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REVIEW

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Neuroinflammation and humoral immunity across chronic diseases: mechanisms, biomarkers, and therapeutic implications

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Abstract

Neuroinflammation and humoral immunity form an integrated, bidirectional framework underpinning the onset, progression, and treatment of major neurological diseases, including multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and stroke. All five neurological diseases show a clear, age-dependent increase in incidence. Neuroinflammatory cascades, driven by microglial and astrocytic activation, cytokine/chemokine networks, complement activation, and blood–brain barrier dysfunction, intersect with adaptive humoral mechanisms involving B-cells, immunoglobulins, and immune complexes. Although humoral and neuroinflammatory biomarkers have improved disease characterization, enabling earlier detection, patient stratification, and treatment monitoring, their broader clinical implementation remains limited by issues such as assay standardization and cross-platform reproducibility. The most reliable biomarkers highlight the importance of linking measurement strategies directly to the key biological mechanisms of each disease. Progress now depends on harmonized protocols, large-scale longitudinal validation, and integration of fluid biomarkers with imaging, genomic, and clinical phenotyping. Therapeutic strategies should be guided by stage-specific and endotype-specific biomarker profiles. A precision neuroimmunology paradigm, grounded in standardized, composite biomarker panels and integrative analytics, offers the most credible path to disease modification and improved patient-centred outcomes.

Keywords: Neuroinflammation, humoral immunity, multiple sclerosis, Alzheimer's disease, amyotrophic lateral sclerosis, ageing, precision medicine

Introduction

Neuroinflammation is now recognized as a driver, rather than a mere bystander, across neurological diseases, shaping disease onset, trajectory, and therapeutic response [1]. Neuroinflammation is primarily driven by microglia, astrocytes, cytokine networks, and blood–brain barrier (BBB) breakdown [2, 3]. The pathogenic aspect emphasizes glial–neuronal crosstalk, inflammasome signaling, mitochondrial dysfunction, oxidative stress, and impaired resolution of inflammation [2-4]. Reciprocal glial–neuronal communication is mediated through cytokines, chemokines, purinergic signaling, and damage-associated molecular patterns, collectively altering neuronal excitability and synaptic homeostasis [1, 4]. Compounding these processes, BBB breakdown permits peripheral immune cells and circulating cytokines to infiltrate the central nervous system (CNS), reinforcing chronic inflammatory loops [2]. The adaptive immune system, on the other hand, consists of two major coordinated branches: the cell-mediated and the humoral response [5]. While T cells drive the cell-mediated arm, the humoral immune response is a subdivision of the adaptive immune system mediated by B cells and the antibodies they produce [6]. Humoral responses function by generating antigen-specific antibodies, enabling neutralization of pathogens, opsonization, and complement activation, while the broader adaptive immune system also includes T cell–driven mechanisms such as cytotoxicity and immune regulation [5, 7].

Humoral immunity plays a major role in the pathogenesis, progression, and potential treatment of multiple neurological diseases [8]. Crosstalk between microglia, astrocytes, and B cells, integrating cytokines, chemokines, and antigen-presenting interactions, creates a bidirectional signaling network that shapes both protective and pathogenic

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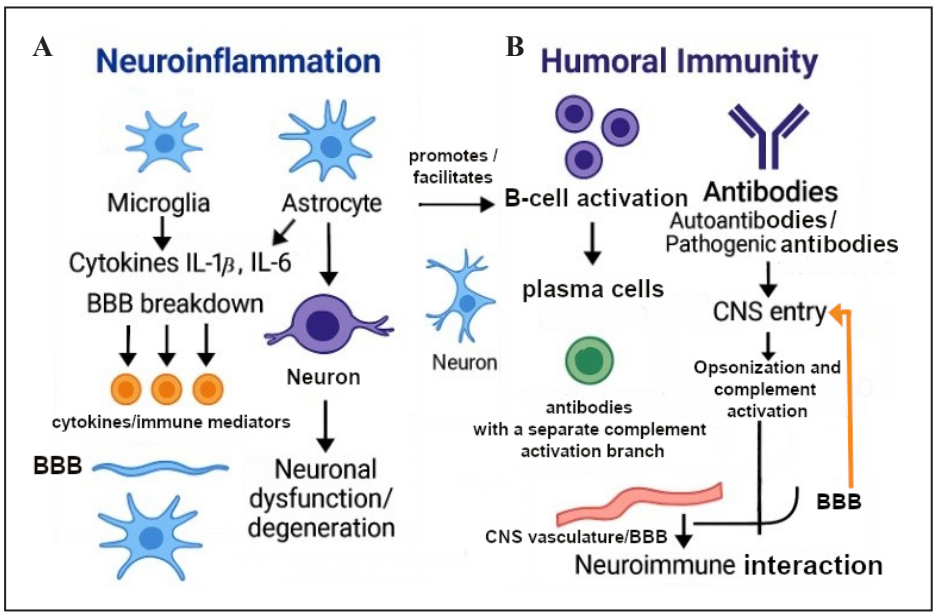


Figure 1. Neuroinflammatory and humoral immune mechanisms contributing to neuronal dysfunction. **(A)** Activated microglia and astrocytes release pro-inflammatory cytokines (e.g., IL-1β, IL-6) and disrupt the blood–brain barrier (BBB), promoting neuronal dysfunction and degeneration. **(B)** Peripheral B cell activation generates antibodies that may enter the CNS following BBB disruption. Antibodies and complement components mediate opsonisation, complement activation, and neuroimmune crosstalk, contributing to neuronal injury.

aspects of humoral immunity within the CNS [5]. Each neurological disease features a distinct interplay of these mechanisms (Figure 1).

Recent advances in neuroimmunology have clarified how antibodies, B cell subsets, and immune–brain communication contribute to neuroinflammation, neurodegeneration, and autoimmunity [8]. Across neurological diseases, humoral immunity plays diverse roles, from pathogenic autoantibody-driven injury in multiple sclerosis (MS) to complex protective *vs*. inflammatory B cell functions in Alzheimer's disease (AD), and broad immune–brain interactions in Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and stroke (Table 1) [9-12]. Biomarkers rooted in humoral activity increasingly support diagnosis, monitoring, and therapeutic development, while targeted immunotherapies are reshaping treatment paradigms [13-16].

All of the above reinforce the concept of neurological diseases as systemic disorders involving central–peripheral immune crosstalk. Therefore, this review presents a multi-disease comparative analysis (MS–AD–PD–ALS–stroke), focusing on autoimmune, neurodegenerative, and cerebrovascular diseases, presenting mechanisms of neuroinflammation and humoral immunity in the context of ageing, strengths and limitations of biomarkers, therapeutic implications, analysis of challenges, controversies, and future directions.

Comparative contribution of neuroimmune mechanisms across major neurological diseases

Neuroimmune mechanisms represent a shared but highly heterogeneous axis across major neurological diseases. Rather than acting as isolated processes, neuroinflammatory and humoral immune pathways form interconnected, disease-specific networks, whose relative contributions define distinct immunopathological profiles ranging from classical autoimmunity to secondary immune activation (Table 2).

Neuroinflammatory mechanisms

Across neurological disorders, neuroinflammation con-

Table 1. Strengths and limitations of disease-specific IgG/isotype patterns across neurological diseases.

Neurological disease	Key IgG/isotype findings	Strengths	Limitations
AD	Isotype-dependent anti-Aβ IgG activity; Fc-mediated plaque clearance varies by subclass	Strong Fc-dependent clearance mechanisms	Not AD-specific; patterns not standardized
PD	α-syn immunotherapy often IgG1-based (cinpanemab)	Useful for synucleinopathy targeting	High variability; no specific isotype pattern
ALS	Humoral immune activation; no defined IgG isotype pattern	Reliable immune involvement markers	Not ALS-specific; no stable pattern
MS	Intrathecal IgG1 and IgG3 OCBs; IgM OCBs possible	OCBs strong diagnostic marker	LP required; biomarkers not standardized
Stroke	Post-injury CNS antibodies; no defined isotype profile	Useful in acute CNS injury	Low specificity; high variability

Notes: MS: multiple sclerosis; AD: Alzheimer's disease; PD: Parkinson's disease; ALS: amyotrophic lateral sclerosis; IgG: immunoglobulin G; OCBs: oligoclonal bands; IgM: immunoglobulin M; Aβ: amyloid-beta; Fc: fragment crystallizable; CNS: central nervous system; LP: lumbar puncture.

