The Journal of Prevention of Alzheimer's Disease 13 (2026) 100515

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Review

Neuronal autoantibodies in neurodegenerative dementia: From evidence to clinical framework

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ARTICLE INFO

Keywords:
Neuronal autoantibody
Dementia
Neurodegeneration
Screening
Clinical decision-making
Autoimmune encephalitis

ABSTRACT

Neuronal autoantibodies, including against neuronal surface receptors or intracellular antigens, are established pathogenic mediators and therapeutic targets in autoimmune encephalitis (AIE) and paraneoplastic neurological syndromes (PNS). These antibodies are now increasingly reported in patients with clinically diagnosed neurodegenerative dementia, prompting re-evaluation of a neurodegenerative etiology. Within neurodegenerative trajectories, whether such antibodies act as pathogenic drivers, non-causal markers, or immune modulators remains unresolved, and heterogeneous cohorts, assays, and endpoints limit inference and clinical translation. This review integrates current research at the intersection of autoimmunity and neurodegeneration and highlights accumulating evidence for a biological continuum. This model suggests that antibody-mediated mechanisms may extend beyond acute inflammation, with sustained exposure contributing to time-dependent neurodegeneration. To facilitate clinical translation, we advance a standardized diagnostic workflow comprising three sequential stages: (i) a pretest-probability triage that defines high-risk constellations prompting antibody testing, stratifies patients accordingly; (ii) a specimen-and-assay pathway for standardized testing workflow and structured interpretation of results; and (iii) post-test integrated analysis to adjudicate pathogenic relevance based on phenotype-antibody concordance. By bridging observational research to clinical decision-making, the framework supports identification of an immunologically modulated neurodegenerative subtype with potential for therapeutic intervention, while reducing false positives and avoiding non-essential immunotherapy in low-probability contexts.

1. Introduction

Dementia is a clinical syndrome characterized by progressive cognitive decline and loss of daily function, frequently accompanied by psychiatric symptoms that substantially impair quality of life and social functioning [1,2]. With population aging, global prevalence and associated socioeconomic burden continue to rise [3,4]. Etiologies of dementia include neurodegenerative causes and non-neurodegenerative causes [3,5]. Among the latter, autoimmune encephalitis (AIE) and paraneoplastic neurological syndromes (PNS) are treatable conditions in which immune responses target central nervous system antigens [6–8]. Neuronal autoantibodies are broadly categorized as neuronal surface antibodies against extracellular epitopes of synaptic or membrane proteins, including NMDAR, LGI1, GABABR, AMPAR, CASPR2, DPPX, IgLON5, and GlyR, and intracellular antibodies against cytoplasmic or nuclear antigens, including Hu, Ri, Yo, CV2, Amphiphysin, SOX-1, Titin, and ZIC4 [8–10]. The direct pathogenic mechanism of neuronal autoantibodies and their roles as immunotherapeutic targets have been well established in AIE and PNS [11–14]. Increasingly, neuronal autoantibodies are detected in patients clinically diagnosed with neurodegenerative dementia [15]. Current evidence indicates that neuronal autoantibodies have been repeatedly identified among patients clinically diagnosed with dementia. Studies initiating from neurodegenerative cohorts generally report lower but non-negligible antibody

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https://doi.org/10.1016/j.tjpad.2026.100515
Received 10 November 2025; Received in revised form 3 February 2026; Accepted 16 February 2026
Available online 27 February 2026

frequencies. For example, in a memory-clinic cohort of 93 patients with established neurodegenerative disorders, neuronal surface antibodies were detected in 13.8 % of cases [15]. In contrast, a larger retrospective cohort of 920 patients with presumed neurodegenerative dementia identified neuronal autoantibodies in 0.8 % of patients after stringent multi-assay confirmation [16]. In addition to these larger cohorts, several smaller cross-sectional studies have reported neuronal autoantibody positivity rates ranging from approximately 5 % to 16 % among patients with clinically diagnosed dementia [17–20]. This variability is further underscored by a systematic review and meta-analysis of neuronal surface autoantibodies in dementia, which reported highly heterogeneous antibody frequencies across studies and emphasized methodological limitations [21]. The roles of neuronal antibodies within neurodegenerative processes remain uncertain, and the clinical implications of antibody testing and immunotherapy are not yet defined. Notably, existing studies have applied divergent conceptual definitions of autoimmune dementia, with substantial variability in diagnostic assumptions, clinical scope, and biological emphasis, each associated with inherent strengths and limitations. This conceptual heterogeneity, together with differences in enrollment criteria, assay methodology, and outcome assessment, limits comparability and external validity across studies.

In this review, we adopt a clinician-oriented framework. We first delineate autoimmune red-flag features to estimate pretest probability and specify when testing is warranted. Second, we further outline a standardized specimen-assay pathway for neurodegenerative settings and appropriate quality control. Finally, we translate observational results into clinical management. This framework aims to enhance the clinical utility of antibody testing during neurodegeneration and to provide an operational baseline for future studies addressing diagnostic thresholds, temporal ordering of events, and potential windows of reversibility.

2. Part I. Current evidence and intersections

2.1. Clinical phenotypes and mechanistic hypotheses

Neuronal autoantibodies in patients with clinically diagnosed dementia were first noted in case reports [22–25]. Flanagan et al. proposed the concept of autoimmune dementia, primarily emphasizing subacute onset, inflammatory features, and potential responsiveness to immunotherapy [26]. However, accumulating evidence from subsequent studies has demonstrated that neuronal autoantibodies can also be detected in patients with slowly progressive cognitive syndromes, including mild cognitive impairment (MCI), Alzheimer's disease (AD), Frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), and Parkinson's disease (PD) [17,18,27]. These observations have challenged the original dichotomous distinction between autoimmune encephalitis and primary neurodegeneration, prompting the development of updated, spectrum-based conceptual frameworks [28]. Studies have shown that antibody-positive patients consistently demonstrate comparable severity in global cognitive decline relative to matched antibody-negative patients, but are more likely to present with prominent psychiatric and behavioral symptoms as well as extrapyramidal features [29–31]. Some antibody-positive patients exhibit chronic and progressively deteriorating cognitive impairment without clinical or paraclinical evidence suggesting autoimmune etiology, while others present with red flags such as acute onsets, fluctuating course, seizures, and psychiatric symptoms. In particular, typical inflammatory markers, including CSF abnormalities (pleocytosis or hyperproteinorrhachia) and imaging features of inflammation (MRI T2/FLAIR hyperintensities) commonly associated with AIE, are generally absent in these individuals [15,16,20]. The similarity of clinical features complicate diagnosis and motivates exploration of antibody-associated mechanism within the neurodegenerative spectrum (Table 1).

