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Review Article

Dysregulated immunity and autoantibodies: Unraveling their roles in neurological disease pathogenesis

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Abstract

Autoantibodies, generated by B lymphocytes following the breakdown of immune tolerance, are pathological immunoglobulins that erroneously target host tissues. Substantial evidence underscores their pivotal involvement in neurological pathologies linked to immune dysregulation. Given the escalating global burden of neurological disorders as leading contributors to morbidity and mortality, elucidating the mechanistic contributions of autoantibodies to these conditions remains a research imperative. The blood-brain barrier (BBB), a critical guardian of central nervous system homeostasis, has been demonstrated in our prior work to be vulnerable to autoimmune attack—specifically, SLE-derived monoclonal autoantibodies were found to downregulate tight junction protein expression, thereby compromising BBB integrity. These findings not only advance our understanding of autoantibody-mediated neuropathology but also motivate a comprehensive reappraisal of their multifaceted roles. This review systematically examines the dual participation of autoantibodies in both autoimmune and non-autoimmune contexts, with particular emphasis on their pathogenic mechanisms in immune-associated neurological disorders. Through comparative analysis of central and peripheral nervous system pathologies, we aim to delineate novel molecular targets and establish a refined conceptual framework to guide precision diagnostics and targeted therapeutic development.

Keywords: Autoantibodies, Dysimmunity related neurological diseases, Diagnosis, Therapy, Pathogenesis

Background

The blood-brain barrier (BBB), while essential for neuroprotection, has historically led to the underestimation of autoantibody-mediated neuropathological sequelae. Emerging evidence over the past decade has established autoantibodies as pathogenic drivers in neurological disorders through immune dysregulation mechanisms [1]. Crucially, BBB integrity compromise has been documented across diverse neuroimmune conditions, including antiphospholipid syndrome and neuropsychiatric systemic lupus erythematosus (NPSLE), where breached barrier permeability facilitates autoantibody infiltration into the CNS parenchyma. This process initiates neuroinflammatory cascades culminating in cognitive deficits, autoimmune encephalitis, and structural neural damage [2,3]. The centrality of autoantibodies in neuroimmunopathology is further exemplified in neuromyelitis optica spectrum disorder (NMOSD), where anti-aquaporin-4 IgG (AQP4-IgG) binds astrocytic aquaporin-4 (AQP4) channels, triggering complement-dependent cytotoxicity cascades. This results in astrocytopathy, secondary BBB disruption, and ultimately oligodendrocyte loss with demyelination [5].

Despite these advances, critical knowledge gaps persist regarding autoantibody pathomechanisms in immune-mediated neurological diseases. The precise molecular interplay underlying neuropsychiatric manifestations of lupus (NPSLE), multiple sclerosis (MS), and myasthenia gravis (MG) remains enigmatic, as does their contribution to neurodegenerative processes. Current therapeutic paradigms

lack targeted strategies to neutralize pathogenic autoantibodies or mitigate their neural toxicity [6]. Addressing these challenges necessitates a systematic deconstruction of autoantibody-mediated neuroimmunopathology. This review synthesizes cutting-edge evidence on dual-phase autoantibody actions—both in classical autoimmune disorders and emerging neurodegenerative contexts—employing a systems biology approach to map their spatiotemporal disease impacts. By integrating mechanistic insights from central and peripheral nervous system pathologies, we propose novel molecular frameworks to advance precision diagnostics and develop immunomodulatory therapies with blood-brain barrier penetrance, thereby addressing critical unmet needs in neuroimmunology.

Beyond Autoimmunity: The Emerging Roles of Autoantibodies in Multifactorial Disease Pathogenesis

Autoantibodies represent a class of pathogenic immunoglobulins generated following the collapse of immune tolerance, characterized by their aberrant reactivity toward self-antigens, thereby instigating tissue-specific inflammatory cascades [7,8]. The conceptual evolution of autoimmunity traces back to Paul Ehrlich's 1900 "horror autotoxicus" hypothesis, which posited an inherent prohibition against self-directed immunity—the "side-chain theory" of antibody specificity [9]. This paradigm was revolutionized by Burnet's 1959 clonal selection theory, which established the molecular basis for immune diversity while implicating defective clonal deletion in the emergence of pathogenic autoantibodies underlying autoimmune pathogenesis [10].

Beyond their etiological roles, autoantibodies serve dual functions as both disease mediators and diagnostic biomarkers. In systemic lupus erythematosus (SLE), archetypal autoantibodies (anti-dsDNA, anti-Sm) drive multi-organ damage through immune complex deposition in renal glomeruli, dermal-epidermal junctions, and cerebral microvasculature [12]. While anti-dsDNA antibodies exhibit therapeutic targeting potential via intracellular epitope engagement [13], their limited diagnostic utility (sensitivity: 33% for anti-dsDNA, 27% for anti-Sm) and poor specificity impede both SLE differential diagnosis and precision therapeutic development [11], underscoring ongoing controversies in their clinical translation.

The diagnostic landscape differs in rheumatoid arthritis (RA), where anti-citrullinated protein antibodies (ACPA) demonstrate superior clinical validity, present in 60-70% of patients and correlating with radiographic progression and cachexia [14,15]. Mechanistically, ACPA orchestrates osteoclast activation through RANKL-independent pathways while perpetuating synovial inflammation via NETosis induction and citrullinated fibrinogen recognition [16,17]. In IgA nephropathy, galactose-deficient IgA1 (gd-IgA1) autoantibody complexes deposit within glomerular mesangium, activating alternative complement pathways and IL-6-driven inflammatory loops—a process partially mitigated by corticosteroid regimens targeting FcαRI-mediated signaling [18,19].

Systemic sclerosis (SSc) presents a unique paradigm where antinuclear antibodies (ANA) achieve >90% diagnostic specificity, yet their pathogenic heterogeneity complicates therapeutic targeting [20]. Distinct ANA subtypes, such as anti-RNA polymerase III antibodies, demonstrate intracellular internalization capacity, directly interfering with transcriptional machinery and predicting rapid cutaneous fibrosis progression [21–23]. Current challenges in SSc precision medicine stem from the involvement of >240 dysregulated pathways, necessitating high-resolution epitope mapping to develop antibody-receptor interaction inhibitors [24,25].