Table 2. Comparative contribution of neuroinflammatory and humoral immune mechanisms across major neurological diseases.

Neurological disease	Neuroinflammation	Humoral immunity
MS	Microglia, astrocytes, cytokines, BBB breakdown, cell infiltration	Strong B cell/antibody involvement, complement, ectopic follicles
AD	Chronic microglial activation, inflammasomes, TREM2	Complement near plaques, therapeutic antibodies > endogenous pathology
PD	α-syn-induced microglial activation, TLR signaling, T cell infiltration	Autoantibodies to α-syn, experimental antibody therapies
ALS	Glial activation, cytokines, infiltration	Complement, regulatory cytokines, mild antibody involvement
Stroke	Acute cytokine surge, leukocyte infiltration, BBB disruption	Later antibody entry, complement, repair cytokines (IL-10, TGF-β)

Notes: MS: multiple sclerosis; AD: Alzheimer's disease; PD: Parkinson's disease; ALS: amyotrophic lateral sclerosis; BBB: blood–brain barrier; TREM2: triggering receptor expressed on myeloid cells 2; α-syn: alpha-synuclein; TLR: Toll-like receptor; IL-10: interleukin-10; TGF-β: transforming growth factor β.

sistently emerges as the central pathological framework, yet its origin and immunological architecture differ fundamentally (Figure 2A). At one end of the spectrum, MS exemplifies a fully integrated neuroinflammatory–adaptive immune process, in which peripheral immune activation directly initiates CNS pathology [17]. Disruption of the BBB enables sustained infiltration of autoreactive T lymphocytes and myeloid cells, driving demyelination and axonal injury [18]. Within the CNS, activated microglia and astrocytes amplify this response through cytokine release, chemokine signaling, and reactive oxygen species (ROS) production, establishing a chronic, self-sustaining inflammatory environment tightly coupled to adaptive immunity (Figure 2B) [19].

In contrast, neurodegenerative diseases such as AD, PD, and ALS are characterized by neuroinflammation that arises primarily as a response to intrinsic neuronal pathology, yet progressively assumes a pathogenic role. In AD, neuroinflammation is dominated by chronic microglial activation and impaired protein clearance, particularly of amyloid-β (Aβ), accompanied by inflammasome activation and immunometabolic dysfunction [11]. The transition of microglia from a homeostatic to a pro-inflammatory phenotype results in sustained cytokine production, synaptic injury, and progressive neuronal loss, positioning innate immunity as the primary driver of disease propagation rather than a secondary epiphenomenon (Figure 2C) [20].

A similar but mechanistically distinct pattern is observed in PD, where misfolded α-synuclein acts as a potent trigger of innate immune activation. Through interaction with microglial receptors, including Toll-like receptors, α-synuclein induces pro-inflammatory signaling and neurotoxicity [21]. Although BBB dysfunction and T cell infiltration are present, they remain subsidiary to innate immune activation and do not reach the pathogenic prominence seen in MS (Figure 2D) [22].

ALS further expands this paradigm by combining robust glial activation with emerging adaptive immune contributions. Persistent activation of microglia and astrocytes generates a toxic inflammatory milieu that directly contributes to motor neuron degeneration [23, 24]. At the same time, recent evidence of autoreactive $CD4^+$ T-cell responses indicates that adaptive immunity may influence disease heterogeneity and progression, although it does not dominate the process to the same extent as in autoimmune disorders [25]. Neuroinflammation in ALS thus represents a feed-forward system in which degeneration and immune activation reinforce each other (Figure 2E).

Stroke represents a fundamentally different context, defined by an acute and temporally dynamic neuroinflammatory response. Within minutes of ischemic injury, metabolic failure and oxidative stress activate microglia and astrocytes, initiating a cascade of cytokine release, BBB disruption, and leukocyte recruitment [26, 27]. Unlike chronic diseases, neuroinflammation in stroke evolves through distinct phases, from early innate activation to later immune cell infiltration and tissue remodeling, making it both a driver of secondary injury and a determinant of recovery (Figure 2F) [28].

Taken together, neuroinflammation across these conditions can be conceptualized along a continuum, from adaptive immune–driven (MS) to innate-dominant (AD, PD, ALS, stroke), with important variations in timing, cellular composition, and pathological impact.

Humoral immune mechanisms

In contrast to the central role of neuroinflammation, humoral immunity demonstrates a highly variable and context-dependent contribution, ranging from primary pathogenic driver to secondary modulator.

MS again represents the clearest example of pathogenic humoral immunity, where B cells actively shape disease evolution beyond antibody production alone [17]. Through antigen presentation and interaction with T cells, B cells reinforce inflammatory circuits and can form ectopic lymphoid structures within the meninges [10]. Intrathecal IgG synthesis, reflected by oligoclonal bands (OCBs), indicates compartmentalized CNS immune activity and remains a defining diagnostic hallmark [10, 29]. Importantly, IgG, particularly complement-activating subclasses such as IgG1 and IgG3, directly contributes to demyelination via classical complement activation, establishing humoral immunity as a co-dominant pathogenic

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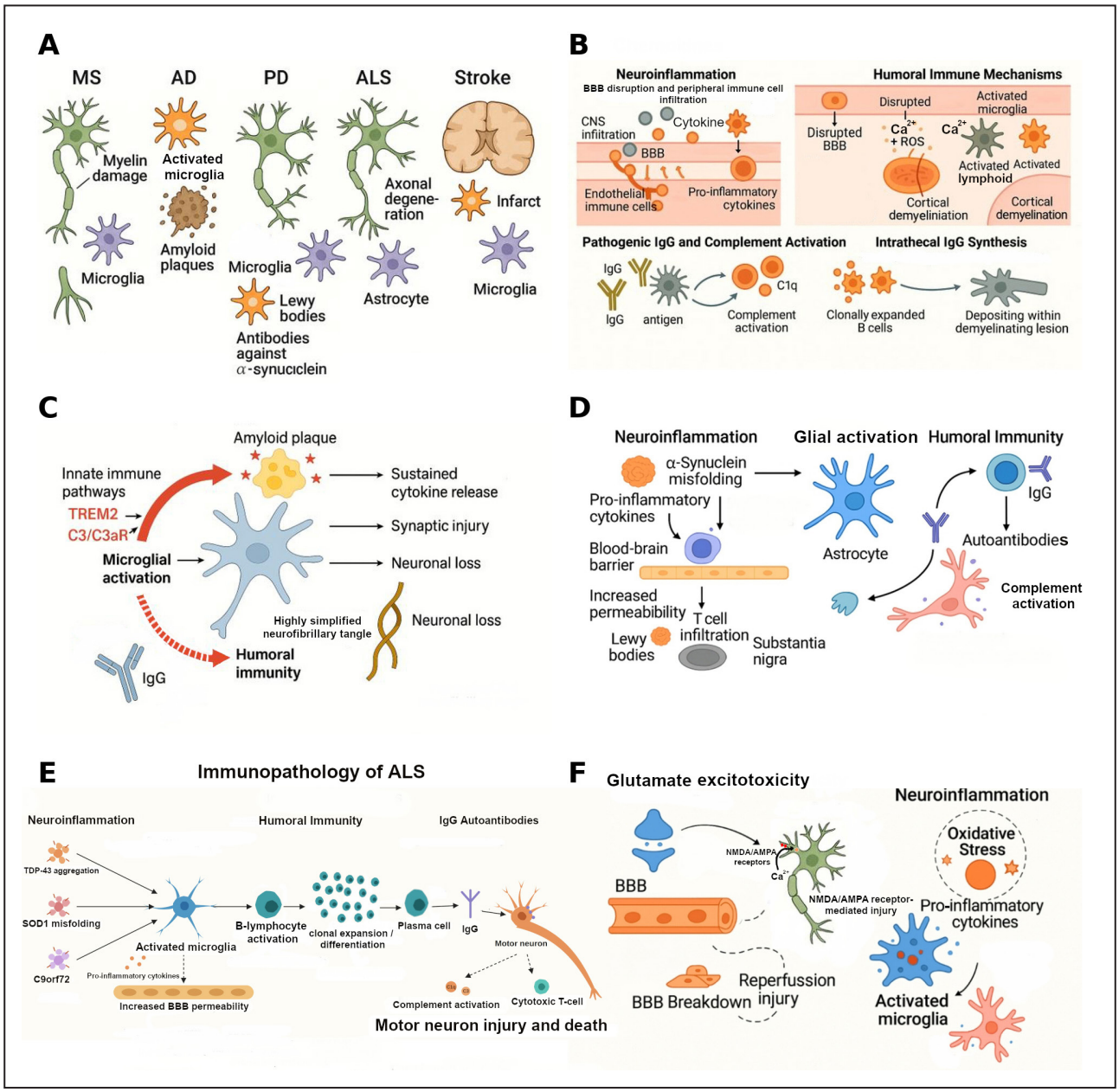