Current research confirms the prevalence of neuronal autoantibodies

Table 1
Conceptual evolution of autoimmune mechanisms in dementia, contrasting classical syndrome-based autoimmune dementia with emerging spectrum-oriented frameworks.

	Autoimmune Dementia (Flanagan et al., 2010)	Updated Spectrum-Oriented Framework (Hansen et al., 2025)
Conceptual focus	Syndrome-based entity primarily considered a treatable mimic of neurodegenerative dementia	Spectrum-oriented framework emphasizing heterogeneous immune contributions across dementia phenotypes
Onset	Subacute (< 3 months), rapidly progressive	Subacute (> 6 months), insidious
Disease course	Fluctuating course with episodic deterioration	Slowly progressive course, often mimicking typical neurodegeneration
Core clinical features	Cognitive decline accompanied by prominent immune features (e.g., seizures, psychosis, movement disorders)	Predominantly cognitive impairment (memory and/or executive dysfunction), with absent or subtle inflammation features
Relationship to autoimmune encephalitis	Frequently overlapping with or considered a late manifestation of autoimmune encephalitis	Conceptually distinguished from acute autoimmune encephalitis; includes primary chronic or smoldering presentations
Neuroimaging (MRI)	T2/FLAIR hyperintensities, commonly involving limbic or temporal regions	Often normal, or showing neurodegeneration-like atrophy (e.g., hippocampal or global), or non-specific white matter changes
Functional imaging (FDG-PET)	Variable or inflammatory-related metabolic changes	Hypometabolism patterns that may resemble AD or FTD, or display immune-associated patterns
Neuronal autoantibodies	Predominantly high-risk neuronal surface antibodies (e.g., NMDAR, LGI1, AMPAR) and intracellular antibodies	Broader spectrum including high-risk and low-risk/minor antibodies (e.g., GlyR, ARHGAP26), detected in serum and/or CSF
Antibody localization and context	Antibody presence often interpreted as directly pathogenic	Antibody significance interpreted in biological context, including antibody type, sample (serum vs. CSF), and intrathecal synthesis
Pathophysiological emphasis	Acute inflammatory processes consistent with encephalitis	Chronic immune-mediated mechanisms, including synaptic dysfunction and immune–neurodegeneration interaction
Inflammatory markers	Frequently present (CSF pleocytosis, elevated protein, oligoclonal bands)	Often absent or subtle; intrathecal immune activity may be mild or context-dependent
Clinical objective of framework	Identification of highly treatable autoimmune mimics requiring urgent immunotherapy	Stratification and interpretation of immune involvement within chronic dementia phenotypes

This overview summarizes the conceptual progression of autoimmune dementia frameworks, from the classical syndrome-based criteria emphasizing subacute onset, inflammatory features, and treatment responsiveness, to more recent spectrum-oriented perspectives informed by emerging evidence, including Hansen et al. (2025). The updated framework acknowledges heterogeneous immune contributions to dementia, including chronic and insidious presentations that may clinically overlap with primary neurodegenerative disorders.

The antibody-positive neurodegenerative phenotype discussed in this review is positioned within this updated conceptual spectrum to facilitate clinical and

biological interpretation. This framework is intended for conceptual clarification and research stratification, rather than to propose new diagnostic criteria or replace established diagnostic pathways.
Abbreviations: CSF, cerebrospinal fluid; FDG-PET, fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging.

in this context, predominantly involving neuronal surface targets, such as NMDAR, LGI1, CASPR2, GABABR, AMPAR, GlyR, and IgLON5 [15,16,18,20,32,33]. Among these antibodies, pathophysiological mechanisms of IgLON5 antibody and anti-AMPA GluA3 antibody further exemplify the intersection between autoimmunity and neurodegeneration. IgLON5 antibody can induce receptor internalization with tau hyperphosphorylation and neuronal loss [34–36]. Similarly, anti-AMPA GluA3 antibody has been reported in a subset of 20 %-25 % frontotemporal lobar degeneration (FTLD), correlating with increased tauopathy and cortical atrophy [37–39]. These observations suggest that sustained antibody exposure may contribute to structural change, but they do not yet establish generalizable causality across the broader antibody spectrum [37,39]. While studies on intracellular neuronal antibodies remain limited, their exact contribution to neurodegeneration and links to underlying pathology, however, are unresolved.

This clinicobiological overlap creates a diagnostic gray zone and motivates systematic evaluation rather than reflex attribution to either neurodegeneration or autoimmunity. Accordingly, conceptual frameworks have been proposed to explain the association between neuronal autoantibodies and neurodegeneration, which differ in their diagnostic focus, mechanistic assumptions, and intended clinical application (Table 2). Three conceptual frameworks have been proposed to explain the associations between antibodies and neurodegeneration [14,40,41]. The pathogenic-driver hypothesis proposes that antibodies may directly or indirectly (e.g., by mediating autoimmune responses or chronic neuritis) initiate or amplify neurodegenerative processes. In contrast, non-causal-markers hypothesis views antibodies as secondary immunologic markers of antigen exposure during injury or degeneration, without causal effect [42]. The modulatory role hypothesis suggests that under conditions of sustained antibody exposure, immune-mediated effects may progress from functional interference to structural injury and, in a time-dependent manner, continue to neurodegenerative change, constituting a temporally evolving autoimmune-neurodegeneration axis. Determining the operative role in individuals remains challenging. Clarifying the pathogenicity of antibodies requires standardized, prospective longitudinal data and mechanistic validation.

2.2. Immunotherapeutic efficacy and treatment windows

Clinical management of antibody-positive dementia has largely been extrapolated from AIE, including non-selective immunotherapies, glucocorticoids, intravenous immunoglobulin (IVIG), plasma exchange (PLEX) [43–45], monoclonal antibody, alkylating agent, and plasma cell-depleting agents [46–48]. Treatment responses are heterogeneous and highly depend on antibody specificity, timing of initiation, antibody isotypes and titer, often with limited improvement and a therapeutic window.

