This is supported by histopathological studies showing T cell infiltrates in very close proximity to neurons, a finding also observed in a form of encephalitis associated with antibodies against the intracellular target GAD65, which is not typically paraneoplastic.[94,95] However, in this condition, plasma cells are also observed early in the disease, highlighting importance of both adaptive immune system limbs.[95]

Blood and CSF

Elevated fractions of activated HLA-DR^+ $CD4^+$ and $CD8^+$ T cells have been reported in the blood and CSF of patients with GAD65-antibodies, and intrathecal $CD8^+$ fractions correlate inversely with hippocampal volume in MRI studies.[96] Additionally, the finding of somatic hypermutation in GAD65-antibodies evidences $CD4^+$ T cell help in their generation.[97,98]

As most autoantibodies appear as IgGs, and need mutations to acquire high affinities for their target antigens, it may be that T-helper cells are key mediators of pathogenicity. Indeed, it appears logical that, given class switch and new IgMs are observed at relapses, T cell help is also key at this critical disease stage. (ref Damto Theorell PNAS 2022) A study examining the circulating $CD4^+$ T_H cells in the blood of NMDA receptor- and LGI1-antibody encephalitis showed reduced numbers of $CD154^+$, NR-1 reactive $CD4^+$ T cells with a lower cytokine production in patients with NMDA receptor-antibody encephalitis, by comparison to age- and gender-matched controls.[104] This suggests that in NMDA receptor-antibody encephalitis, $CD4^+$ T cells might play a regulatory role. Interestingly, the group could not detect differences in $CD154^+$, LGI1-reactive CD4+ T cells in patients with LGI1-antibody encephalitis, by comparison to controls,[104] suggesting the absence of LGI1-reactive T cells. This represents

an apparent paradox given the high frequencies of mutations in LGI1-reactive patient-derived monoclonal antibodies.[43] – please also ref Ramberger et al 2020 Brain

HLA

HLA associations have been described for several CNS diseases with autoantibodies. Indeed, Hu-antibody disease is associated with both HLA-DQB1*02 and HLA-DRB1*03,[99,100] and Yo-antibody disease with DQA1*01:03-DQB1*06:03- DRB1*13:01 in patients with ovarian cancer.[99,100] The HLA-association in GAD65-antibody disease remains unclear. The most common haplotype in a French as well as a German study in sporadic GAD65-antibody associated neurological syndrome was DQA1*05:01-DQB1*02:01-DRB1*03:01.[101,102] Additionally, in a German study, numerous genes that could influence the development of GAD65-antibody disease have been identified, including those responsible for innate and adaptive immunity, and genes encoding aspects of neuronal structure and function.[102]

In LGI1-antibody encephalitis, around 90% of patients carry the HLA-DRB1*07:01 gene [70,103,104]. CASPR2-antibody encephalitis is associated with HLA-DRB1*11:01, carried overall by 50% of patients, a value which increases to around 90% when focused on patients with a limbic encephalitis phenotype.[67] Lastly, IgLON5-antibody disease is associated with both HLA-DRB1*10:01 and HLA-DQB1*05:01,[105,106] whereas the HLA-association of AQP4-antibody disease is complex and ethnicity-dependent.[107–111]

Immune trafficking to the CNS

Immune trafficking to the CNS is an underexplored area in CNS autoantibody-associated diseases. Yet, the log-fold higher absolute peripheral autoantibody levels and some observed BCR clonal overlaps between peripheral and central compartments provides evidence for their

entry to the CNS [13]. Moreover, there is neuropathological evidence for CNS infiltration of different immune lineages: $CD20^+$ memory B cells and plasma cells in NMDA receptor- and LGI1-antibody encephalitis, contrasted to cytotoxic T cells in many onconeuronal- and GAD-65-antibody diseases.[112] It is therefore important to consider potential differential mechanisms through which varied leucocytes migrate into the CNS.