Emerging evidence extends autoantibody pathobiology beyond classical autoimmunity. Cardiovascular pathologies involve antiphospholipid antibodies inducing endothelial glycocalyx shedding and monocyte TF/VEGF overexpression, while GPIHBP1 autoantibodies disrupt lipid metabolism via lipoprotein lipase sequestration, precipitating chylomicronemia syndromes [26–28]. The COVID-19 pandemic has further unveiled virus-induced autoantibody networks targeting IFN-α/ω and MAS-related G protein-coupled receptors, correlating with disease severity through IL-1β/IL-6 hyperactivation [29]. These findings underscore the imperative to delineate context-dependent autoantibody roles across immune-metabolic interfaces.

Autoantibody-Mediated Neuroimmunopathology: Decoding Molecular Mechanisms in Central and Peripheral Nervous System Disorders

Neurological disorders represent a formidable and escalating global health challenge, significantly contributing to both disability and mortality worldwide [30]. The sobering statistic of an approximate 30% rise in their global mortality rate in recent years underscores the intensifying burden these conditions impose on human health [31]. Given the pivotal role autoantibodies play—not only in driving the pathogenesis of immune-mediated neurological diseases but also as critical targets for therapeutic intervention—deciphering their precise functions and underlying mechanisms becomes paramount. To systematically explore this complex landscape, we have adopted a structural framework by categorizing neurological disorders based on their primary site of involvement: the central nervous system (CNS) versus the peripheral nervous system (PNS). This categorization aims to illuminate the distinct and potentially divergent roles autoantibodies assume across the diverse spectrum of neurologic disease.

Autoantibodies and central nervous system disorders

Autoantibodies directed against neuronal or glial surface antigens are frequently central to the pathogenesis of central nervous system (CNS) autoimmune disorders. These autoantibodies specifically bind to proteins expressed on the external membranes of neural cells, disrupting their normal function. A prime example is neuromyelitis optica spectrum disorder (NMOSD), where autoantibodies targeting astrocytic aquaporin-4 water channels directly initiate the characteristic inflammatory damage. This paradigm underscores a critical point: identifying and characterizing pathogenic autoantibodies is not merely correlative, but pivotal for both precise diagnosis and the development of targeted therapies in CNS autoimmunity. Consequently, the subsequent discussion delves into the specific roles and mechanistic underpinnings of autoantibodies in key CNS disorders. By dissecting these examples, we aim to illuminate how understanding autoantibody-antigen interactions translates into concrete diagnostic tools and paves the way for rationally designed therapeutic interventions, thereby offering crucial targets and focused research avenues for combating these debilitating conditions.

Neuromyelitis spectrum disorder (NMOSD): Neuromyelitis optica spectrum disorder (NMOSD) stands as a distinct autoimmune entity within the CNS, clinically manifesting through

devastating symptoms like sensory loss and visual impairment. Central to its pathogenesis is the autoantibody AQP4-IgG, which targets aquaporin-4 (AQP4), a critical water channel protein densely expressed on astrocyte end-feet. The genesis of this pathogenic antibody involves a dysregulated immune cascade: T helper cells, potentiated by inflammatory cytokines like IL-6, drive B cell differentiation and the subsequent production of AQP4-IgG [32]. The ensuing damage unfolds in a critical sequence: Upon crossing into the CNS, AQP4-IgG binds astrocytic AQP4. This binding serves as the crucial first step, triggering the classical complement cascade (C1q binding and MAC formation). This complement-mediated attack directly lyses astrocytes, disrupting the vital blood-brain barrier and neuroprotective functions they provide. The resultant astrocytic damage and inflammatory milieu create a permissive environment for massive granulocyte infiltration, which further amplifies tissue injury. This inflammatory storm, coupled with the loss of astrocyte support, precipitates secondary oligodendrocyte death (demyelination) and ultimately culminates in irreversible neuronal loss. It is this multi-stage, antibody-initiated neurodestructive cascade—beginning with astrocyte targeting and propagating through inflammation and secondary cell death—that underlies the characteristic and often severe neurological deficits (sensory loss, visual impairment) observed in NMOSD patients [5].

Neuromyelitis optica (NMO), a prototypical condition within the NMOSD spectrum, involves pathogenic mechanisms extending beyond the well-characterized AQP4-IgG pathway. A critical, non-AQP4-dependent entry route for pathogenic antibodies is facilitated by autoantibodies targeting Glucose-regulated protein 78 (GRP78). GRP78, an endoplasmic reticulum chaperone aberrantly expressed on the surface of brain microvascular endothelial cells (BMECs), serves as a binding site for specific recombinant autoantibodies (rAb IgG) found in NMO patients. Crucially, the binding of these non-AQP4-specific rAb IgGs to GRP78 activates BMECs via the canonical NF-κB signaling pathway. This activation triggers a deleterious cascade: downregulation of the critical tight junction protein Claudin-5, leading to increased blood-brain barrier (BBB) permeability. This compromised barrier function acts as a 'gateway,' permitting the subsequent infiltration of pathogenic AQP4-IgG into the CNS parenchyma, thereby enabling its attack on astrocytes.

Simultaneously, the complement system, particularly C1q, emerges as a potent driver of neuronal damage. Independent research positions C1q not only as a complement initiator but also as a direct inducer of axonal damage, contributing to neurological decline and loss of immunoreactivity in spinal cord neurons [33–35]. Furthermore, the AQP4-IgG bound astrocyte itself becomes an active participant in amplifying complement-mediated injury. These astrocytes respond by upregulating transcription and secretion of complement component C3. The elevated C3 levels engage C3a and C3b receptors on microglia, acting as a potent activation signal. This microglial activation triggers a significant increase in C1q synthesis. The resultant surge in C1q, coupled with its inherent neurotoxicity and role in classical complement activation, creates a highly destructive microenvironment. It is this amplified, microglia-driven C1q production, synergizing with direct complement pathway effects, that critically underlies the early motor deficits observed in NMO patients [36,37].