Across antibody-positive cognitive syndromes, treatment effects are heterogeneous but show a consistent stage dependence. In anti-IgLON5 disease, approximately three quarters of patients stabilized with long-term immunotherapy, and time to treatment was a major predictor; delayed initiation coincided with weaker responses and higher mortality, in keeping with late-stage neuronal loss and tau deposition [49]. Studies revealed that early immunotherapy improved cognition, notably domain of learning and memory. Clinical features, such as subacute or acute onset, fluctuating course, and inflammatory changes on CSF or MRI have served as practical predictors of clinical benefits [26]. Symptom domains also differ, in a retrospective series with scheduled methylprednisolone over six months, mood and affect improved more than global cognition, and similar domain-selective responses have been noted in LGI1-associated dementia [50,51]. Reversal of cognitive deficits has been reported in DLB with anti-NMDAR IgG after immunotherapy, with concordant neuroimaging improvement, but such evidence remains case-based [22]. Small cohorts suggest that high anti-NMDAR titers with CSF inflammatory corroboration identify subgroups more likely to respond, whereas isolated, low-titer serum reactivity seldom predicts benefit [18,24]. Responses do not always track titers; for example, semantic dementia with GlyR antibodies improved after glucocorticoids despite stable titers [52]. IgA/IgM reactivities are frequently interpreted as bystander responses secondary to neurodegeneration, with weaker pathogenicity and overall response rates below one half [18]. Baseline NfL and GFAP may estimate injury burden and delineate therapeutic windows; higher levels correlate with poorer treatment response and likely reflect advanced structural damage [49]. Future directions should prioritize biomarker-guided stratification. Genetic context may further stratify risk, as HLA-DRB1*10:01 in anti-IgLON5 disease with susceptibility, higher serum titers, and adverse outcomes. Mechanistically selective strategies, such as FcRn inhibition (e.g., efgartigimod) and antigen-specific B-cell elimination, may improve specificity and risk–benefit balance, but they require long-term evaluation [46].

Overall, current immunotherapies yield modest improvement in global cognition but more consistent benefits on non-cognitive symptoms. Functional neuroimaging appears more sensitive than clinical scales for detecting treatment effects and can help guide management. These observations suggest that antibody-positive dementia may comprise both irreversible degenerative injury and a partly reversible antibody-mediated immune process, earlier immunomodulation may help inhibit the latter. Nevertheless, direct experimental evidence of immunotherapy efficacy is lacking, and the impact of antibody specificity and titer on response remains undefined. Large, standardized, longitudinal studies are required to establish response thresholds and therapeutic windows.

2.3. Limitations

Current evidence is constrained by substantial heterogeneity in reported findings, particularly regarding prevalence estimates and clinical relevance. This epidemiological discordance stems from limitations, including small cohort sizes, short follow-up durations, inconsistent case definitions, and non-standardized antibody testing with heterogeneous panels [27]. This section delineates variability in participant selection, specimen handling and assay platforms, and study design. Priorities for future work include large, prospective, multicenter cohorts; harmonized and comprehensive antibody profiling and longitudinal, multimodal endpoints that integrate clinical, imaging, and fluid biomarkers to establish thresholds for risk stratification and individualized management.

2.3.1. Cohorts

Comparability and generalizability are limited by heterogeneous enrollment frames. Most reports are retrospective series with site-specific data capture and variable quality control. Case definitions diverge: some studies enrolled patients with clinically diagnosed neurodegenerative dementia who happened to test antibody-positive [15,30], whereas others enrolled AIE mimicking dementia syndromes [20,23,31]. Degeneration-led and immune-led pathways are therefore mixed within and across cohorts. Exclusion criteria are also non-uniform, particularly for malignancy, recent infection, systemic autoimmune disease, and prior immunotherapy. Because these potential confounders can generate or amplify antibodies and shape the inflammatory milieu, inconsistent handling inflates or deflates apparent seroprevalence and distorts between-group comparisons, weakening inferences linking antibody status to clinical outcomes [53–56].

Phenotypic composition varies widely. Some cohorts include

Table 2
Neuronal autoantibodies identified in neurodegenerative dementias: clinical manifestations, pathological associations, and supporting evidence.

Antibody	Subtype	Sample	Testing Method	Number	Titer	Dementia Identified	Clinical Manifestations	Pathogenicity Conclusion	Supporting Evidence
NMDAR	IgA	Serum CSF	LN	7/23 (30.4%)	1:32-1:32000 (serum); 1:3.2-1:10 (CSF)	UD[a]	• Slow cognitive decline • Executive dysfunction	Patient-derived IgA decreases the density of NMDAR and other synaptic proteins, and alters synaptic current.	Prüss et al. 2012
	IgA IgM IgG	Serum	CBA	46/286 (16.1%)	>1:100 (serum); ≤1:10 (CSF)	AD, FTD, DLB, PDD, PSP, CBS, UD	• Fluctuating course • CSF abnormalities (elevated protein)	Whether antibodies result from or contribute to the neurodegenerative disorder remains unknown	Doss et al. 2014
	IgA IgM	Serum	CBA	20/134 (14.9%)	N/A	AD, SIVD, FTD, MCI	• Slow cognitive decline • Psychosis and depression	Antibodies correlate with comorbid depressive or psychotic states, suggesting a role in pathophysiology	Busse et al. 2014
	IgA IgM	Serum	CBA	36/156 (23%)	N/A	AD, SIVD, FTD, MCI	• Poor outcome • No hippocampal atrophy • Disturbed blood-CSF-barrier	The origin and biological impact of antibodies is still unresolved. Blood-CSF-Blood barrier dysfunction enables antibodies access neurons, accelerating cognitive decline	Busse et al. 2018
	IgG	Serum CSF	CBA+LN+IHC	1/920 (0.1%)	N/A	AD	• Subacute deterioration • Myoclonus • Autoimmune history	Whether antibodies result from or contribute to the neurodegenerative disorder remains unknown	Bastiaansen et al. 2023
LGI1	IgG	Serum CSF	CBA+LN+IHC	1/920 (0.1%)	N/A	AD	• Subacute deterioration • Myoclonus • Autoimmune history	Whether antibodies result from or contribute to the neurodegenerative disorder remains unknown	Bastiaansen et al.2023
	IgG	Serum	CBA	2/93 (2.2%)	1:100 (serum)	DLB, UD	• RBD • Reflex myoclonus	The significance of antibodies and their possible primary or secondary roles need to be investigated	Giannoccaro et al. 2021
CASPR2	IgG	Serum	CBA	1/93 (1.1%)	1:100 (serum)	PSP	• Parkinsonism • Hypersomnia during worsening with pathological sleep latency	The significance of antibodies and their possible primary or secondary roles need to be investigated	Giannoccaro et al. 2021
IgLON5	IgG	Serum CSF	CBA+IHC	3/920 (0.3%)	N/A	AD	• Slow cognitive decline • Other synergistic symptoms[b]	Antibody-induced receptor internalization; tau hyperphosphorylation and neuronal loss	Bastiaansen et al. 2023; Gelpi et al., 2024; Sabater et al., 2014
GluA3 (AMPAR)	IgG	Serum CSF	CBA	41/175 (23.4%)	N/A	FTD	• Behavioral variant FTD • Bilateral temporal atrophy (MRI)	Antibodies reduced synaptic GluA3 subunits and dendritic spine loss, with increased levels of neuronal tau	Borroni et al., 2017
	IgG	Serum CSF	ELISA	37/111 (33.3%)	OD	FTLD	• Impaired judgment/ impulsivity • Hyperorality • Inattention	Antibodies reduced glutamate release with AMPAR dysfunction	Palese et al. 2020
$GABA_AR$ $GABA_BR$	IgG	Serum	CBA	4/93 (4.3%)	1:100-1:400 (serum)	PSP, UD	• Slow cognitive decline • Parkinsonism • Mood changes (depression, emotional lability)	The significance of antibodies and their possible primary or secondary roles need to be investigated	Giannoccaro et al. 2021
GlyR	IgG	Serum	CBA	6/93 (6.4%)	1:100-1:400 (serum)	AD, UD, UP[c]	• Slow cognitive decline • Parkinsonism • Sleep disorder	The significance of antibodies and their possible primary or secondary roles need to be investigated	Giannoccaro et al. 2021
DPPX	IgG	Serum CSF	CBA+LN+IHC	1/920 (0.1%)	N/A	DLB	• Cognitive decline and fluctuating disease course • Asymmetric hypokinetic-rigid syndrome, • Slurred speech, orthostatic hypotension, obstipation,	Whether antibodies result from or contribute to the neurodegenerative disorder remains unknown	Bastiaansen et al. 2023