Figure 2. **Spectrum of neuroinflammatory architectures across major neurological disorders. (A)** Comparative neuroinflammatory mechanisms across major neurological diseases. Overview of shared and disease-specific neuroinflammatory features in multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and stroke. Representative pathological hallmarks include myelin damage (MS), amyloid plaques (AD), Lewy bodies (PD), axonal degeneration (ALS), and infarct formation (stroke), highlighting the central roles of microglia and astrocytes in disease-associated neuroinflammatory cascades underlying diverse neurological diseases. **(B)** Neuroinflammatory and humoral immune mechanisms in multiple sclerosis. Left: Blood–brain barrier (BBB) disruption enables infiltration of peripheral immune cells and release of pro-inflammatory cytokines, chemokines, and reactive oxygen species (ROS), promoting microglial activation, oxidative stress, and myelin and axonal damage. Right: B-cell activation, meningeal lymphoid aggregates, and intrathecal IgG synthesis contribute to demyelination through opsonisation, complement activation (*e.g.*, C1q), and antibody-mediated injury. Clonal expansion of B cells and antibody deposition within lesions further support their pathogenic and diagnostic roles in multiple sclerosis. **(C)** Immunopathological mechanisms in Alzheimer's disease. Amyloid plaque accumulation triggers sustained activation of innate immune pathways, leading to microglial activation and upregulation of immune receptors, including TREM2 and complement signaling components (C3/C3aR). Activated microglia release pro-inflammatory cytokines, promoting chronic neuroinflammation, synaptic dysfunction, and neuronal loss. Humoral immune responses further amplify inflammatory signaling, while neurofibrillary tangle formation and progressive neurodegeneration represent downstream consequences of these interacting immune and neurodegenerative processes. **(D)** Neuroinflammatory and humoral immune processes in Parkinson's disease. **Left**: Misfolded α-synuclein initiates neuroinflammatory cascades characterized by microglial activation, pro-inflammatory cytokine release, BBB dysfunction, and T-cell infiltration into the substantia nigra. Astrocytes and activated microglia further amplify inflammatory signaling associated with Lewy body pathology. **Right**: IgG and autoantibody responses promote complement activation and immune-mediated neuronal injury. Together, these pathways contribute to the progression of Parkinson's disease. **(E)** Neuroinflammatory and humoral immune mechanisms in amyotrophic lateral sclerosis. Genetic and molecular drivers of ALS—TDP-43 aggregation, SOD1 misfolding, and *C9orf72* expansion—converge to activate microglia, triggering release of pro-inflammatory cytokines and increased BBB permeability. This facilitates formation of circulating immune complexes and cytokines, driving clonal expansion of B lymphocytes into plasma cells and subsequent IgG production. IgG autoantibodies target motor neurons directly and via complement activation (C1q, C3) and T-cell–mediated cytotoxicity, ultimately leading to motor neuron injury and death. **(F)** Neuropathological processes following stroke. Cerebral ischemia induces excitotoxicity, oxidative stress, and BBB disruption, facilitating infiltration of peripheral immune cells. Reperfusion injury further enhances inflammatory responses and tissue damage. Activated microglia and astrocytes release pro-inflammatory cytokines, driving sustained neuroinflammation. Together, excitotoxicity, oxidative stress, BBB dysfunction, and immune activation contribute to acute neuronal injury and secondary neurodegeneration following stroke.

force alongside cellular mechanisms (Figure 2B) [19, 30]. In neurodegenerative diseases, however, humoral immune responses assume a markedly different role. Rather than acting as primary drivers, they are generally secondary, modulatory, or reflective of underlying neurodegeneration. In AD, complement activation is closely associated with amyloid plaques and modulates microglial behavior, influencing phagocytosis and inflammatory signaling [7, 12]. Despite the presence of various autoantibodies, there is no evidence that IgG-mediated cytotoxicity drives disease pathology [31]. Instead, humoral components function within a broader innate immune environment, shaping but not initiating the neuroinflammatory response (Figure 2C). A similar interpretative framework applies to PD, where α-synuclein–reactive autoantibodies and B cell involvement have been described, but remain inconsistent across studies (Figure 2D) [32, 33]. These findings are most probably explained as immune responses to ongoing neuronal damage, rather than causative mechanisms. The absence of reproducible pathogenic IgG signatures further distinguishes PD from classical autoimmune conditions.

In ALS, humoral contributions are more evident at the level of complement activation and immune complex formation, which modulate inflammatory signaling and glial activation [7, 12]. Although autoantibodies are frequently detected, they are generally regarded as biomarkers of neuronal injury rather than direct mediators of pathology [34]. Instead, emerging evidence highlights adaptive T-cell responses as a more credible contributor to disease-specific immune mechanisms (Figure 2E) [25].

In stroke, humoral immunity plays a secondary but dynamically important role, particularly following BBB disruption. The extravasation of IgG into brain tissue promotes complement activation and amplifies microglial responses, contributing to secondary injury [35]. Concurrently, infiltration of B cells and production of cytokines and antibodies reflect systemic immune activation (Figure 2F) [35]. Unlike MS, however, these processes are context-dependent and temporally regulated, arising after the initial insult rather than initiating it [36].

When considered together, these diseases illustrate a spectrum in which the relationship between neuroinflammation and humoral immunity shifts from tight integration to functional dissociation. MS occupies one extreme, defined by synergistic interactions between adaptive cellular and antibody-mediated mechanisms. Neurodegenerative diseases occupy an intermediate position, where innate immune activation dominates and humoral responses serve supportive or reactive roles. Stroke represents a distinct acute model, in which both neuroinflammatory and humoral processes are rapidly induced and temporally coordinated following tissue injury.

Ageing effects across neurological diseases

Ageing impairs BBB and blood–cerebrospinal fluid barrier function, allowing peripheral cytokines and immune cells to access the CNS more readily, which amplifies neuroinflammation and influences disease trajectories in neurological diseases [37]. With ageing, both innate and adaptive immunity decline (thymic involution, skewing toward memory T cells, altered B and natural killer cell function), while chronic low-grade inflammation (inflammaging) increases [38]. Ageing shifts microglia towards pro-inflammatory phenotypes with mitochondrial and lysosomal dysfunction and reduced clearance of proteopathic aggregates [37]. Astrocytes also adopt reactive and senescent states that sustain inflammaging and impair neuronal and synaptic support [39]. Together, these changes increase vulnerability to neurodegeneration, influence disease progression, and may affect therapeutic responses in older adults [37-39].