The preceding evidence solidifies the pivotal role of complement component C3 and its cleavage fragments (C3a/C3b) as critical mediators within the astrocyte-microglia crosstalk driving NMO pathogenesis. Specifically, the AQP4-IgG-triggered astrocytic release and processing of C3 appear to be a linchpin event, facilitating microglial activation and subsequent neuroinflammation. This central positioning prompts a compelling therapeutic hypothesis: targeted inhibition of C3a/C33b generation specifically within the astrocytic compartment in response to AQP4-IgG/AQP4 binding could disrupt this pathogenic signaling axis and halt disease progression.

Emerging research points to Cathepsin L (CTSL), expressed by T cells, as a key enzyme capable of processing C3 into its bioactive fragments C3a and C3b [38]. Crucially, proof-of-concept studies demonstrate that both small-molecule CTSL inhibitors and CTSL-neutralizing antibodies can effectively suppress this CTSL-mediated C3 activation. This establishes CTSL as a mechanistically rational and pharmacologically tractable candidate target for NMO intervention.

However, translating this potential into viable therapies necessitates rigorous investigation across multiple fronts:

Efficacy & specificity: Does inhibiting CTSL *in vivo* robustly block pathogenic C3 fragment generation within the NMO lesion microenvironment, and does this translate to meaningful clinical benefit in relevant models?

Safety & off-target effects: What are the consequences of systemic or localized CTSL inhibition? CTSL has diverse physiological roles (e.g., antigen processing, extracellular matrix remodeling). A critical focus must be identifying whether therapeutic suppression can be achieved without incurring unacceptable adverse effects, potentially through CNS-targeted delivery or exploiting temporal windows of vulnerability.

Modality optimization: While initial chemical inhibitors and blocking antibodies provide tools, comparative assessment of their pharmacodynamic profiles, CNS penetrance, and long-term safety is essential. Furthermore, exploring alternative or next-generation inhibitory strategies (e.g., engineered biologics with enhanced specificity, gene-silencing approaches, or allosteric inhibitors) represents a vital research avenue to potentially improve efficacy and safety margins.

Therefore, CTSL emerges not merely as a potential target, but as a focal point for a multifaceted research program aimed at developing precise immunomodulatory strategies to intercept the destructive C3-driven cascade central to NMO.

Anti-NMDAR encephalitis: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis represents a prototypical synaptic autoimmune disorder characterized by severe cognitive impairment, seizures, and movement abnormalities [39,40]. The core pathogenic mechanism involves autoantibodies directly targeting the NR1 subunit of synaptic NMDARs. Upon binding, these antibodies trigger highly specific molecular events: cross-linking, capping, and internalization of NMDARs from the synaptic surface [44]. Critically, this process selectively depletes synaptic NMDAR density without altering overall synapse structure or other synaptic proteins/receptors. The consequent disruption of NMDAR-mediated synaptic currents directly impairs neuronal communication, underpinning the profound deficits in learning, memory, and neurological function observed clinically [41–43].

Beyond this direct synaptic silencing, a self-perpetuating immunological loop amplifies the disease. The NMDAR GluN1 subunit itself acts as the key autoantigen. Pathologically, GluN1 can aberrantly activate B cells, driving their differentiation and the sustained production of pathogenic anti-NMDAR autoantibodies released into the circulation [44,45]. This creates a dangerous positive feedback cycle: circulating autoantibodies breach the blood-brain barrier, access the CNS, and further accelerate NMDAR internalization upon binding synaptic targets. The resulting progressive synaptic dysfunction—manifesting as decreased receptor localization selectivity and impaired synaptic plasticity—is fundamentally linked to the emergence and persistence of patients' cognitive and neuropsychiatric symptoms [44,45].

Based on the pivotal role of GluN1-activated B cells in anti-NMDAR encephalitis pathogenesis, we propose that selectively depleting these cells could interrupt autoantibody production; recent evidence demonstrates that NMDAR-specific chimeric autoantibody receptor (NMDAR-CAAR) T cells effectively eliminate pathogenic B-cell lines by recognizing multiple patient-derived autoantibodies, triggering cytotoxic effector release, proliferating, and executing targeted killing—resulting in sustained autoantibody reduction [46]—thus positioning NMDAR-CAAR therapy as a promising precision-targeted approach to alleviate this condition.

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a complex neuroimmune disorder characterized by debilitating post-exertional fatigue unrelieved by rest, involves significant autoimmune contributions where autoantibodies against β2-adrenergic (β2AdR) and M3 acetylcholine receptors—key vasoregulatory proteins—are detected in approximately one-third of patients and cause receptor dysfunction linked to core symptoms like fatigue and myalgia, while distinct autoantibodies targeting G protein-coupled receptors (GPCRs) further exacerbate symptoms through complement-mediated inflammation [47–50].

While immunoadsorption (IA) currently represents a moderately effective ME/CFS treatment with some patients showing clinical improvement after cyclic therapy, its efficacy remains inconsistent—with partial non-response or even symptom exacerbation occurring—positioning IA as investigational rather than established; crucially, existing evidence derives from limited patient cohorts [51], necessitating expanded clinical studies with larger populations to robustly validate therapeutic outcomes.

Tumors of the nervous system: Glioma, a glial cell-derived brain tumor, exhibits clinically relevant autoantibody biomarkers where Wei *et al.* demonstrated anti-GFAP antibodies specifically target tumors while correlating with WHO grade and volume—supporting their utility as early diagnostic markers [52]—whereas anti-FLNC antibodies (negatively correlating with tissue FLNC expression that rises with tumor progression) serve as potential serum biomarkers for low-grade gliomas; additionally, though glutamate decarboxylase (GAD) physiologically synthesizes inhibitory GABA, cell-surface GAD-Abs may increase cancer risk warranting patient screening despite unclear mechanistic involvement in tumorigenesis [53–56].