Abbreviations: AD = Alzheimer disease; FTD = frontotemporal dementia; FTLD = frontotemporal lobar degeneration; DLB = Lewy body dementia; PSP = progressive supranuclear palsy; CBA = cell-based assay; LN = live neurons; IHC = immunohistochemistry; ELISA = enzyme-linked immunosorbent assay; OD: optical density; N/A=not available information; NMDAR = N-methyl-D-aspartate receptor; LGI1 = leucin-rich glioma inactivated protein 1; CASPR2 = contactin-associated protein-like 2; IgLON5 = Ig-like domain-containing protein family member 5; AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; $GABA_AR$ = gamma-aminobutyric acid type A receptor; $GABA_BR$ = gamma-aminobutyric acid type B receptor; GlyR = glycine receptor; DPPX = dipeptidylaminopeptidase-like protein 6.
UD[a]: Unclassified dementia, patients who did not satisfy the criteria for any specific disorder were defined as "unclassified"dementia.
Other synergistic symptoms[b]: Patient No.1 showed subacute deterioration in months, severe apraxia, aphasia, myoclonus, hallucinations, delusions, and behavior problems. Admission to a closed psychiatric ward. Patient No.2 showed word retrieval and phrase difficulties. Patient No.3 showed progressive visuoperceptual and spatial disorders, apraxia, dyscalculia, mild behavioral disturbances, restless legs syndrome, and myoclonus. No sleep disorders.
UP[c]: unclassified parkinsonism, patients who did not satisfy the criteria for any specific disorder were defined as "unclassified" parkinsonism.

patients with autoimmune "red flags" such as acute or subacute onset, fluctuation, seizures, or rapid progression [16]; others restrict enrollment to slowly progressive cognitive decline without immune clues [17,37]. These differences shift pretest probability and baseline risk, making antibody positivity rates and effect sizes across studies inherently non-comparable. Age and stage are unevenly addressed. Antibody spectra and baseline biomarker levels vary with age (for example, anti-NMDAR encephalitis tends to present earlier than anti-LGI1), yet age adjustment is often incomplete, inflating between-group variance [43,57]. Disease stage spans months to more than a decade across studies. Antibody titers and CSF inflammatory indices change over time, so cross-sectional analyses that ignore time since onset risk phase confounding, where observed differences reflect position on the trajectory rather than underlying biology [58].

2.3.2. Antibody testing

Standardized testing workflows remain limited. Antibody panels vary widely and often prioritize neuronal surface targets while undersampling intracellular antibodies. Beyond target selection, methodological variables including specimen type, titer, assay platform, and immunoglobulin isotype (IgG, IgA, IgM) are inconsistently reported [32]. These parameters are essential for inferring pathogenic relevance. Incomplete reporting produces ambiguous signals that complicate interpretation and can either exaggerate or underestimate clinical significance [59]. Background reactivity must also be considered. Seroprevalence of specific antibody increases with age in healthy controls, and several low-titer serum intracellular antibodies may function as non-pathogenic markers outside compatible syndromes [14,17,60–63]. Studies relying on serum-only testing, accepting a single low-titer result, or omitting confirmation are prone to false positives and over-interpretation [64,65].

For conformational membrane targets, cell-based assays (CBA) preserve native epitopes and should be the preferred and primary method in current research [66,67]. Borderline or atypical results should be confirmed by tissue immunohistochemistry or live-neuron [68]. Reports should specify antibody titer, antibody index, isotype, and testing methods. Pre-analytical conditions including storage, delay, freeze-thaw cycles should also be documented. Without standardization, cross-study comparisons and clinicophenotypic mapping remain unreliable.

2.3.3. Study design and endpoints

Most available studies are retrospective and underpowered, with few well-characterized prospective cohorts. Clinical instruments for phenotype and cognition, MRI, ^{18}F-FDG-PET, and fluid-biomarker assays differ across reports. Primary and secondary endpoints are seldom prespecified, and assessment windows are rarely synchronized, limiting cross-study synthesis and precluding meaningful meta-analysis.

In participants who receive immunotherapy, interpretation is further constrained by confounding by indication and regimen heterogeneity—timing of initiation, agent, dose, and duration—so observed differences may reflect treatment selection rather than effect. Reporting of paired pre-/post-treatment antibody measures, paired inflammatory markers, and paired clinical assessments is often incomplete. Relapse and retreatment are inconsistently captured, and follow-up intervals vary, undermining estimates of effect size and durability. Because cross-sectional designs cannot establish causality, prospective studies should be structured to test evidentiary chain including temporality, specificity and reversibility. Absence of any element weakens causal inference between antibody status and outcomes. Mechanistic work of antibodies in neurodegeneration remains sparse, partly because the clinical construct is still imprecise. Clearer case definitions, harmonized sampling, standardized time-anchored assessments, and core outcome sets are needed to improve feasibility, comparability, and reporting quality.

3. Part II. Antibody-neurodegeneration axis

Neuronal autoantibodies can mediate neuronal dysfunction through multiple mechanisms, including receptor cross-linking and internalization, complement dependent cytotoxicity, protein-protein binding disruption, antibody-dependent cellular cytotoxicity (ADCC), and receptor antagonism [69–72]. Acute effects primarily manifest as reversible synaptic dysfunction [73]. Within neurodegenerative dementia, direct mechanistic evidence of antibodies remains limited, although converging data suggest a continuum in which sustained antibody exposure promotes degenerative change, including axonal degeneration, synapse loss, and progressive neuronal death [65–68]. This section focuses on two illustrative specificities, IgLON5 and AMPAR-GluA3, whose experimental and clinicobiological findings outline the cascade.