In MS, ageing promotes a shift from relapsing to progressive disease through immunosenescence and inflammaging, resulting in reduced relapse activity but increased neurodegeneration and diminished CNS repair capacity [37, 38].

Ageing is the strongest risk factor for AD, facilitating Aβ and tau pathology through impaired cellular homeostasis, increased neuroinflammation, oxidative stress, and synaptic dysfunction, ultimately accelerating cognitive decline [40].

In PD, substantia nigra dopaminergic neurons are particularly vulnerable to age-associated mitochondrial dysfunction, oxidative stress, impaired proteostasis and chronic neuroinflammation [41]. BBB dysfunction and age-associated changes in cerebrospinal fluid (CSF) biomarkers further reflect more complex disease mechanisms in older patients [42].

Ageing is also a major risk factor for ALS, as key hallmarks of ageing—including genomic instability, loss of proteostasis, mitochondrial dysfunction, impaired autophagy, and chronic inflammation—overlap with core pathogenic mechanisms driving motor neuron degeneration [43].

Similarly, ageing increases stroke susceptibility through endothelial dysfunction, BBB impairment, oxidative stress, and neurovascular decline. These changes exacerbate post-stroke neuroinflammation, worsen neurological outcomes, and reduce the brain's capacity for recovery [44-46].

Comparative framework for neuroinflammatory and humoral biomarkers in neurological diseases

Neuroinflammation has emerged as a central pathological process across a broad spectrum of neurological diseases, and consequently as a major source of candidate biomarkers with diagnostic, prognostic, and monitoring potential. Despite shared inflammatory pathways, including cytokine signaling, glial activation, and immune-mediated tissue injury, the biological meaning, specificity, and clinical utility of neuroinflammatory biomarkers vary substantially across diseases, reflecting their underlying immunopathological architecture. In parallel, humoral biomarkers derived from CSF and blood provide complementary insights into immune activation, neurodegeneration, and systemic responses, though their interpretative value is

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Table 3. Combined humoral and IgG biomarkers across neurological diseases.

Neurological disease	Humoral biomarkers	IgG-related biomarkers	Sample type	Clinical utility
AD	YKL-40 (CHI3L1), sTREM2, complement proteins	Anti-Aβ IgG; anti-tau IgG; IgG–complement complexes	CSF, Serum	Humoral and IgG markers reflect glial activation and immune signaling
PD	α-synuclein antibodies; inflammatory cytokines	IgG autoantibodies to α-synuclein	CSF, Serum	Exploratory biomarkers of α-synuclein–driven humoral response
ALS	CHIT1, complement proteins; autoantibodies	Anti-GM1 IgG (subset); IgG–complement deposition	CSF, Serum	Present in subsets; reflect inflammation and motor neuron injury
MS	OCBs, IgG index, κ-free light chains	Intrathecal IgG synthesis; OCBs (IgG) as core diagnostic markers	CSF, Serum	Central IgG-mediated immune activity; diagnostic and prognostic relevance
Stroke	IL-6, CRP, complement activation products	Post-injury anti-neuronal IgG; IgG leakage due to BBB disruption	Serum, CSF	Reflect BBB breakdown and secondary autoimmune responses

Notes: YKL-40: chitinase-3-like protein 1; MS: multiple sclerosis; AD: Alzheimer's disease; PD: Parkinson's disease; ALS: amyotrophic lateral sclerosis; CSF: cerebrospinal fluid; BBB: blood–brain barrier; OCBs: oligoclonal bands; IgG: immunoglobulin G; CRP: C-reactive protein; IL-6: interleukin-6; CHI3L1: chitinase-3-like protein 1; sTREM2: soluble triggering receptor expressed on myeloid cells 2; GM1: monosialotetrahexosylganglioside; Aβ: amyloid-beta; CHIT1: chitotriosidase.

shaped by disease context, methodological constraints, and variability across patient populations (Table 3).

Comparative performance of neuroinflammatory biomarkers

The clinical utility of neuroinflammatory biomarkers is most robust in diseases where inflammation is proximal to the primary pathogenic mechanism. MS represents the strongest example of this relationship. Because MS is fundamentally an immune-mediated disorder, CSF biomarkers of inflammation closely mirror active CNS pathology. Markers such as chitinase-3-like protein 1 (YKL-40), glial fibrillary acidic protein (GFAP), S100 calcium-binding protein B (S100B), and neurofilament light chain (NfL) consistently show elevation and correlate with disease stage, progression, and phenotypic variation [47]. Longitudinal cytokines and chemokines, including IL-6, chemokine C-X-C motif ligand 13 (CXCL13), and osteopontin, further provide prognostic insight into disease activity and cognitive decline [48]. The emergence of extracellular vesicles as minimally invasive indicators of glial activation extends this framework, enabling dynamic monitoring of immune signaling in real time [49].

However, even in this most favorable context, important limitations persist. Only a limited subset of markers, most notably OCBs, has been integrated into routine clinical practice. Many candidate biomarkers remain insufficiently standardized, and their interpretation is complicated by disease heterogeneity, demographic influences, and differences between CSF and blood measurements, with peripheral markers generally showing reduced specificity [9, 49].

In contrast, in neurodegenerative diseases such as AD, PD, and ALS, neuroinflammatory biomarkers reflect reactive or modulatory processes rather than primary disease drivers, which fundamentally alters their clinical role. In AD, markers of glial activation, including GFAP, YKL-40, and soluble TREM2, capture early immune responses associated with amyloid and tau pathology and show promise for early disease detection, particularly in preclinical stages [50, 51]. Composite inflammatory signatures integrating cytokines, chemokines, and complement components outperform individual markers and more accurately reflect underlying CNS processes, including hippocampal atrophy and neurodegeneration [52, 53]. Importantly, these inflammatory profiles enhance diagnostic models when combined with established biomarkers and genetic risk factors [50, 53]. However, their lack of disease specificity, given that similar elevations occur in other neurodegenerative and inflammatory conditions, limits their standalone diagnostic value. Temporal variability, particularly in markers such as sTREM2, further complicates interpretation across disease stages [54].

A similar pattern of limited specificity and high biological heterogeneity is observed in PD. Inflammatory gene signatures and transcriptomic profiles suggest the existence of biologically distinct subtypes characterized by cytokine dysregulation and altered metabolic pathways [55]. Neuroimaging markers of microglial activation provide additional evidence linking inflammation to clinical severity, bridging molecular and clinical domains [56]. Nevertheless, inflammatory biomarkers alone are insufficient to distinguish PD from related disorders [42], reinforcing the need for multimodal approaches that integrate molecular, imaging, and protein aggregation markers.

In ALS, neuroinflammatory biomarkers provide insight into disease activity and progression, with cytokine profiles in CSF and blood correlating with functional decline and systemic inflammatory indices [57]. However, their clinical utility remains limited by variability and lack of specificity. Notably, neurodegeneration-specific biomarkers, particularly neurofilaments, consistently outperform inflammatory markers in diagnostic and prognostic contexts [58]. This highlights a key distinction: in ALS, inflammation is biologically relevant but not the most informative biomarker domain for clinical decision-making [59, 60].

Stroke introduces an additional layer of complexity

Table 4. Strengths and limitations of neuroinflammatory biomarkers across neurological diseases.