Beyond anti-GFAP and anti-FLNC autoantibodies, established neural autoantibodies (including anti-Hu, Ma2, CV2, and amphiphysin) further validate autoantibodies as diagnostic biomarkers for neural-related tumors; however, their precise mechanistic roles in tumorigenesis remain undefined, creating a significant knowledge gap that currently precludes their therapeutic application in oncology [57].

Anti-IgLON5 diseases: Anti-IgLON5 disease, a rare autoimmune neurological disorder characterized by anti-IgLON5 autoantibodies and neuronal tau accumulation [58], involves IgLON5—a neuronal surface adhesion molecule critical for signaling, development, and synaptogenesis [59]—where *in vitro* studies confirm IgLON5 IgG disrupts hippocampal neuronal cytoskeletons, causing aberrant neurofilament accumulation leading to atrophy and axonal swelling [58]; crucially, antibody-induced human neural stem cell differentiation promotes pathological p-tau accumulation, increases p-tau-positive neurons, and concurrently impairs synaptic structure/function, mechanistically linking autoimmunity to neurodegeneration in this disease [60].

Despite the unresolved pathogenesis of anti-IgLON5 disease precluding mechanism-based therapies, empirical symptom management remains essential—particularly B-cell depletion (e.g., Rituximab) which holds biological plausibility given expanded anti-IgLON5 antibody-producing B-cells in patient CSF [61]; however, the conceptual validity of immunotherapy is paradoxically undermined by evidence indicating antibodies primarily disrupt cytoskeletal-extracellular crosstalk rather than surface antigens [61], yet compelling clinical reality demonstrates 41% short-term and 75% long-term therapeutic responsiveness [59], suggesting that clinical pragmatism must temporarily supersede mechanistic uncertainty until definitive pathological cascades are elucidated.

Limbic encephalitis (LE): Autoimmune limbic encephalitis mediated by LGI1-IgG presents with distinctive faciobrachial dystonia and seizures, yet the precise pathogenic cascade triggered by these autoantibodies remains enigmatic [62,63]. While LGI1's structural architecture—featuring an N-terminal leucine-rich repeat (LRR) domain and C-terminal EPTP domain—explains its hippocampal concentration and functional duality, the antibody's disruption operates at multiple synaptic levels: LGI1-IgG sterically blocks LGI1's interaction with both presynaptic ADAM23 (disrupting Kv1.1 channel complexes) and postsynaptic ADAM22 (impairing AMPAR clustering), effectively uncoupling trans-synaptic signaling. This dual interference precipitates quantifiable reductions in hippocampal Kv1.1 and AMPAR density, directly linking molecular sabotage to clinical manifestations of neuronal hyperexcitability and reversible amnesia. However, the critical mechanistic void persists—we lack a unified model explaining how LGI1 dysfunction dynamically regulates these receptor trafficking pathways. Does antibody binding induce accelerated internalization? Disrupt recycling machinery? Or destabilize scaffold proteins anchoring these complexes? Resolving this fundamental question (designated PMM [64–66]) is essential for developing targeted interventions beyond broad immunosuppression.

While autoantibody-mediated disruption of the LGI1-ADAM22/23 trans-synaptic complex undeniably drives limbic encephalitis pathogenesis—with Kv1.1 channel and AMPAR dysregulation representing a fundamental molecular mechanism potentially relevant to broader neurological hyperexcitability disorders—three critical knowledge gaps impede therapeutic advancement: first, LGI1's extrasynaptic functions remain virtually

unexplored despite evidence of non-synaptic receptor pools; second, the precise spatiotemporal dynamics of how antibody-bound LGI1 orchestrates Kv1.1/AMPAR downregulation (endocytosis? proteasomal degradation? transcriptional silencing?) requires mechanistic dissection; third, the paradoxical persistence of memory deficits in 33% of patients despite favorable corticosteroid responses [67] exposes a fundamental limitation—current immunosuppression fails to reverse established synaptic injury. This necessitates a dual-path strategy: 1) decoding LGI1's moonlighting roles in receptor trafficking beyond canonical complexes, and 2) developing synapse-restorative therapies complementing immunomodulation to address permanent cognitive sequelae.

Autoantibodies and peripheral nervous system diseases

Peripheral nervous system (PNS) autoimmune diseases pivot on demyelination pathophysiology, where myelin—a Schwann cell-derived axonal insulator—becomes both target and casualty. While macrophage-mediated phagocytosis drives myelin destruction in Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), and controversially multiple sclerosis (MS, predominantly CNS-focused), the primacy of autoantibodies in orchestrating this process remains underappreciated. Critically, autoantibodies against nodal/paranodal proteins (e.g., neurofascin-155, contactin-1) don't merely mark disease but actively recruit complement, license macrophage phagocytosis via Fcγ receptors, and disrupt ion channel clustering—transforming myelin from protective sheath to immunogenic trigger. This antibody-macrophage axis creates a self-sustaining inflammatory loop: demyelination exposes new epitopes → epitope spreading → amplified autoantibody production → further demyelination. Though mechanistic details of macrophage activation require elucidation, therapeutic successes with IVIg (Fc blockade) and eculizumab (complement inhibition) in GBS/CIDP empirically validate this pathway. Thus, mapping antigen-specific autoantibody profiles isn't just academically significant—it enables stratified immunotherapies and reveals druggable checkpoints in the demyelination cascade [79,80].

Guillain-Barré syndrome: Guillain-Barré syndrome (GBS) manifests as post-infectious peripheral nerve autoimmunity characterized by demyelination, nerve root lesions, and perivascular inflammatory infiltration, where molecular mimicry drives cross-reactive antibodies against pathogens like *Campylobacter jejuni* lipooligosaccharides to target neural gangliosides GM1/GD1a—causing nerve damage or conduction blockade [61,81]; mechanistically, van den Berg *et al.* establish that in acute motor axonal neuropathy (AMAN), anti-GM1/GD1a antibodies bind nodal antigens (Ranvier regions), activating complement to form membrane attack complexes (MACs) that disrupt voltage-gated sodium channels, triggering paranodal myelin detachment and conduction failure, while in acute inflammatory demyelinating polyneuropathy (AIDP), heterogeneous antibodies target Schwann cell surface antigens, depositing MACs on myelin sheaths and recruiting macrophages that directly execute demyelination [82].