The major limitation in CNS leucocyte transmigration is the restriction imposed by the blood-brain (BBB).[113] Migration of leucocytes across the BBB requires interactions with multiple cell types, including endothelial cells, pericytes and astrocytes. Most evidence surrounds the ingress of T cells into the brain (summarised in[114]). Peripheral pro-inflammatory conditions are broadly considered a pre-requisite to enhance immune trafficking across the BBB, through upregulating selectin and integrin molecules, facilitating leucocyte rolling and adhesion across the endothelium.[115–118] Following endothelial cell adherence, T cells become activated, movement arrests and they can crawl across the endothelial monolayer marshalled by a CNS-homing cytokine and chemokine gradient.[119] The transmigration of B cells is less well studied. Yet, it is likely that some shared molecular mechanisms exist. For example, $CD19^+$ B cell migration can be abrogated through blockade of ICAM-1.[120,121] More recently, activated leucocyte cell adhesion molecule (ALCAM) has been implicated in facilitating transmigration of proinflammatory B lymphocytes subsets into the CNS within humans and mice, highlighting a promising novel therapeutic target.[120,122]

While detailed mechanisms for leucocyte BBB transmigration is beyond the scope of this review and have been discussed in other articles,[119,123] additional leucocyte trafficking insights can be made through observing clinical responses to known modulators of these pathways. For example, natalizumab - a humanised mAb targeting the α4 integrin, a protein

involved in CD8+ T cell BBB trafficking - has demonstrated consistent efficacy in the treatment of multiple sclerosis.[124,125] Early observational studies have also shown improvements following its use in a patient with encephalitis secondary to immune checkpoint inhibitors[126] and in some patients with Susac's syndrome.[127] However, it is associated with adverse outcomes in the B cell-dominant disorder of NMOSD.[128] Similar adverse outcomes occur in NMOSD patients treated with fingolomod, another frequently used disease modifying therapy in MS which inhibits leucocyte egress from the lymph nodes through sphingosine-1-phosphate receptor antagonism.[129] Further studies are required to assess whether inhibiting leucocyte trafficking is beneficial in diseases where T cell-mediated pathology is thought to predominate; particularly where onconeuronal autoantibodies are identified.

Immunotherapeutic approaches

Whilst 'first-line' immunotherapies, including corticosteroids, intravenous immunoglobulins and plasma exchange, are associated with improvements in many CNS autoantibody-mediated diseases, very few patients reach baseline states and many develop adverse effects.[130,131] Hence, there is significant room for improvements. This section explores established and emerging immunotherapeutics in CNS autoantibody diseases, providing parallel insights which help to dissect the specific molecular mechanisms.

The utility of therapies targeting surface markers on B cells is well illustrated by the effectiveness of CD20-depleting therapies in select CNS autoantibody-mediated diseases. CD20 is expressed on most of the B cell lineage, excluding the early pro-B cells and the later LLPCs, and some plasmablasts. Rituximab does not typically lower autoantibody levels,[132–135] yet it appears effective in reducing disability and risk of relapse in NMDA-antibody and

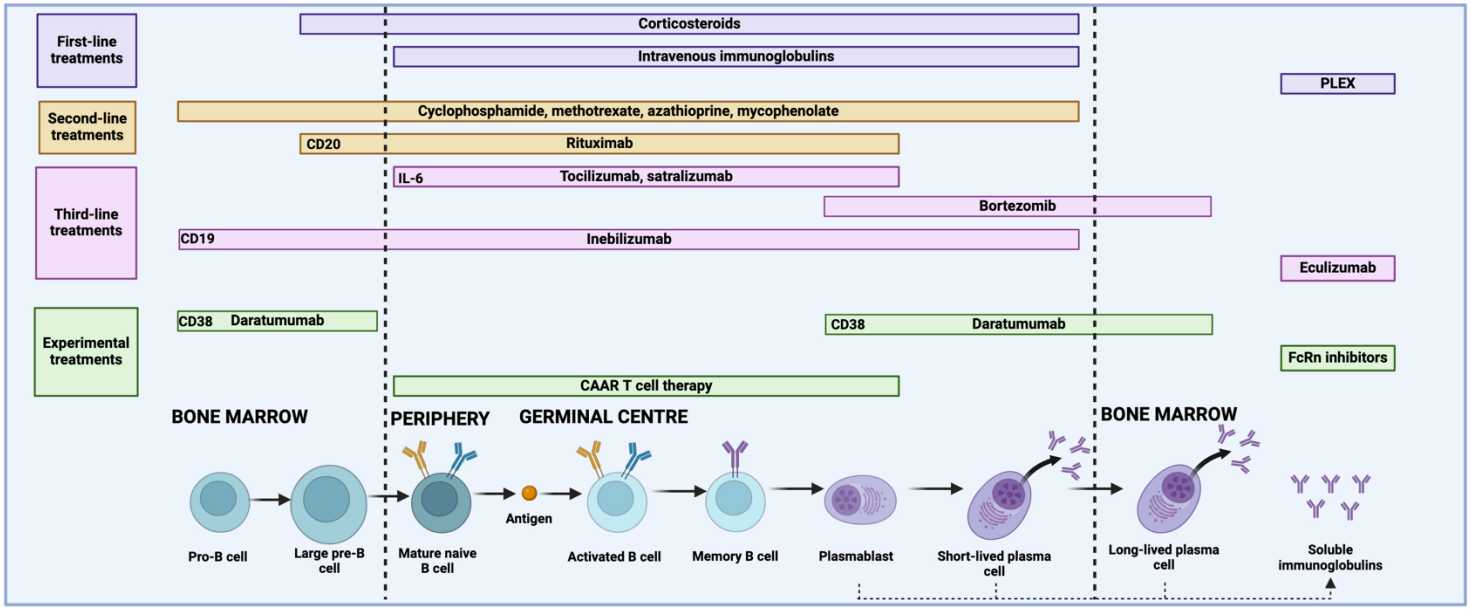
other AE syndromes.[132,133,136] In contrast, CD19-targetting therapies such as inebilizumab, exert an effect on a slightly wider range of the B cell lineage including precursor B cells, plasmablasts and a proportion of plasma cells.[137] While it is assumed that targeting a greater number of B cell subsets offers improved efficacy over CD20 therapies, there are currently no direct comparative analyses, and if NMOSD is driven dominantly by recurrent autoimmunisation events within GCs, both could be equally beneficial. Another therapeutic B cell surface target is the CD38 protein. Daratumumab is a humanised CD38-directed mAb used which targets most plasma cells, and is efficacious in multiple myeloma. This treatment may have utility in CNS-autoantibody associated conditions. Yet, studies to date have shown limited value in a small heterogenous cohort, with short follow-up.[138]