Neurological disease	Strengths	Limitations
MS	IL-6, CXCL13 reflect active inflammation; CXCL13 aids differential diagnosis	Not MS-specific; fluctuate with relapse and therapy
AD	YKL-40 indicates microglial activation; correlates with progression	Overlap with other disorders; modest variable changes
PD	IL-1β, TNF-α indicate neuroinflammation	Low specificity; influenced by systemic inflammation
ALS	IL-6, MCP-1 correlate with progression rate	Not ALS-specific; high variability
Stroke	IL-6, CRP reflect acute inflammation; prognostic value	Time-dependent; affected by comorbidities

Notes: MS: multiple sclerosis; AD: Alzheimer's disease; PD: Parkinson's disease; ALS: amyotrophic lateral sclerosis; IL-6: interleukin-6; CXCL13: C-X-C motif chemokine ligand 13; YKL-40: chitinase-3-like protein 1; IL-1β: interleukin-1 beta; TNF-α: tumor necrosis factor-alpha; MCP-1: monocyte chemoattractant protein-1; CRP: C-reactive protein.

through its temporal dynamics. Neuroinflammatory markers such as IL-1β, IL-6, TNF-α, and IL-8 rise rapidly following ischemic injury and correlate with infarct size, neurological deterioration, and systemic complications [61, 62]. Later increases in anti-inflammatory cytokines reflect repair processes [61]. Easily accessible systemic indices, such as the neutrophil-to-lymphocyte ratio, provide practical prognostic indicators [62]. However, the rapidly evolving and bidirectional nature of post-stroke inflammation limits the utility of single time-point measurements [61]. Moreover, the non-specific nature of inflammatory responses prevents these markers from replacing neuroimaging in acute diagnosis [63, 64] (Table 4).

Comparative role of humoral biomarkers

Humoral biomarkers provide a second, complementary dimension, but their contribution varies markedly depending on whether humoral immunity is pathogenic, reactive, or secondary to tissue injury. In MS, humoral biomarkers are deeply embedded in disease biology. Intrathecal IgG synthesis, reflected by OCBs, remains a defining diagnostic feature, while NfL has emerged as a critical marker of neuroaxonal injury with strong correlations to magnetic resonance imaging activity, relapse frequency, and long-term disability [9, 49]. Advances in ultrasensitive detection methods have enabled reliable measurement of NfL in blood, supporting longitudinal monitoring [49, 65]. Despite these strengths, limitations remain significant: NfL lacks disease specificity and is influenced by physiological variables such as age and body composition, while broader humoral markers, including cytokines and B cell activation signatures, show substantial variability and lack standardized interpretation frameworks [49, 66].

In AD, the landscape of humoral biomarkers has undergone rapid transformation, particularly with the development of blood-based assays reflecting amyloid and tau pathology. Plasma biomarkers such as Aβ42/40 ratio and phosphorylated tau isoforms show strong correspondence with core disease mechanisms and cognitive decline, and recent technological advances have significantly improved sensitivity and scalability [50, 67]. Nevertheless, these markers do not consistently map to specific cognitive domains, and questions remain regarding their impact on patient outcomes and appropriate use in population-level screening. Methodological variability across assays further complicates implementation.

In PD, humoral biomarker development has focused on detecting misfolded α-synuclein, with seed amplification assays representing a major advance in diagnostic accuracy. These assays provide strong molecular evidence of synucleinopathy and address limitations of traditional biomarkers [68]. However, many other humoral candidates, including inflammatory and lysosomal proteins, lack specificity and show overlap with related disorders. Practical challenges such as reliance on CSF, pre-analytical variability, and lack of standardization continue to limit widespread clinical adoption [68].

In ALS, humoral biomarkers, particularly NfL and phosphorylated neurofilament heavy chain, demonstrate the most consistent diagnostic and prognostic performance across neurological diseases [59, 69]. These markers correlate strongly with disease progression, survival, and therapeutic response, and have been successfully integrated into clinical trials [60]. Emerging exosome-derived biomarkers further expand the field by capturing intracellular pathological proteins and molecular signatures [70]. Despite this progress, no biomarker has achieved full clinical validation, and issues of specificity, cohort variability, and methodological inconsistency remain unresolved.

In stroke, humoral biomarkers reflect the broad systemic and CNS response to acute injury, encompassing coagulation, inflammation, endothelial dysfunction, and neuronal damage [64]. Multi-marker panels and machine-learning–derived signatures demonstrate improved diagnostic performance compared to individual markers, highlighting the value of integrative approaches [13, 15]. However, substantial variability across populations and the inability of any biomarker to reliably distinguish stroke from mimics in the acute phase limit their current clinical use, maintaining neuroimaging as the diagnostic gold standard (Table 5).

Integrated comparative perspective

The comparative analysis highlights a fundamental principle: biomarker performance is determined not only by analytical sensitivity, but by alignment with disease biology. Neuroinflammatory markers are most informative when inflammation directly drives pathology, while

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Table 5. Strengths and limitations of humoral biomarkers in specific neurological diseases.

Neurological disease	Key humoral biomarkers (CSF/blood)	Strengths	Limitations
AD	Aβ42, Aβ42/40 ratio, p-tau181, p-tau217, p-tau231, t-tau, NfL, GFAP	High diagnostic value; strong early-detection biomarkers	Some biomarkers CSF-only; blood markers not fully standardized; NfL not AD-specific
PD	α-synuclein, NfL, DJ-1, GCase activity	Useful for synucleinopathy; NfL improves sensitivity for progression	α-syn highly variable in blood; limited specificity
ALS	NfL, pNfH, CHIT1, YKL-40, genetic markers	Highly reliable for diagnosis and tracking; strong progression markers	Not ALS-specific; genetic markers not useful for monitoring
MS	OCB, IgG index, NfL, CXCL13, GFAP	OCB is gold standard; NfL effective for activity monitoring	OCB requires LP; several biomarkers not standardized
Stroke	NfL, GFAP, S100B, MMP-9, IL-6, TNF-α	Useful in acute phase; GFAP differentiates hemorrhage	Low specificity; short detection window; high variability

Notes: MS: multiple sclerosis; AD: Alzheimer's disease; PD: Parkinson's disease; ALS: amyotrophic lateral sclerosis; CSF: cerebrospinal fluid; Aβ: amyloid-beta; p-tau: phosphorylated tau; t-tau: total tau; NfL: neurofilament light chain; GFAP: glial fibrillary acidic protein; α-syn: alpha-synuclein; DJ-1: protein deglycase DJ-1; GCase: glucocerebrosidase; pNfH: phosphorylated neurofilament heavy chain; CHIT1: chitotriosidase; OCB: oligoclonal band; CXCL13: C-X-C motif chemokine ligand 13; S100B: S100 calcium-binding protein B; MMP-9: matrix metalloproteinase-9; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha; LP: lumbar puncture.

humoral biomarkers achieve maximal relevance when they reflect either core disease mechanisms or quantifiable tissue injury.

Future progress will depend on integrating these domains into multimodal biomarker frameworks, combining inflammatory, neurodegenerative, molecular, and imaging data. Such approaches are essential to overcome current limitations in specificity, reproducibility, and clinical translation, and to enable precision diagnostics across heterogeneous neurological diseases.

Therapeutic implications

Neuroinflammation and humoral immunity represent interdependent therapeutic targets across MS, AD, PD, ALS, and stroke, but their relative importance varies by disease biology and stage, defining distinct treatment strategies and therapeutic windows (Table 6).

In MS, given the central role of autoreactive lymphocytes, B cell–mediated immunity, trained innate immune responses, and compartmentalized CNS inflammation, therapeutic strategies primarily aim to suppress adaptive immune activation while increasingly targeting chronic neuroinflammatory processes. Treatment has classically focused on adaptive immunity through disease-modifying therapies such as anti-CD20 B cell depletion (CD20), sphingosine-1-phosphate modulators, interferons, and glatiramer acetate [71]. However, expanding evidence indicates that innate immune reprogramming ("trained immunity") and compartmentalized CNS inflammation contribute to progression [72]. This has shifted attention toward brain-border immune niches (meninges, choroid plexus, perivascular spaces) and local immune regulation, including microglial modulation, Treg-based approaches, and emerging cell therapies. These strategies are increasingly integrated with microbiome modulation and BBB-preserving approaches [73]. Clinically, biomarker-guided personalization (*e.g.*, B-cell profiles, cytokines, NfL) and combination approaches targeting both adaptive and innate pathways are becoming central, particularly in progressive MS, where controlling smouldering inflammation remains a key challenge [9, 66].