Despite plasma exchange and IVIg being standard Guillain-Barré syndrome (GBS) treatments, 20% of patients experience significant persistent disability [83], necessitating advanced therapies targeting the pivotal complement activation pathway; promisingly, the C5 inhibitor eculizumab demonstrates safety and tolerability when combined with IVIg in early studies [84–86], yet limited cohort sizes preclude definitive conclusions regarding efficacy and variability—mandating expanded clinical trials to validate this therapeutic strategy.

Chronic inflammatory demyelinating polyneuropathy: Chronic inflammatory demyelinating polyneuropathy (CIDP) represents a complex autoimmune neuropathy where anti-neurofascin-155 (NF155) antibodies emerge as pivotal pathogenic drivers—these autoantibodies directly bind Schwann cell-surface NF155, triggering its selective depletion and consequent failure of paranodal septate-like junction assembly, which critically disrupts axon-glia adhesion domains and saltatory conduction [87–89]; importantly, this molecular sabotage manifests clinically as recalcitrant ataxia/tremor and explains the characteristic intravenous immunoglobulin (IVIg) resistance observed in NF155+ CIDP patients, positioning anti-NF155 seropositivity not merely as a diagnostic biomarker but as a predictor of therapeutic refractoriness that should redirect clinicians toward B-cell-targeted biologics (e.g., rituximab) rather than conventional immunotherapy.

Building upon the established pathogenicity of anti-NF155 antibodies in CIDP—where autoantibody-mediated depletion of paranodal NF155 disrupts axoglial junctions—we propose two therapeutic axes: intercepting antibody-Schwann cell binding or suppressing pathogenic B-cell clones; however, critical knowledge gaps persist regarding the precise targeting mechanism (Fc-independent vs. complement-assisted?) and NF155's homeostatic regulation, wherein rodent and human studies paradoxically demonstrate that lentiviral-driven NF155 overexpression enhances remyelination [88,90], suggesting compensatory upregulation could bypass autoimmune destruction—yet this reparative strategy warrants caution due to potential ectopic NF155 expression consequences and unresolved questions: does exogenous NF155 evade antibody recognition? Would remyelination persist amid ongoing autoimmunity? Until mechanistic clarity emerges, pharmacologic NF155 potentiation represents a high-risk/high-reward interim approach demanding rigorous in vivo validation alongside parallel development of targeted immunotherapies.

While anti-NF155 antibodies represent a mechanistically compelling CIDP subtype characterized by paranodal disruption rather than classic macrophage-mediated demyelination [91], their restricted seroprevalence (≈15-20% of CIDP patients) fundamentally challenges the notion of CIDP as a monolithic entity and exposes critical knowledge gaps: first, why do seronegative patients exhibit identical clinical phenotypes? Second, how does IVIg/SCIG achieve therapeutic effects in anti-NF155+ patients without targeting Contactin-1 or directly neutralizing antibodies [92]? This paradox positions anti-NF155 primarily as a stratification biomarker—identifying patients with treatment-refractory disease who may benefit from B-cell depletion (e.g., rituximab)—while underscoring the urgent need to: 1) map alternative autoantibody systems in seronegative cohorts, 2) dissect IVIg's immunomodulatory mechanisms beyond simple neutralization, and 3) develop antigen-specific therapies that preserve physiological NF155 functions rather than broadly suppressing immunity. Until then, anti-NF155 remains a diagnostic stepping stone toward precision medicine in inflammatory neuropathies, not a therapeutic endpoint.

Fisher syndrome: Fisher syndrome (MFS) exemplifies pathogenic precision in neuroimmunology—triggered by molecular mimicry when microbes like Haemophilus influenzae express GQ1b

gangliosides [93], inducing anti-GQ1b IgG antibodies that launch a spatially targeted attack on cranial nerve synapses and neuromuscular junctions where GQ1b is abundantly expressed (oculomotor, trochlear, abducens, and dorsal root ganglia) [94,95]; crucially, this antibody-complement axis doesn't indiscriminately destroy tissue but selectively disrupts presynaptic voltage-gated calcium channels and postsynaptic acetylcholine receptors through MAC-mediated pore formation—a functional channelopathy explaining the hallmark triad of ophthalmoplegia, ataxia, and areflexia without neuronal apoptosis. This anatomical specificity (sparing GQ1b-poor regions) and reversible electrophysiological blockade (contrasting Wallerian degeneration in GBS) illuminate why MFS often self-resolves, yet also rationalize emerging therapies like C5 inhibitors to accelerate recovery by halting complement-driven synaptic silencing.

Fisher syndrome (MFS) faces diagnostic challenges due to phenotypic overlap with GBS variants, brainstem strokes, and myasthenia gravis—where reliance on non-specific cerebrospinal fluid (CSF) protein elevation (60% sensitivity) risks underdiagnosis—making anti-GQ1b IgG serology the indispensable biomarker that simultaneously reveals the disease's actionable core: pathogenic antibody binding at neuromuscular junctions (NMJs) [96,97]. Critically, mouse NMJ models demonstrate intravenous immunoglobulin (IVIg) exerts dual therapeutic effects: 1) competitive displacement of anti-GQ1b antibodies from presynaptic gangliosides, and 2) complement interception preventing MAC formation—yet this neutralization-centric view overlooks IVIg's immunomodulatory functions in humans (FcγRIIB upregulation, anti-idiotypic suppression) that likely contribute to clinical efficacy beyond mere blocking [96,97]. This mechanistic duality exposes a translational gap: while mouse models validate antigen-specific neutralization, human treatment requires combinatorial strategies addressing downstream calcium toxicity and nerve terminal remodeling—urging development of GQ1b-targeted biologics (e.g., ganglioside mimetics) for precision intervention without IVIg's broad immunosuppression. While the mouse neuromuscular junction (NMJ) model provides a mechanistically valuable platform for studying IVIg's blockade of anti-GQ1b binding [96,97], its translational relevance is constrained by fundamental interspecies differences in ganglioside density and blood-nerve barrier physiology—limitations particularly acute for modeling human cranial nerve vulnerability in MFS; moreover, this model reveals a critical point of no return in antibody-mediated injury: complement-triggered calcium influx induces calpain hyperactivation that irreversibly degrades presynaptic cytoskeletal scaffolds (neurofilaments, spectrin) within nerve terminals [98,99], explaining why IVIg alone fails in late-presenting patients where structural damage supersedes functional blockade. This calcium-calpain-cytoskeleton axis represents an actionable therapeutic frontier—calcineurin inhibitors like tacrolimus could theoretically dampen calcium-induced toxicity, yet their systemic immunosuppression risks outweighing benefits in a typically self-limiting disease; instead, focal delivery of calpain inhibitors (e.g., SNJ-1945 via retrobulbar infusion) or voltage-gated calcium channel modulators (e.g., ziconotide) might achieve selective neuroprotection without compromising immune surveillance, transforming MFS management from passive antibody clearance to active synaptic preservation with implications for other complement-mediated neuropathies.