Monoclonal antibodies targeting the interleukin 6 (IL-6) receptor have been approved for use in NMOSD[139] and appear to show some benefits in select patients with NMDA receptor-antibody encephalitis[140]. IL-6 is a pleotropic cytokine, with effects on many cell types within and beyond the immune system. Yet, the main therapeutic effects of drugs targeting this pathway have been attributed to inhibition of T-helper 17 differentiation and preventing activation of B cells and plasmablasts [141]

Immunotherapies have also been used to inhibit effects downstream of B cells, at the level of the IgGs themselves. For example, complement inhibitors have been highly effective treatments in NMOSD randomised control trials by preventing relapses.[142] They are thought to work because complement dependent cytotoxicity is a key pathomechanism in AQP4-antibody induced astrocytic damage. The role of complement-mediated neural injury in other CNS autoantibody-associated diseases is currently unclear. An additional target downstream of B cells includes drugs which prevent IgG recycling through inhibition of the neonatal

fragment crystallisable receptor (FcRn). This is being studied in LGI1-antibody encephalitis and MOGAD. If beneficial, this approach may be translated to other autoantibody-associated CNS diseases.[143]

Emerging therapeutic paradigms include the use of chimeric autoantibody receptor (CAAR) T cells which can either target all B cells or can be used to deplete antigen-specific B cells.[144] CAAR T cell therapy appears an elegant solution to achieve specificity. Yet, based upon data from chimeric antigen receptor (CAR) T cell therapy, the risk of side effects are high and includes cytokine release syndrome – a complication occurring in around 30% of patients, which can be life-threatening.[145] Therefore, the potential clinical role of CAAR T cell therapy in CNS autoantibody diseases is unclear but could be most practical in refractory cases.



F***igure 4*** *Immunotherapeutics used in CNS autoantibody diseases.*

Current immunotherapies in CNS autoantibodies aligned with their specific B cell lineage target(s).

CAAR = chimeric autoantibody receptor, FcRn = neonatal fragment crystallisable receptor, PLEX = plasma exchange

Conclusions

The immunological processes underlying CNS autoantibody-associated diseases highlight the mechanisms through which pathogenic NSAbs can emerge. It is essential for treating clinicians to be familiar with these core processes that underpin different clinical phenotypes and are likely to reflect individualised treatment responses. Further research is required to decipher the origins of different CNS autoantibody diseases, discover consistent markers of *bona fide* relapses and apply these to bespoke treatment algorithms. The continued and rapid expansion of the CNS autoantibody field holds promise for further improved diagnostic and therapeutic paradigms, ultimately leading to further optimisation of patient outcomes.

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