In AD, because Aβ accumulation initiates downstream tau

Table 6. Comparative therapeutic strategies across neurological diseases.

Neurological disease	Key drivers of neuroinflammation	Humoral immunity role	Therapeutic strategies
MS	Early immune cell infiltration; compartmentalized microglial activation	Strong B-cell and antibody involvement	Peripheral immune depletion; homing blockade; BTK inhibitors
AD	Microglial/astrocyte activation from amyloid/tau	Complement-mediated synaptic pruning	Microglial modulation; antibody-based therapy; CNS-penetrant immunomodulators
PD	α-synuclein-driven microglial activation	Limited humoral role	Microglial modulation; neuromodulation (DBS); pathway targeting
ALS	Genetic and glial-driven inflammatory injury	Complement and antibody activity	Glial-targeted anti-inflammatory strategies; hypothermia via A1AR agonist
Stroke	Acute immune infiltration; chronic microglial activation	Complement involvement in acute damage	Early immunomodulation; microglial-targeted chronic therapy; hypothermia

Notes: MS: multiple sclerosis; AD: Alzheimer's disease; PD: Parkinson's disease; ALS: amyotrophic lateral sclerosis; BTK: Bruton's tyrosine kinase; CNS: central nervous system; DBS: deep brain stimulation; A1AR: adenosine A1 receptor; α-synuclein: alpha-synuclein.

pathology, microglial activation, and neuroinflammatory signaling, current therapeutic approaches focus on reducing amyloid burden while expanding toward multi-target interventions addressing neuroinflammation and neurodegeneration. Disease-modifying therapy has advanced with anti-amyloid monoclonal antibodies such as lecanemab and donanemab, which reduce amyloid burden and modestly slow clinical decline [74, 75]. However, the limited magnitude of clinical benefit has reinforced the view that monotherapy is insufficient, and that AD requires combination strategies targeting tau pathology, neuroinflammation, and vascular dysfunction [76, 77]. Treatment implementation depends on biomarker-based patient selection and careful safety monitoring (*e.g.*, amyloid-related imaging abnormalities [ARIA]) [78], while blood-based biomarkers increasingly support scalable detection and follow-up [50]. The field is moving toward integrated, multi-target interventions aligned with disease stage and biology.

In PD, as α-synuclein aggregation and microglia-driven innate immune activation contribute to progressive neuronal loss, emerging therapies increasingly target both pathological protein accumulation and associated inflammatory pathways. Therapeutic development is increasingly oriented toward microglial modulation and innate immune signaling pathways, particularly those linked to α-synuclein [79]. Pathological α-synuclein activates inflammatory cascades (*e.g.*, NOD2/RIPK2), offering novel immunotherapeutic targets [21]. Early, even presymptomatic, intervention is considered critical, supported by biomarker frameworks such as translocator protein (TSPO) positron emission tomography (PET) and fluid markers [14, 56]. Alongside symptomatic dopaminergic therapy, approaches targeting neuroinflammation, including miRNA regulation and monoclonal antibodies against α-synuclein, are being explored, although clinical efficacy remains variable [80]. Neuromodulation strategies (*e.g.*, deep brain stimulation) further illustrate the bidirectional interaction between neural circuits and immune signaling [81].

In ALS, given the contribution of protein aggregation, complement activation, and dysregulated innate and adaptive immune responses to motor neuron degeneration, therapeutic development is shifting toward integrated multi-mechanistic interventions. ALS represents a paradigm of therapeutic complexity and heterogeneity, driving a shift toward multi-mechanistic and adaptive trial designs. Current strategies aim to combine modulation of innate inflammation, enhancement of Treg function, and targeting of protein aggregation [23, 82]. Complement activation (C1q, C3) has emerged as a key mechanism, supporting the development of complement inhibitors, while additional approaches include antisense therapies and metabolic interventions [82]. Biomarker-based stratification and adaptive platform trials are increasingly used to improve efficiency and personalize treatment allocation [82]. Despite progress, therapeutic translation remains challenging, requiring careful safety monitoring and better alignment of interventions with disease subtypes.

In stroke, because ischemic injury triggers BBB disruption, innate immune activation, cytokine release, and secondary inflammatory damage, therapeutic strategies aim to limit acute tissue injury while modulating post-stroke neuroinflammation. Immunotherapy is fundamentally shaped by timing and the acute nature of injury. Beyond reperfusion, therapeutic strategies target cytokine pathways (*e.g.*, IL-1, IL-6), promote anti-inflammatory signaling (IL-10, TGF-β), and aim to preserve BBB integrity to limit secondary damage, including IgG extravasation [83]. Modulation of neutrophil, microglial, and T-cell responses, particularly γδ T cells and IL-17 pathways, represents additional avenues [84, 85]. Biomarkers such as NLR, PLR, SII, and cytokine panels support risk stratification and may guide treatment timing [83, 85]. However, variability and rapid temporal dynamics require precise, stage-specific intervention strategies.

Cross-disease clinical framework and shared themes

Across diseases, several shared principles emerge (Table 7). First, peripheral immunomodulation is most effective in early or acute stages (*e.g.*, MS, stroke), whereas microglial and astrocyte targeting becomes critical in chronic neurodegeneration (AD, PD, ALS, progressive MS) [86, 87]. Second, humoral therapies, particularly monoclonal antibodies, are most effective where pathogenic proteins or B-cell–mediated mechanisms are central, as in MS and AD. Third, preserving BBB integrity and limiting secondary inflammatory amplification confer cross-disease benefits.

Importantly, therapeutic efficacy increasingly depends on biomarker-driven precision approaches, integrating fluid and imaging markers (*e.g.*, NfL, cytokines, complement, PET imaging, TSPO) to align treatment with disease stage and immunopathological endotype. This has led to a shift toward combination immunotherapy, reflecting the polymechanistic nature of neurological diseases, such as combining anti-amyloid and anti-inflammatory treatments in AD, adaptive and innate targeting in MS, dopaminergic and immunomodulatory approaches in PD, or complement and T-cell modulation in ALS [71, 77, 79, 82].

Finally, these advances highlight the need for robust clinical infrastructure and safety frameworks, including monitoring for treatment-related complications (*e.g.*, ARIA, infection risk, immunosuppression), and emphasize shared decision-making and long-term follow-up as integral components of modern neuroimmunological therapy [88].

Challenges and controversies

Distinguishing pathogenic from bystander antibodies in the inflamed CNS

A persistent challenge is distinguishing antibodies that actively drive neuroinflammation from those that arise secondarily due to tissue injury or immune activation. Pathogenic antibodies typically bind extracellular neuronal or glial targets and induce direct functional effects, such as receptor internalization, complement activation, or microglial fragment crystallizable receptor-mediated

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Table 7. Mechanism–target–therapy framework across neurological diseases.