Summary and Outlook

While **Tables 1** and **2** categorize autoantibody pathogenesis into three mechanistic classes—complement-mediated cytotoxicity (e.g., NMOSD's AQP4-IgG/MAC attack), receptor functional modulation (NMDAR internalization, AChR blockade), and

Table 1. Autoantibodies associated with central nervous system diseases.

Autoantigens of the target	Diseases	Antibody pathogenicity	Refs
APQ4	NMOSD	Complement activation, inflammatory response destroys receptors and induces p-Tau accumulation.	[34,68]
NMDAR	Anti-NMDAR encephalitis	NMDAR internalization, disruption of NMDAR/EphB2R receptor.	[44–46]
LGI1	Anti-LGI1 encephalitis	Inhibits the interaction of LGI1 with ADAM22/23 and decreases Kv1 and AMPA receptor levels.	[69–71]
	Epilepsy	Reduced AMPA-R expression, downregulates inhibitory neuronal networks, leading to hyperexcitability of neuronal networks.	[72]
CASPR2	Anti-CASPR2 encephalitis	Inhibits Caspr2 interaction with contactin-2.	[73]
AMPAR	Anti-AMPAR encephalitis	AMPAR internalizes and degrades.	[74]
DPPX	Anti-DPPX encephalitis	Reduced DPPX and Kv4.2 membrane expression.	[74,75]
β2AdR, mAChR	Myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS)	Receptor dysfunction, exact mechanism unknown.	[49]
GAD	Stiffman syndrome, SMS	Decreases GABA levels and increases nervous system excitability.	[54,76,77]
IgLON5	Anti-IgLON5 disease	Disruption of the neuronal cytoskeleton induces p-tau accumulation, disruption of synapses.	[54,60]
Neurexin-3α	Encephalitis	Reduces the total number of synapses in developing neurons by causing a decrease in neurexin-3α specificity.	[40,78]

Table 2. Autoantibodies associated with peripheral nervous system diseases.

Autoantigens of the target	Diseases	Antibody pathogenicity	Refs
GM1, GD1a	Acute motor axonal neuropathy (AMAN)	Complement activation, MAC formation, clear of axons by macrophages.	[81,82]
	Acute inflammatory demyelinating polyneuropathy (AIDP)	Complement activation, MAC formation, macrophages invade the myelin sheath.	
	Acute motor sensory axonal neuropathy (AMSAN)	Complement activation, conduction was impaired at the nodes of Ranvier, obstruction of motor fiber axonal conduction.	
CRPS	Complex regional pain syndrome (CRPS)	Release of inflammatory mediators, sensitive of primary sensory neurons, central sensitization was observed in the spinal dorsal horn.	[100,101]
GT1a	Pharyngocervicobrachial variation (PCB)	Complement activation, disruption of axonal glial or neuromuscular junctions.	[102,103]
GQ1b	Miller-Fisher syndrome (MFS)	Release of Ach in large and quantitative quantities, disruption of neuromuscular transmission.	[104–106]
NF155	Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Selective depletion of NF155 (in peripheral nerves), inhibition of glial junction formation in the paranodal axis, interference with nerve conduction.	[87,89]

signaling pathway disruption (GAD65-mediated GABA depletion)—this taxonomy risks oversimplifying the dynamic interplay observed clinically: in reality, most neuroautoimmune diseases employ hybrid mechanisms (CIDP combines complement-dependent myelinolysis with NF155-mediated paranodal destabilization), and critically, the classification fails to capture temporal evolution where initial receptor blockade progresses to irreversible synaptic loss via calcium-dependent cascades (MFS) or epitope spreading (GBS). Moreover, the framework neglects emerging dimensions like autoantibody-triggered glial activation (anti-IgLON5's tauopathy induction) and blood-brain barrier dysregulation (LGI1-mediated CLDN5 downregulation)—underscoring the need for a fourth category: neuroimmune network disruption. This mechanistic stratification remains clinically vital, however, as complement-driven diseases respond to eculizumab, receptoropathies to IVIg/plasmapheresis, and signaling defects to pathway-specific modulators—yet optimal therapeutics must address concurrent mechanisms through staged combinatorial approaches. Complement-mediated cytotoxicity represents a final common pathway in diseases like GBS and NMOSD, where autoantibody-antigen binding (e.g., gangliosides in GBS **(Figure 2)**, AQP4 in NMOSD) triggers terminal complement cascade activation—generating membrane attack complexes (MACs) that not only induce voltage-gated sodium channel disintegration but create focal membrane breaches enabling calcium influx, calpain activation, and irreversible axo-glial detachment; this explains why demyelination progresses despite immunotherapy once MACs embed, necessitating early complement inhibition (eculizumab) to prevent structural annihilation. Conversely, precision synaptic sabotage defines anti-NMDAR encephalitis **(Figure 1)**: antibodies induce highly specific NMDAR internalization via epitope-dependent capping, depleting synaptic receptors without structural synapse loss—causing reversible glutamate hypofunction that manifests as cognitive-psychiatric symptoms, yet this "functional lesion" paradoxically permits recovery with timely B-cell depletion (rituximab) or antibody clearance, distinguishing it from complement's destructive finality. Critically, these exemplify neuroimmunology's mechanistic spectrum—from indiscriminate complement demolition to targeted receptor editing—demanding disease-specific therapeutic strategies: MAC interception for structural rescue versus receptor saturation/recycling for functional restoration. Autoantibody-induced dysregulation of signaling pathway proteins represents a distinct pathogenic axis beyond complement/receptor mechanisms—exemplified in anti-DPPX encephalitis where antibodies target the Kv4.2 potassium channel regulatory subunit **(Figure 1)**, triggering a dual-tiered sabotage: direct DPPX downregulation destabilizes the Kv4.2 complex, while secondary Kv4.2 loss amplifies neuronal hyperexcitability through impaired A-type currents, ultimately causing dendritic integration defects and cerebellar dysfunction [74]. This illustrates a broader paradigm: signaling disruptors like anti-GAD65 (GABA depletion), anti-mGluR1 (cerebellar LTD impairment), and anti-DPPX operate as molecular saboteurs that alter synaptic computation without structural destruction—yet their clinical impact is profound due to network-level reverberations. Critically, this category demands specialized therapeutic approaches; while complement inhibitors or receptor modulators are ineffective, strategies restoring ion channel trafficking (e.g., 4-AP for Kv4.2 dysfunction) or bypassing blocked pathways (e.g., GABAergic drugs for GAD65 deficiency) may prove more efficacious than broad immunosuppression. The insidious nature of signaling interference—often presenting as progressive cognitive/motor decline rather than acute deficits—underscores the need for functional neuroimaging biomarkers to detect synaptic dysrhythmia before irreversible circuit rewiring occurs.