3.1. Anti-IgLON5 antibody

IgLON5 encephalitis is a recently defined autoimmune neurological disorder that lies at the interface of autoimmunity and neurodegeneration, extending contemporary concepts of tauopathy [74–77]. Tau is a microtubule-associated protein that maintains cytoskeletal stability and axonal transport. In AD and other neurodegenerative conditions, tau becomes pathologically hyperphosphorylated and forms neurofibrillary tangles [78]. Neuropathological studies in IgLON5 encephalitis demonstrate neuronal loss with deposits of hyperphosphorylated tau in the brainstem tegmentum and hypothalamus, with mixed 3R/4R tau isoforms [35,79,80]. In human iPSC-derived neurons, IgLON5 IgG induces irreversible internalization of IgLON5, reduces synaptic density, produces time-dependent accumulation of phosphorylated tau, and ultimately causes neuronal death with sustained exposure, indicating a durable pathogenic effect [34]. Rodent models corroborate these observations: exposure to IgLON5 antibodies disrupts neurofilament architecture, produces axonal swelling, elevates CSF NFL, and after intracerebroventricular administration, reproduces tau deposition in hippocampal and brainstem regions [81,82]. Inflammatory activation appears early and may persist, with lymphocytic activation and increased number and activation of microglia, whereas neuronal tau deposition tends to emerge later in the course. These findings suggest that tau pathology may arise secondary to a sustained inflammatory response triggered by IgLON5 antibodies [83,84]. Additional markers support parallel immune-neurodegenerative coupling in IgLON5 antibody disease. Serum glial fibrillary acidic protein (GFAP) has been elevated, consistent with astrocytic activation [49]. Co-deposition of TDP-43 or phosphorylated TDP-43 with tau has been observed in a subset of patients, suggesting mixed proteinopathies may contribute to the phenotype [83].

Taken together, clinical, cellular, and animal data support a cascade from functional synaptic disturbance to structural injury and regionally selective tau aggregation driven by persistent IgLON5-directed autoimmunity. This framework helps explain cognitive and degenerative features in IgLON5 disease. Important uncertainties remain, including the precise causal sequence and the relative contributions of antibody binding, downstream inflammatory signaling, and intrinsic degenerative processes. Further validation in controlled, longitudinal animal models is required to define temporality, dose–response thresholds, and the potential for reversibility.

3.2. Anti-AMPA GluA3 antibody

Frontotemporal lobar degeneration (FTLD) is a progressive neurodegenerative syndrome characterized by frontal and temporal lobe atrophy, pathological heterogeneity, and complex genetics [85]. Epidemiological and genetic studies indicate enrichment of immune-related signals, including a higher burden of systemic autoimmune comorbidity and associations within the human leukocyte antigen (HLA) region [85–89]. These observations implicate immune pathways

in a subset of frontotemporal lobar degeneration and support evaluation of immune-targeted strategies.

The prevalence of AMPAR GluA3 antibodies in FTLD has been reported to reach 20-25 % [39]. AMPA receptors are excitatory glutamatergic receptors implicated in FTLD. Excessive receptor activity can drive neurodegeneration and has been linked to activity-dependent tau release [37,90]. In human iPSC-derived neurons and rat hippocampal cultures, incubation with AMPAR GluA3 antibodies reduces synaptic localization of GluA3 subunit, produces dendritic spine loss, elevates tau levels, and impairs glutamatergic transmission through reduced presynaptic glutamate release and diminished postsynaptic AMPAR availability, which together account for the observed spine pathology [39]. Studies showed that reduced AMPAR abundance and dysfunction in mice frontal cortex induced FTLD-like behavioral deficits, providing convergent support for an antibody-driven mechanism [91].

A passive-transfer model using patient-purified anti-GluA3 IgG produced postsynaptic p-tau accumulation and dendritic spine loss in the prefrontal cortex; in a subsequent clinical series, CSF p-tau levels were higher in antibody-positive FTLD compared with antibody-negative patients [38]. Post-mortem studies further showed reduced postsynaptic expression of GluA3-containing AMPARs in the temporal cortex of FTLD-tau, and in vivo neurophysiologic assessments of excitatory glutamatergic circuits revealed greater deficits in GluA3-positive patients, corroborating antibody-associated harm [92].

Together, these data delineate a clinically meaningful FTLD subgroup in which anti-AMPAR antibodies appear to remodel glutamatergic neurotransmission and promote synaptic vulnerability. Current evidence supports an autoimmune contribution to frontotemporal neurodegeneration and motivates personalized therapeutic strategies for GluA3 antibody–positive patients.

Despite growing convergence across cellular systems, animal models, and patient cohorts, the molecular sequence and causal directionality remain incompletely defined. For IgLON5 antibodies, a continuous causal link from antibody-mediated cytoskeletal disruption to activation of tau kinases has not been demonstrated, and real-time tracking of tau conformational dynamics or seeded aggregation is limited. For GluA3 antibodies, receptor internalization and calcium dyshomeostasis have been shown, but an in vivo cascade connecting AMPAR perturbation to tau phosphorylation has not been confirmed. At the immune-neural interface, the roles of microglial activation in driving tau deposition and of complement-mediated synaptic pruning in facilitating tau release require causal dissection with target-engagement interventions. Longitudinal evidence that early immunomodulation reverses tauopathy is lacking, and it remains uncertain whether mechanisms inferred from IgLON5 and GluA3 generalize to other antibodies. Prospective studies with staged biomarker readouts, mechanistic endpoints, and predefined response thresholds are needed to establish temporality, dose response, and reversibility.

4. Part III. From evidence to practice:a standardized diagnostic workflow

To address the diagnostic inconsistency and epidemiological heterogeneity characterized in prior literature, we outline a structured clinical framework. This proposed workflow serves as a reference to guide the transition from clinical suspicion to decision-making, aiming to maximize diagnostic specificity within the current evidence landscape. The process proceeds sequentially: (1) Pretest-probability triage, designed to mitigate spectrum and selection biases inherent in non-stratified screening, optimizing the positive predictive value of subsequent testing; (2) Specimen-and-assay protocol, which emphasizes rigorous standards for biosample acquisition and analytical validation; and (3) Post-test integrated analysis, wherein immunological evidence is contextualized within a multi-dimensional clinical and paraclinical profile to inform management.

4.1. Pretest-probability triage

To reduce spectrum and selection biases introduced by heterogeneous screening and enrollment in prior studies, we propose a pretest-probability triage based on the Graus–Dalmau diagnostic framework of AIE [6]. Patients are stratified into high-, intermediate-, and low-risk categories, with the dual aims of providing an operational pathway for when and how to test and interpret antibodies in degenerative presentations, and increasing positive predictive value while minimizing misclassification [44,93,94].