Neurological disease	Key mechanisms	Therapeutic targets	Current/emerging therapies
MS	Autoreactive T-and B-cell responses; trained immunity; compartmentalized CNS inflammation	B-cell depletion; lymphocyte trafficking; microglial activation; immune regulation	Anti-CD20 antibodies; S1P modulators; interferons; glatiramer acetate; BTK inhibitors; Treg-based and cell therapies
AD	Aβ accumulation; tau pathology; microglial activation; neuroinflammation	Amyloid plaques; tau-related pathways; inflammatory signaling	Lecanemab; donanemab; anti-tau therapies; anti-inflammatory and multimodal therapeutic approaches
PD	α-synuclein aggregation; microglial activation; innate immune signaling	α-synuclein pathology; NOD2/RIPK2 pathways; neuroinflammatory cascades	Anti-α-synuclein antibodies; immunomodulatory therapies; miRNA-based approaches; deep brain stimulation (DBS)
ALS	Protein aggregation; complement activation; innate and adaptive immune dysregulation	Complement cascade; Treg dysfunction; pathogenic gene expression	Complement inhibitors; antisense oligonucleotides; Treg-based therapies; metabolic interventions
Stroke	BBB disruption; cytokine release; innate immune activation; secondary inflammatory injury	IL-1 and IL-6 signaling; BBB integrity; inflammatory cell recruitment	Anti-cytokine therapies; BBB-preserving strategies; reperfusion combined with immunomodulatory approaches

Notes: MS: multiple sclerosis; AD: Alzheimer's disease; PD: Parkinson's disease; ALS: amyotrophic lateral sclerosis; CNS: central nervous system; Aβ: amyloid-beta; BTK: Bruton's tyrosine kinase; Treg: regulatory T cell; S1P: sphingosine-1-phosphate; NOD2: nucleotide-binding oligomerization domain-containing protein 2; RIPK2: receptor-interacting serine/threonine-protein kinase 2; miRNA: microRNA; DBS: deep brain stimulation; BBB: blood–brain barrier; IL: interleukin; CD20: cluster of differentiation 20.

synaptic stripping, thereby amplifying neuroinflammatory cascades involving NLRP3 inflammasome activation, TNF-α/IL-1β release, and ROS production [3, 7, 32, 89]. In contrast, many "bystander" antibodies recognize intracellular antigens exposed during neurodegeneration and correlate more with debris-driven microglial phagocytosis, astrocyte A1 polarization, and complement tagging rather than causal pathogenicity [89]. Intrathecal synthesis accompanied by elevated CSF cytokines (*e.g.*, CXCL13, IL-6), microglial NLRP3 inflammasome activation, and complement deposition strengthens evidence of pathogenicity, while isolated low-titre serum findings rarely indicate active neuroinflammatory disease [3, 7]. These findings complicate a binary assignment of antibodies as "driver" or "epiphenomenon", and suggest that cellular state, ligand avidity, and local complement availability determine whether humoral signals amplify or merely accompany neuroinflammation [7]. Distinguishing these categories remains essential for neurological diseases where neuroinflammation and humoral immunity coexist, including MS and neurodegenerative diseases.

Assay variability and standardization problem

Classical immunoassays such as enzyme-linked immunosorbent assay, chemiluminescent enzyme immunoassay, and single molecule array remain central to fluid-based detection, offering high sensitivity and clinical validation [65, 67]. However, assay variability complicates interpretation in neurological diseases where neuroinflammation and humoral activity intersect. Interpretation of autoantibody results remains limited by assay design (antigen conformation, live *vs*. fixed substrates), secondary reagents (complement-containing *vs*. IgG1-specific detection), and threshold definitions. Live cell-based assays outperform fixed assays for sensitivity while maintaining high specificity [90, 91]. Recent real-world evidence shows that flow-cytometric live-cell immunofluorescence offers superior sensitivity compared with fixed-cell assays [90]. Insufficient assay specificity risks misinterpreting systemic immune background activity as CNS autoimmunity, while inadequate sensitivity may result in the loss of genuinely pathogenic signals [90, 91]. Harmonized protocols, external quality controls, and orthogonal validation are especially important for antibodies whose pathogenicity depends on conformational epitopes that modulate glial activation, BBB integrity, or local complement amplification [7]. Without such standardization, non-specific inflammatory background in serum can be misinterpreted as disease-relevant autoimmunity.

Interpretation of serum *vs.* CSF findings

Distinguishing serum from CSF antibody profiles is crucial in neurological diseases where central neuroinflammation drives compartmentalized immune responses [92]. Antibodies detected only in serum may indicate systemic immune activation rather than CNS pathology, whereas CSF-restricted antibodies typically coexist with evidence of intrathecal inflammation, such as OCBs, CXCL13 elevation, microglial activation markers, and BBB compromise [92, 93]. For example, in diseases with strong neuroinflammatory components, such as MS, CSF findings more accurately reflect pathogenic processes, including microglial cytokine release, inflammasome signaling, and complement-mediated injury [19]. Elevated CXCL13 in lesions and CSF correlates with B cell aggregates and immunoglobulin synthesis, and its index (CSF/serum adjustment) has prognostic value for subsequent MS activity [92]. Differentiating systemic humoral activity from CNS-compartmentalized inflammation remains essential to minimize diagnostic pitfalls.

Current gaps in neuroinflammatory biomarkers beyond proteinopathy

Despite advances in profiling humoral immunity, many neurological diseases lack validated biomarkers that capture the interplay between antibodies and neuroinflammation. In ALS and PD, reproducible extracellular autoantibodies remain elusive, even though neuroinflammatory processes such as microglial activation (TSPO, CSF1R), astrocyte A1 conversion, mitochondrial dysfunction, and complement cascade engagement are well documented [33, 34, 94]. Similarly, in AD, fluid biomarkers predominantly reflect proteinopathy rather than inflammatory or humoral mechanisms, leaving a gap in tools capturing complement-mediated synaptic loss, BBB dysfunction, B cell activity, or cytokine-driven microglial activation [52, 53]. The lack of validated biomarkers linking humoral and innate inflammatory mechanisms highlights the need for integrated neuroimmune indicators.

Conflicting roles for humoral immunity in neurodegenerative diseases

Neurodegenerative disorders present conflicting data on how humoral immunity interacts with neuroinflammation. Autoantibodies against tau, Aβ, α-synuclein, and TDP-43 have been variably reported as pathogenic, protective, or merely epiphenomenal, reflecting the complexity of inflammatory microenvironments characterized by activated microglia, complement deposition, NLRP3 activation, BBB dysfunction, and astrocyte reactivity [5-7, 31, 32, 95]. In AD, complement-driven microglial synaptic pruning exacerbates pathology, yet natural autoantibodies may enhance clearance of toxic species [6, 7, 31]. In PD, the relationship between α-synuclein antibodies and disease progression is modulated by microglial polarization (M1 *vs*. M2), inflammasome activation, cytokine milieu, and regional BBB permeability [33, 79]. Such heterogeneity underscores the need for integrative mechanistic studies linking humoral signals to spatially resolved neuroinflammatory microenvironments [8].

Humoral responses in AD, PD, and TDP-43 proteinopathies can be double-edged [6, 32, 95]. Complement-driven microglial pruning accelerates early synapse loss in AD mice, and inflammasome activation (NLRP3–caspase-1) promotes Aβ clearance failure and tau pathology [3, 7]. Conversely, antibody therapies in PD targeting α-synuclein (prasinezumab, cinpanemab) show acceptable safety and pharmacodynamic target engagement, but efficacy signals remain inconsistent across phases and endpoints [96, 97]. Meta-analyses of endogenous α-synuclein autoantibodies reveal small and heterogeneous effects, particularly in early PD, reinforcing the assay- and cohort-dependence of conclusions [33]. For TDP-43, whose pathological emergence was established only after 2006, the immune consequences are increasingly recognized, yet established extracellular antibody targets remain sparse. The field instead centers on cell-intrinsic RNA–protein pathology [95, 98]. The outcome is that spatial context (parenchyma *vs.* meninges *vs.* vasculature), glial state, and biophysical features of aggregates likely determine whether humoral immunity is pathogenic, neutral, or protective at a given disease stage [95, 98].

Methodological limitations

The controversy persists due to three unresolved methodological limitations. First, many biomarkers reduce microglial or astrocyte states to single readouts. Emerging radioligands and spatial -omics now enable mapping of pro-inflammatory *vs*. reparative glia *in situ* [94, 99]. Second, there is a lack of standardized multimodal panels that combine amyloid/tau/neurodegeneration with immune–vascular axes (complement, CXCL13 index, BBB permeability), which would clarify when humoral mechanisms are upstream drivers *vs*. downstream responders [93, 100]. Third, the field requires trial designs that incorporate immune phenotyping (autoantibody isotypes/affinity, complement activity, CSF chemokines) to explain heterogeneous outcomes in immunotherapies targeting misfolded proteins [7]. Without these advances, apparent contradictions will persist, reflecting measurement limitations rather than biology.