Autoantibodies with high titers are widely acknowledged as pivotal clinical indicators of autoimmune diseases and have been extensively utilized as diagnostic biomarkers across various autoimmune conditions. In recent decades, the landscape of neurological disease diagnostics has witnessed a paradigm shift with the discovery of numerous novel autoantibodies, significantly enhancing our ability to accurately diagnose complex neurological disorders. For example, the identification of serum autoantibodies against aquaporin-4 (AQP4) has revolutionized the diagnosis of neuromyelitis optica spectrum disorder (NMOSD), providing a highly specific and sensitive diagnostic marker that has improved clinical decision-making [107,108].

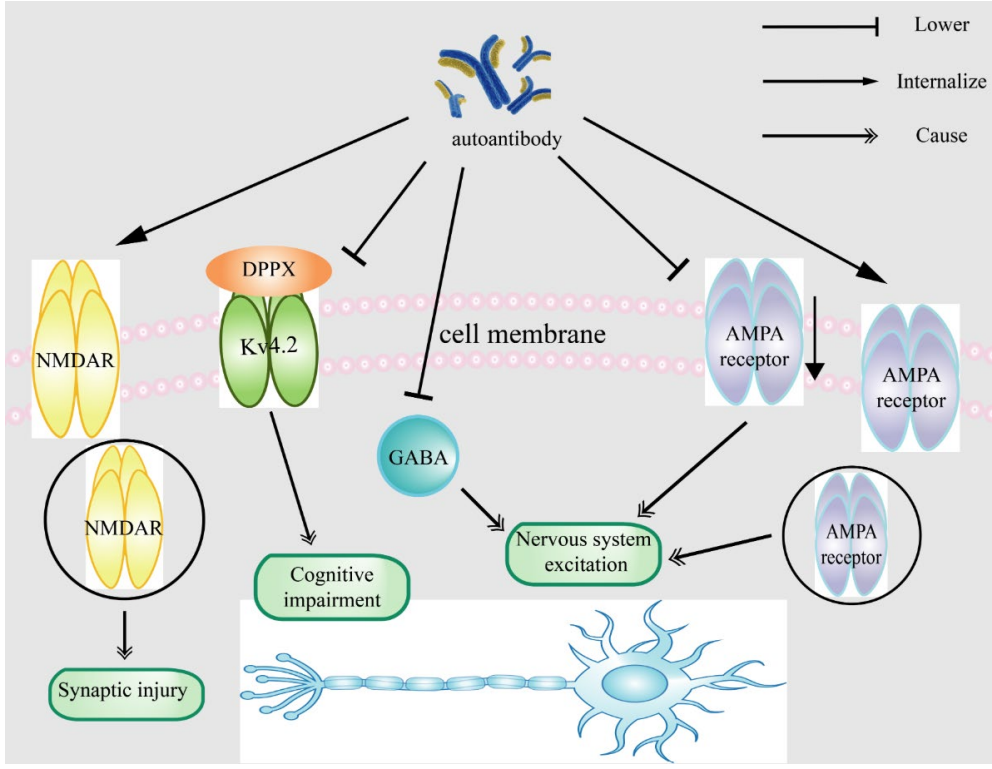

Figure 1. Mechanistic pathways of autoantibodies in the central nervous system.