High-risk presentations are defined by any of the following: acute onset, rapidly progressive course, seizures, or prominent psychiatric symptoms; or auxiliary inflammatory signals, specifically T2/FLAIR abnormalities suggestive of encephalitis on MRI, or CSF pleocytosis >5/μL, EEG with epileptic or slow-wave activity [6,14,33,95]. These conditions are derived from diagnostic criteria for AE. A single criterion suffices, and priority escalates when clinical and paraclinical features co-occur. These patients should undergo immediate antibody testing, and where clinical judgment supports it, early initiation of immunotherapy given the strong prior for an antibody-mediated, potentially reversible synaptopathy.

Intermediate-risk presentations show subacute onset or a fluctuating progressive course together with features that are atypical for neurodegeneration yet suggest immune involvement, including REM sleep behavior disorder, myoclonus, cerebellar ataxia, dysautonomia, or extrapyramidal signs [6,76,96,97]. Contextual amplifiers include a prior infectious or paraneoplastic setting such as previous herpes simplex encephalitis (HSE) or established tumor risk [98], as well as new-onset psychiatric or behavioral symptoms that are not explained by an existing degenerative diagnosis [99]. By design, these patients do not meet clinical criteria for AIE, but they display convergent features compatible with an immune contribution. In this context, neuronal autoantibody testing may be considered in a targeted manner. Beyond canonical synaptic antibodies, selected phenotype-associated antibodies that have been reported in cognitive-predominant or dementia-mimicking presentations, including ARHGAP26, mGluR5, glycine receptor, and recoverin antibodies, may be evaluated when specific clinical features, paraneoplastic context, or system-specific involvement increase biological plausibility [100–105]. The purpose of the intermediate-risk category is to raise situational awareness, frame the differential between immune-mediated and neurodegenerative pathways and prioritize longitudinal assessment. Neuronal autoantibody testing is recommended. This stratification operationalizes a watchful, hypothesis-driven posture that preserves diagnostic agility while minimizing overattribution in cases that occupy the gray zone between AIE and neurodegenerative dementia [106,107].

Low-risk presentations, representing an incidental antibody subgroup, show slowly progressive decline with otherwise concordant biomarkers and imaging, and no acute or subacute onset, marked fluctuation, seizures, abrupt psychiatric change, or inflammatory MRI or CSF findings. In this context, antibody testing should be selective and stepwise, triggered by prespecified conditions: (1) an unresolved differential diagnosis in which adjudication among degenerative and inflammatory, paraneoplastic, or post infectious mechanisms would alter management; (2) biomarker discordance, such as AT(N) mismatch or persistently elevated age adjusted NfL that is disproportionate to apparent degenerative burden [108]; (3) atypical MRI or FDG-PET showing limbic or other noncanonical patterns; and (4) mild superimposed change on a progressive duration, such as minor fluctuation, late onset mild seizures, or a subtle behavioral shift that does not meet intermediate or high risk thresholds [26]. When these triggers are present, a CSF first approach with paired serum is preferred, using a preferentially focused CBA panel (NMDAR, LGI1, CASPR2, AMPAR, IgLON5) with expansion as indicated [109]. Indeterminate or low titer results should be confirmed and reported in a standardized format that specifies titer, antibody index when applicable, dilution curves, and

relevant preanalytical conditions to minimize misdiagnosis and false-positive interpretations [33,110–112].

Interpretation across tiers follows the same principle: an antibody finding in neurodegenerative presentations may delineate an actionable, immune-modifiable subtype, but attribution should be evidence-weighted. Most serum-only low-titer results without CSF support should be documented with strengthened follow-up rather than immediate disease-defining labels. Conversely, CSF positivity or intrathecal synthesis that is concordant with even mild clinical change, sustained NfL elevation, or network-level abnormalities on imaging may indicate a plausible immune contribution, warranting planned reevaluation at predefined intervals and, where appropriate, a monitored therapeutic trial within a multidisciplinary framework. This triage pathway operationalizes antibody testing where it is most informative, protects against false positives, and creates a reproducible bridge from evidence to practice (Fig. 1).

4.2. *Specimen-and-assay pathway*

Antibody testing should be explicitly coupled to pretest probability in order to maximize analytic validity and clinical interpretability while limiting false positives. Triggers follow a tiered scheme: immediate sampling in high-risk presentations, expedited sampling in intermediate-risk settings, and selective stepwise sampling in the low-probability incidental-antibody subgroup when there is biomarker discordance, atypical imaging/network patterns, mild superimposed change on a slow degenerative trajectory, a defined need for differential diagnosis, or research-grade stratification. Before sampling, alternative causes of acute encephalopathy and important confounders (tumor, recent infection, immune-checkpoint inhibitors) should be reviewed to guide both the choice and interpretation of assays.

Specimen strategy prioritizes CSF with paired serum whenever feasible [33,109]. CSF improves the positive predictive value for neuronal surface antibodies and permits assessment of intrathecal synthesis, while pairing preserves interpretability across platforms and time [59,113]. Preanalytical conditions and comparability should be recorded with specificity, including time to sampling procedures, freezing, storage temperature, and the number of freeze-thaw cycles. Primary assays should use CBA as the anchor for neuronal surface antibodies and intracellular antibodies, live-neuron cultures (LN) or immunohistochemistry (IHC) are acceptable as screening tools [10,16,114]. All runs should include appropriate positive and negative controls, dilution series, and blinded reads when practicable. Indeterminate or low-titer findings require predefined confirmation. Single low-titer serum signals should not be attributed causality. Confirmation consists of repeat sampling in CSF and serum using the same primary platform, together with at least one orthogonal method such as IHC or LN where available. The interval between index and confirmatory tests should be documented, and particular caution is advised in older adults, in whom nonspecific serum reactivity is more frequent.