Future directions

Single-cell multiomics of B cells in neurological diseases

Single-cell multiomics is transforming our understanding of how B cells integrate into neuroinflammatory architectures [101]. Studies reveal B cell and plasma-cell niches embedded within microglia-rich, complement-active, cytokine-dense environments, particularly in MS, where CSF and meningeal microenvironments show expansion of B lineage and plasma cells and disease-specific transcriptional states [66, 101]. In parallel, tertiary lymphoid structures in the meninges provide BAFF- and APRIL-dependent niches supporting B cell survival and intrathecal maturation, with links to severe cortical pathology and progression [10, 102]. These inflamed niches shape clonal expansion, somatic hypermutation, and antibody secretion, while microglia and astrocytes provide survival cues (BAFF, APRIL), antigen presentation, and pro-inflammatory signaling (IL-6, TNF-α) [66, 102]. Studies using scRNA/scBCR-seq in CSF, along with integrative compendium analyses, map clonal expansion and maturation of B and plasma cell populations, providing the substrate to connect clonotypes with local glial states and intrathecal cytokines and complement [101]. The lymphocyte–microglia–astrocyte axis, driven in part by C1q and complement, is prominent at chronically active lesion rims and frames how B-cell responses may interact with resident glia [71]. Linking B cell clonotypes to local glial activation states and complement deposition will clarify which humoral clones truly drive neuroinflammation [7, 71]. A key next step is to link B cell clonotypes in space and time to microglial (*e.g*. microglia inflamed in MS) and astroglial states and complement deposition, to distinguish truly pathogenic humoral clones from reactive or reparative ones [66].

High-sensitivity autoantibody profiling

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Next-generation platforms (PhIP-Seq, REAP, microarrays, multiplex assays), recent advances in digital immunoassays, and fast protein liquid chromatography offer unprecedented sensitivity for detecting rare antibodies associated with neuroinflammatory processes such as microglial fragment crystallizable receptor activation, astrocyte cytotoxicity, and complement amplification [65, 103-105]. As sensitivity increases, functional validation is essential to determine whether identified antibodies modulate neuronal excitability, induce inflammasome activation, disrupt BBB integrity, amplify synaptic pruning, or interact with glial cytokine networks [3, 7, 32]. As these platforms become clinically scalable, they may distinguish disease-driving humoral signatures from background reactivity generated during chronic glial activation or proteinopathy-associated inflammation [106].

Novel targets for PET imaging

Beyond TSPO, emerging PET tracers aim to visualize neuroinflammatory–humoral interactions *in vivo* by targeting B cell markers (CD19, CD20), complement activation fragments (C1q, C3b), and microglial states (CSF1R, P2X7, P2Y12) [99]. Tracers marking pro-inflammatory microglia have yielded multicenter data in PD and early signals in MS, though kinetic and quantification challenges remain to be addressed [56, 99, 107]. Progress on P2Y12 (homeostatic/anti-inflammatory microglia) has produced the first brain-permeable tracers, with preclinical and early clinical indications of BBB penetration and phenotype sensitivity [108]. Imaging CSF1R, a regulator of microglial survival, also offers a potential alternative to TSPO for quantifying microglial mass and state [94]. In combination with ultra-high field MRI markers (*e.g.*, paramagnetic rim lesions (PRL)) and complement-targeted trials, such tracers may enable spatial mapping and illuminate how antibody-producing niches interface with inflammatory microenvironments characterized by microglial-mediated synaptic pruning, astrocyte reactivity, and cytokine release [7].

Overcoming challenges in BBB penetration and tracer kinetics is essential, but immuno-PET has the potential to map neuroimmune circuits relevant for both antibody-mediated and purely inflammatory disorders [8, 107].

Personalized immune profiling and precision medicine

Personalized immune profiling integrates humoral immunity (antibody specificity, clonotypes, isotypes), neuroinflammation (microglial activation markers, CSF cytokine and complement signatures), and imaging signals to stratify patients and guide targeted therapy [9, 66]. This approach enables precise targeting of B-cell depletion, complement inhibition, cytokine blockade, or neuroprotective anti-inflammatory strategies [71]. A personalized immune profile should integrate (i) humoral features (specificities, clonotypes, isotypes or affinity), (ii) intrathecal biomarkers (CXCL13 index, OCBs, complement), (iii) microglial or astrocyte activation readouts, and (iv) multimodal imaging, to define endotypes and guide targeted therapy [92]. This approach is particularly impactful where antibody-driven and neuroinflammatory mechanisms coexist, such as in MS and AD with complement-mediated synapse loss [7, 66]. In AD, anti-Aβ antibodies (*e.g.*, lecanemab) require risk stratification for ARIA (apolipoprotein E ε4 [APOE4] status, antithrombotics, prior microhemorrhages) and longitudinal monitoring, highlighting the need for immune safety panels within precision medicine workflows [74, 78, 88]. Longitudinal immune fingerprinting could also predict treatment response or adverse inflammatory complications such as ARIA [78].

Integrative models combining humoral, cellular, and neuroimaging data

Multimodal machine learning (ML/DL models) integrating antibody profiles, B cell receptor repertoires, cytokine networks, microglial activation states, complement markers, MRI changes (including PRL and atrophy), and next-generation PET signals (TSPO, P2X7, P2Y12, CSF1R) could provide unprecedented insight into how humoral immunity interacts with neuroinflammation to drive pathology [107-111]. Incorporating biological priors (*e.g.*, glial inflammasome pathways, complement-dependent synaptic pruning, BBB breakdown, lymphoid follicle formation) improves interpretability and helps distinguish causal inflammatory processes from reactive changes [110]. In AD, Alzheimer's Disease Neuroimaging Initiative (ADNI)-based multimodal work shows the benefits of fusing PET/MRI with blood biomarkers to predict amyloid burden and support early diagnosis—a template for similar integrations in neuroimmune diseases [50, 110, 111]. Such integrative models are poised to accelerate biomarker discovery, refine patient endotypes, and enhance precision therapy optimization across neuroimmune and neurodegenerative diseases [8].

Conclusions

Neuroinflammation and humoral immunity form an integrated, bidirectional framework underpinning pathology in MS, AD, PD, ALS, and stroke. All five neurological diseases show a clear, age-dependent increase in incidence. Ageing remains the most powerful epidemiological driver for the rising incidence of major neurological diseases. It not only increases incidence and prevalence but also modulates disease phenotype, treatment responsiveness, and progression.

Although humoral and neuroinflammatory biomarkers have advanced disease characterization, enabling earlier detection, patient stratification, and treatment monitoring, current limitations in specificity, assay standardization, and cross-platform reproducibility restrict widespread clinical use. The most reliable signals (such as neurofilaments in ALS, OCBs in MS, amyloid/tau panels and glial markers in AD) demonstrate the value of aligning biomarkers with biological proximity to core mechanisms. Further progress depends on harmonized protocols, multicenter longitudinal validation, and adoption of integrated analytical models that combine fluid biomarkers with imaging, genomics, and clinical phenotyping.

Therapeutically, rational combinations, anti-amyloid plus

anti-tau/anti-inflammatory (in AD), disease-modifying therapies plus innate reprogramming and CNS-niche targeting (in MS), dopaminergic therapy plus microglia-focused immunomodulation (in PD), complement/regulatory T cell strategies within adaptive platform trials (in ALS), and timed cytokine blockade with BBB preservation (in stroke)—should be guided by stage-specific and endotype-specific biomarker profiles. Robust safety frameworks (*e.g.*, ARIA monitoring, infection risk management, and immunosuppression oversight) and shared decision-making are essential for clinical translation.

Future directions emphasize single-cell B cell multiomics, high-sensitivity autoantibody profiling, immuno-PET targets, and personalized immune "fingerprinting". Ultimately, a precision neuroimmunology paradigm, grounded in standardized, composite biomarker panels and integrative analytics, offers the most credible path to disease modification and improved patient-centred outcomes.

Declarations

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