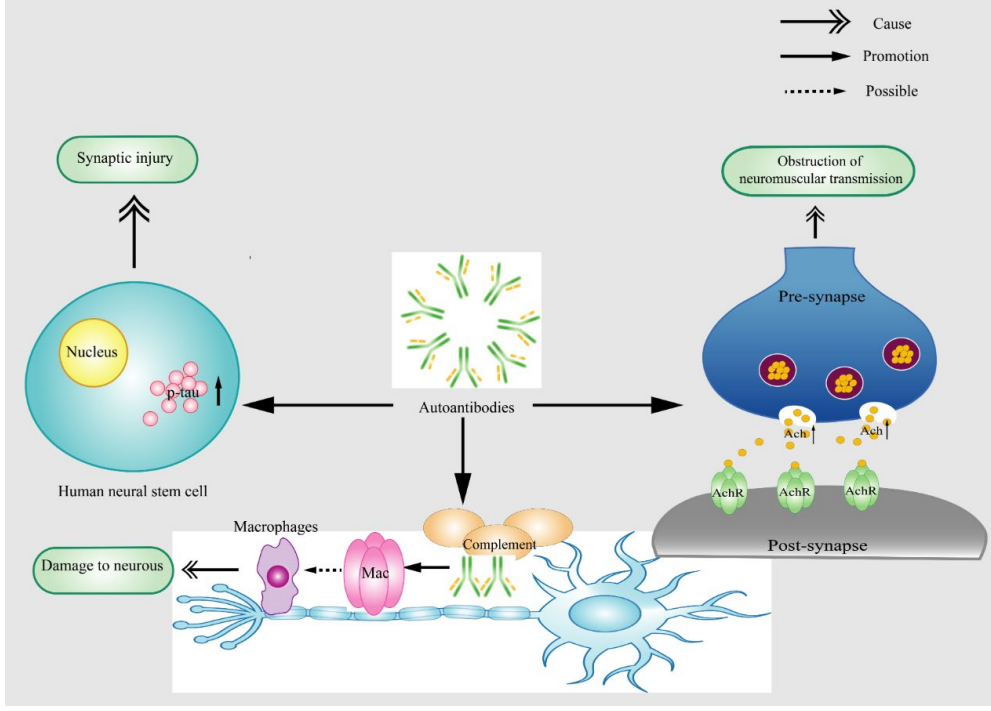

Figure 2. Mechanistic pathways of autoantibodies in the peripheral nervous system.

Moreover, in the context of glioma, emerging evidence suggests that GFAP autoantibodies, along with anti-FLNC autoantibodies, whose expression levels exhibit an inverse relationship with FLNC expression, hold promise as potential serum biomarkers for the early detection of low-grade gliomas. Early identification of these autoantibodies could potentially facilitate timely intervention, thereby improving patient prognosis. Additionally, several autoantibodies, although not yet established as definitive diagnostic markers for neurological diseases, show substantial potential for clinical application. Notably, in patients with anti-IgLON5 disease, the positive correlation between the serum anti-IgLON5 IgG titer and disease duration, as reported by previous studies [59], strongly suggests that the expression level of IgLON5 IgG could serve as a valuable diagnostic criterion. This correlation not only aids in disease staging but also provides insights into disease progression, underscoring the importance of monitoring autoantibody levels in clinical practice [109–114].

These discoveries not only expand the diagnostic toolkit for neurological diseases but also open new avenues for understanding disease pathogenesis. As we continue to uncover the intricate relationship between autoantibodies and neurological disorders, future research should focus on validating these potential biomarkers through large-scale, multicenter studies. Establishing standardized detection methods and defining clear diagnostic thresholds will be crucial for translating these findings into routine clinical practice, ultimately leading to more personalized and effective treatment strategies for patients with neurological autoimmune diseases. In chronic inflammatory demyelinating polyneuropathy (CIDP), Contactin-1 and anti-NF155 antibodies have emerged as promising diagnostic markers. These antibodies can directly modulate the function of key target proteins that are integral to CIDP pathogenesis [88,89], thereby serving as not only indicators of the disease but also potential contributors to understanding its underlying mechanisms. Similarly, in Guillain-Barré syndrome (GBS), anti-GM1 and anti-GD1α antibodies play a dual role: they can directly initiate disease onset by activating the complement system and simultaneously serve as valuable diagnostic tools.

The utility of autoantibodies as diagnostic markers in neurological diseases has been increasingly recognized, with substantial evidence from numerous studies supporting this concept [82]. The potential of an autoantibody to be a reliable diagnostic marker hinges on several critical factors. High-titer expression is often a prerequisite, as it generally reflects a more robust immune response associated with the disease state. Additionally, involvement in key pathogenic pathways is essential; autoantibodies that directly impact disease-causing mechanisms are more likely to have high diagnostic specificity and sensitivity. Finally, establishing clear pathogenicity is crucial, as it distinguishes causative autoantibodies from those that may be present incidentally. Understanding these criteria not only enhances our diagnostic capabilities but also paves the way for developing targeted therapies. Future research should focus on elucidating the complex interactions between autoantibodies and neurological disorders, validating these markers through rigorous clinical trials, and integrating them into standardized diagnostic algorithms to improve patient outcomes in neurological diseases.

A substantial body of literature underscores the pivotal role of autoantibodies in immune-mediated neurological disorders, yet the precise mechanisms of action for certain autoantibodies remain poorly defined, and a systematic compilation of autoantibody mechanisms across neurological diseases is notably absent. This knowledge gap hampers the development of targeted therapeutic strategies, as understanding causative mechanisms is fundamental to implementing evidence-based treatments. Consequently, accelerating research into the roles and mechanisms of autoantibodies in neurological diseases emerges as a critical priority for advancing the field. This review aims to dissect the functional roles and mechanistic underpinnings of autoantibodies in immune-related neurological conditions, systematically synthesizing their mechanisms in disorders such as neuromyelitis optica spectrum disorder (NMOSD), anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, and chronic inflammatory demyelinating polyneuropathy (CIDP). By integrating existing evidence, this synthesis not only enables researchers to design more targeted experimental investigations but also fosters a deeper understanding of neuroimmunology's evolving landscape. Such insights hold significant implications for improving diagnostic accuracy, therapeutic strategies, and patient management in neurological disorders. For instance, the anti-NF155 antibody, a marker of CIDP, exemplifies how mechanistic insights into autoantibodies could unlock novel directions for diagnostic tools and therapeutic interventions in clinical practice. Beyond outlining the pathogenesis of immune-mediated neurological diseases, this review explicitly identifies current research gaps and highlights the translational potential of autoantibody studies in neurology. By bridging mechanistic understanding with clinical application, it not only advances the field's theoretical framework but also provides tangible guidance for the diagnosis, treatment, and prevention of neurological disorders, thereby shaping the future trajectory of autoantibody-driven research in neuroimmunology.

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Ethics Approval and Consent to Participate

This review did not involve human participants, animal subjects, or clinical trials. Ethical approval was not required in accordance with institutional and national regulations.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

Authors' Contributions

Cheng Xue: Conceptualization, Investigation, Formal Analysis, Writing – Review & Editing.

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