Reporting must be standardized to support cross-study comparison and longitudinal interpretation. A standard reporting set includes specimen type and timing, assay platform and laboratory, antibody target, titer, epitope and immunoglobulin class, dilution curves and control performance, relevant preanalytical conditions, and whether tissue confirmation was performed. Interpretation is anchored to the

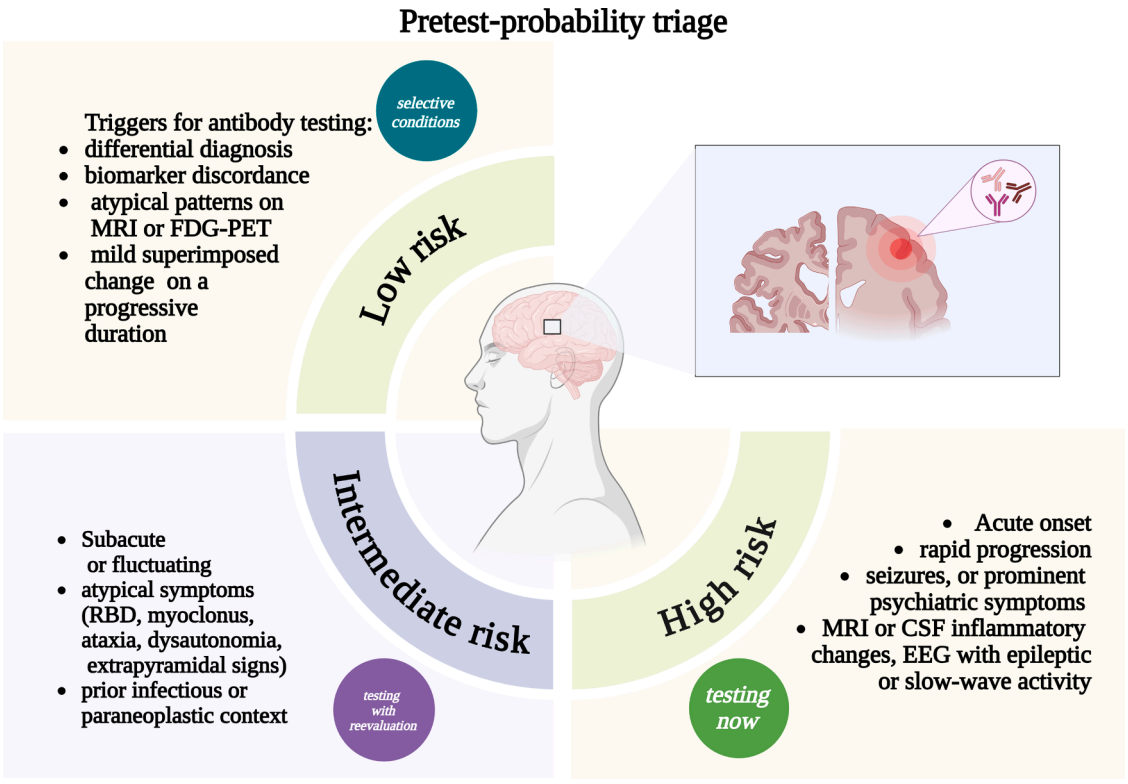

Fig. 1. Pretest-probability triage for neuronal antibody testing in neurodegenerative presentations. Patients are stratified into high, intermediate, and low pretest-probability groups to guide when and how to test and interpret neuronal antibodies. High risk (blue): acute onset or rapid progression; seizures or prominent psychiatric symptoms; or inflammatory signals including MRI T2/FLAIR changes, CSF pleocytosis, or slow-wave activity on EEG. Action: test immediately; where clinically justified, consider early immunotherapy. Intermediate risk (green): subacute or fluctuating duration, atypical features for neurodegeneration, prior infectious or paraneoplastic context or new-onset psychiatric/behavioral change cannot be explained by a degenerative diagnosis. Action: test with planned re-evaluation. Low risk (purple): slowly progressive course with otherwise concordant degenerative biomarkers and imaging. Testing is selective, triggered by predefined conditions. Across tiers, interpretation is evidence-weighted: serum-only low-titer findings usually warrant documentation and follow-up rather than disease-defining labels, whereas CSF positivity or intrathecal synthesis concordant with clinical or biomarker change supports planned re-assessment and, where appropriate, a monitored therapeutic trial. Created in https://BioRender.com.

pretest tier and contemporaneous data, including MRI, FDG-PET or other network measures, and biomarkers such as NfL and the core AT(N) profile. Evidence consistent with immune modulation, for example CSF positivity or intrathecal synthesis that aligns with mild clinical change, sustained NfL elevation, or atypical network abnormalities, supports intensified monitoring and planned re-evaluation [115]. Escalation to time-limited, goal-directed immunotherapy should be reserved for situations in which evidence converges and the pretest probability has risen. Retesting windows should be prospectively specified. When the phenotype continues to evolve despite negative or indeterminate results, retesting can be considered after six to twelve months in the incidental-antibody subgroup, and more frequent intervals in intermediate or high-risk trajectories, ideally with paired CSF and serum and the same primary platform to enable within-patient comparison [106] (Fig. 2).

4.3. Post-test integrated analysis

Detection of neuronal autoantibodies alone is insufficient to establish autoimmune dementia; a final integrative clinical assessment is required to minimize overdiagnosis and guide subsequent management.

High phenotype-antibody concordance may be inferred when a high- or intermediate-risk clinical phenotype identified during pretest stratification converges with high-confidence immunological evidence, such as intrathecal antibody synthesis, high-titer serum antibodies, or additional biological signals suggestive of central nervous system immune involvement. In such cases, comprehensive clinical re-evaluation and close longitudinal monitoring are warranted. Rather than automatic, non-selective immunotherapy, structured follow-up enables detection of accelerated progression, emerging inflammatory features, or new neurological manifestations, thereby allowing timely consideration of a carefully monitored immunotherapeutic trial when disease dynamics support an immune-mediated contribution.

By contrast, low phenotype-antibody concordance is more likely when antibody positivity is limited to isolated, low-titer serum findings in patients with a low pretest probability and without supportive cerebrospinal fluid, imaging, or inflammatory biomarkers. This pattern, frequently encountered as an incidental finding in neurodegenerative cohorts, should prompt caution against causal attribution. In such scenarios, a conservative strategy is generally favored, consisting of documentation of antibody status without assigning an autoimmune diagnosis, avoidance of premature immunosuppression, and periodic reassessment to ensure continued alignment with a primary neurodegenerative trajectory.

Standardized documentation is essential to align post-test interpretation with prior diagnostic steps. Recording the inferred level of antibody certainty supports longitudinal clinical reassessment and promotes consistency across management decisions and future studies. Collectively, this post-test framework underscores that antibody findings should inform, rather than dictate, clinical decision-making, preserving diagnostic specificity while identifying patients who may benefit from timely immunomodulatory intervention.

5. Part IV. Future directions

Although several cross-sectional studies have described clinical features of antibody-positive dementia, results remain heterogeneous and retrospective designs do not establish causality. Future work should prioritize a standardized specimen-and-assay workflow to reduce false positives and improve reproducibility. This framework should be integrated into multicenter prospective cohorts with harmonized enrollment and follow-up to track cognition, imaging and network metrics, and fluid biomarkers. Pre-specified retesting windows for antibody titers are needed to evaluate treatment-related dynamics and to clarify the temporal relationship between immune activity and neurodegenerative trajectories.

