Caspian Journal of Neurological Sciences
"Caspian J Neurol Sci"

Journal Homepage: http://cjns.gums.ac.ir

Review Paper

Proteomic Biomarkers for Sustainable Diagnosis of Major Neurodegenerative Disorders: A Review

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Citation Narayanan M, Rajinikanth V. Proteomic Biomarkers for Sustainable Diagnosis of Major Neurodegenerative Disorders: A Review. Caspian J Neurol Sci. 2026; 12(1):1-16. https://doi.org/10.32598/CJNS.12.44.571.1

Running Title Proteomic Biomarkers in Major Neurodegenerative Disorders

https://doi.org/10.32598/CJNS.12.44.571.1

Article info:

Received: 12 Feb 2025

First Revision: 12 May 2025

Accepted: 28 May 2025

Published: 01 Jan 2026

ABSTRACT

Background: Neurodegenerative illnesses, including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), are marked by progressive neuronal degeneration and presently lack adequate diagnostic and prognostic instruments.

Objectives: This review analyzed recent developments in proteomic methodologies and their uses in the identification and validation of biomarkers for AD, PD, and ALS. It offers a comparative proteome analysis of several significant neurodegenerative illnesses, highlighting both common and unique molecular markers. The review identified translational obstacles from biomarker discovery to clinical use, providing information that can improve comprehension of disease mechanisms and inform the creation of viable therapeutic options.

Materials & Methods: A thorough literature analysis was performed on proteomic studies concerning cerebrospinal fluid (CSF), blood, urine, and brain tissue in patients with AD, PD, and ALS. The review examined papers from January 2020 to June 2025 across prominent databases utilizing specified proteomic terminology. The inclusion criteria mandated that studies concentrate on human or validated animal proteomic analysis of disease-specific biomarkers. The literature underwent qualitative analysis to discern prevalent biomarkers, developing molecular networks, and trends among the three disorders, highlighting translational significance and methodological advancements.

Results: Comparative proteomic investigations demonstrated both shared and unique molecular pathways across AD, PD, and ALS, including synaptic degradation, mitochondrial dysfunction, and neuroinflammation. The amalgamation of proteomic data with genomic, systems biology, and transcriptomic, methodologies is expediting the identification of therapeutically pertinent biomarker panels. Innovative methods, like single-cell proteomics and artificial intelligence-based analysis are improving sensitivity and specificity in biomarker detection.

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Conclusion: The proteomic biomarkers offer considerable potential for early diagnosis, disease classification, and tailored therapy approaches in neurodegenerative disorders. Addressing existing translational obstacles will be essential for the effective application of precision medicine in neurodegeneration.

Keywords: Neurodegeneration, Proteomics, Biomarkers, Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS)

Highlights

- Proteomics provides insight into the mechanisms of neurodegeneration.
- Principal biomarkers were identified in AD, PD, and ALS.
- Mass spectrometry improves the precision of biomarker identification.
- Early detection is achievable by proteome profiling.
- Biomarkers facilitate the development of targeted treatments.

Introduction

Neurodegenerative illnesses, such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), pose a significant public health challenge, especially in the elderly populations [1]. These illnesses are characterized by gradual and selective neuronal degeneration, resulting in cognitive deterioration, motor impairment, and eventually, loss of autonomy and life. Despite their clinical diversity, they exhibit common characteristics, like protein misfolding, synapse dysfunction, mitochondrial impairment, and persistent neuroinflammation. AD is chiefly linked to memory impairment and the presence of amyloid-β and tau pathology; PD is defined by the degradation of dopaminergic neurones and the accumulation of α-synuclein, whereas ALS is marked by motor neurone degeneration, with critical proteins, like TDP-43 and superoxide dismutase 1 (SOD1) involved in its pathogenesis (Figure 1) [2].

A significant obstacle to controlling these illnesses is the absence of early, precise, and non-invasive diagnostic instruments. Contemporary diagnostic techniques frequently depend on clinical manifestations and neuroimaging, which identify the disease solely after significant brain degeneration has transpired. Identifying disease-specific genetic alterations during the prodromal or preclinical phases could markedly enhance prognosis and therapy results [3]. This highlights the critical necessity for reliable biomarkers that can differentiate between overlapping clinical symptoms, forecast disease onset, monitor progression, and inform treatment methods [4, 5].

The proteomics—the extensive examination of proteins and their modifications has emerged as a revolutionary methodology [6]. In contrast to genomics, which conveys static data, proteomics encapsulates the dynamic and functional conditions of cells and tissues. Utilizing sophisticated mass spectrometry (MS) and bioinformatics, proteomics facilitates extensive characterization of protein abundance, structure, interactions, and post-translational alterations in body fluids and tissues pertinent to neurodegeneration [7]. Crucially, it facilitates the discovery of established disease hallmarks and potential novel biomarker candidates that could function as early indicators or treatment targets.