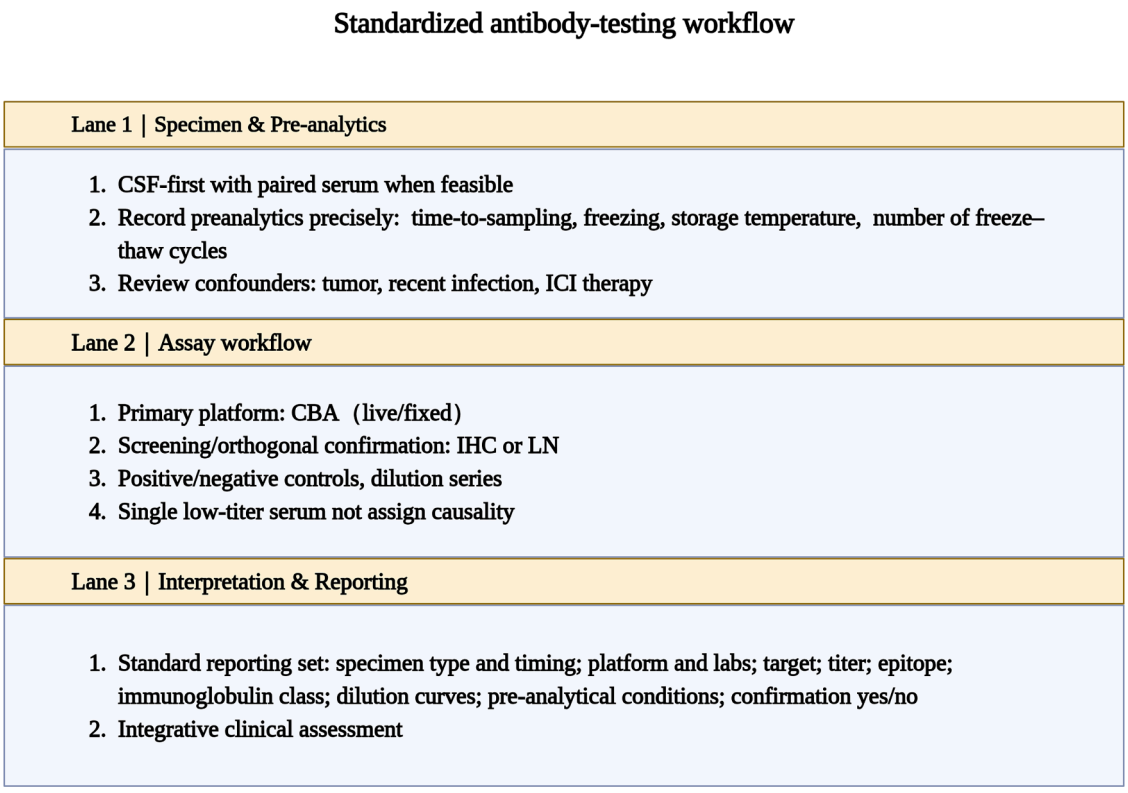

Fig. 2. Standardized specimen-and-assay pathway for neuronal antibody testing in dementia. The workflow is organized into three sequential lanes to guide the process from sample collection to clinical action, aiming to maximize analytic validity and clinical interpretability. CSF: cerebrospinal fluid; CBA: cell-based assay; IHC: immunohistochemistry; LN: live-neuron culture assay; ICI: immune-checkpoint inhibitor.

Building on rigorously characterized prospective cohorts, multicenter interventional trials may be justified in selected patient subsets. Given the marked clinical and biological heterogeneity of antibody-associated dementia, trial eligibility should be informed by stratification frameworks integrating pretest probability, assay confidence, and phenotype–antibody concordance, rather than broad, non-selective enrollment. Harmonized cognitive and biological endpoints will be critical to delineate therapeutic windows and to distinguish disease-modifying effects from transient symptomatic responses. In parallel, immunologic profiling at the cellular and molecular levels should define peripheral and central activation signatures and compare these patterns with typical AIE and degenerative dementia cohorts in order to identify immune phenotypes that align with reversibility. Finally, mechanistic studies should test the direct pathogenicity of antibodies using human iPSC-derived neuron models to assess effects on synaptic ultrastructure and pathological protein homeostasis, and transgenic animal models to model sustained antibody exposure and its impact on neurodegenerative phenotypes, with longitudinal readouts to resolve temporality, thresholds, and reversibility [116,117]. By integrating experimental readouts with clinical longitudinal measures, these programs will determine whether and when antibodies act as drivers in dementia, enable biomarker-guided subtyping, and support the development of individualized immunomodulatory strategies with the potential to improve outcomes.

6. Conclusion

Neuronal autoantibodies are increasingly detected in neurodegenerative dementias. This review integrates clinical evidence with mechanistic hypotheses and advances testable models. Evidence centered on anti-IgLON5 and AMPAR-GluA3 supports a cascade from synaptic dysfunction to structural injury and regionally restricted protein aggregation, whereas generalizability across other antibodies remains limited. Coupling a pretest-probability triage with a standardized antibody-testing workflow can increase reproducibility and reduce false positives. The next phase should delineate immune-active endophenotypes and validate targets in prospective multicenter cohorts, enabling early, mechanism-guided immunotherapy that may redirect a subset of patients from progressive decline toward stabilizable or reversible trajectories.

Availability of data and materials

No datasets were generated or analyzed during the current study.

Funding

This study was supported by National Natural Science Foundation of China (No. 82471450), the STI2030-Major Projects (No. 2021ZD0201802), and the Science and Technology Special Project of Xicheng District (No. XCSTS-SD2024-02).

Competing interests

All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be interpreted as potential conflicts of interest.

Ethical approval and consent to participate

This article does not involve any studies with human participants or animals conducted by any of the authors.

Consent for publication

As this study does not involve human participants or animals, formal informed consent was not required.

Declaration of generative AI and AI-assisted technologies in the writing process

We have not used any AI at all.

CRediT authorship contribution statement

Heya Luan: Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xiaodong Han:** Writing – review & editing, Supervision, Software. **Chang Xu:** Formal analysis, Data curation, Conceptualization. **Aidi Shan:** Supervision, Software, Data curation. **Xin Wang:** Project administration, Methodology. **Shaoqi Li:** Visualization, Software, Methodology, Investigation. **Qi Yao:** Project administration, Methodology, Formal analysis. **Tong Cui:** Supervision, Software, Formal analysis, Data curation. **Jinxuan Guo:** Visualization, Validation, Supervision. **Boye Wen:** Writing – original draft, Visualization, Software, Resources. **Yao Sun:** Software, Formal analysis. **Chuqiao Li:** Visualization, Validation. **Qingyuan Sun:** Supervision, Software, Methodology. **Cuibai Wei:** Writing – original draft, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

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 paper.

Acknowledgments

The authors would like to thank all participants and their guardians for their cooperation and contribution to this research, as well as our colleagues at Xuanwu Hospital for the collaboration in data collection and management.

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