This review examined the changing dynamics of proteomic biomarker identification in AD, PD, and ALS. Furthermore it used a comparative proteomics approach, spanning AD, PD, and ALS, in contrast to prior reviews that mainly concentrate on proteome results within specific neurodegenerative illnesses. By synthesizing molecular signatures from different illnesses, we sought to clarify common and disease-specific protein modifications that can enhance early diagnosis and facilitate personalized treatment. This work offers essential insights into the translational obstacles that hinder the advancement of proteomic findings from research to clinical application, thereby presenting a fresh integrative and translational perspective on neurodegenerative biomarker research.

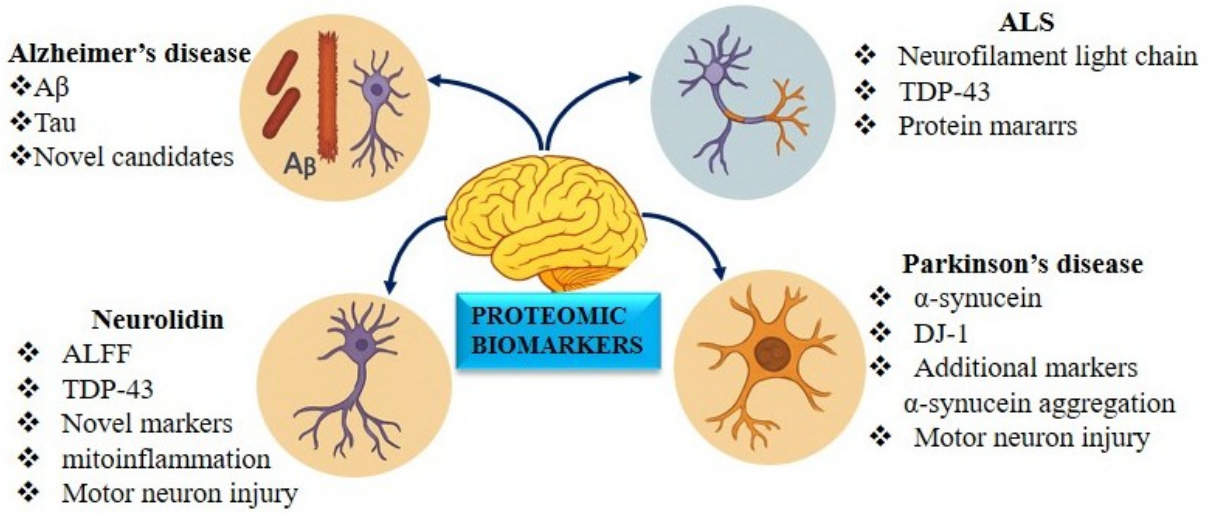

Figure 1. Emerging proteomic biomarkers in neurodegeneration decoding

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Materials and Methods

Search methods

A thorough literature review was performed to find pertinent research on proteomic biomarkers linked to AD, PD and ALS. The search was conducted across various electronic databases, notably PubMed, Scopus, and Web of Science, encompassing papers published from January 2020 to September 2025. The search approach employed combinations of terms, including AD, ALS, neurodegeneration, PD, proteomics, protein biomarkers, and proteomic profiling, linked by Boolean operators (inclusion and exclusion criteria). Only studies published in English that concentrated on human subjects or pertinent model experiments were included. Original research articles and extensive reviews that presented proteomic studies identifying diagnostic, prognostic, or mechanistic biomarkers were included. Studies not related to proteomics, conference abstracts, case reports, duplicates, and journals lacking available full texts were eliminated. Further references were identified through the manual examination of citations from chosen studies. The ultimate selection was determined by the scientific significance and contribution of each work to the comprehension of new proteome biomarkers and their mechanistic functions in neurodegenerative illnesses.

Results

The research demonstrated significant progress in the identification of proteomic biomarkers linked to AD, PD, and ALS. In AD, consistent modifications were noted in proteins associated with amyloid processing, tau phosphorylation, and synaptic integrity. Increased concentrations of p-tau181, p-tau217, amyloid-β peptides, and NfL have proven to be dependable markers of neuronal damage and disease advancement. In PD, proteome analysis revealed the dysregulation of α-synuclein, DJ-1, and mitochondrial complex I proteins, underscoring mitochondrial dysfunction, oxidative stress, and compromised protein degradation as major causes. Changes in proteins associated with autophagy and dopamine metabolism were also significant, indicating the gradual degeneration of dopaminergic neurons. In ALS, the overexpression of TDP-43, FUS, and ubiquitin-related proteins signifies protein aggregation and impaired RNA metabolism, whereas increased levels of GFAP, S100B, and complement components (C1q, and C3) indicate glial activation and neuroinflammation. A comparative examination of AD, PD, and ALS identified common proteomic signatures associated with mitochondrial failure, oxidative stress, and inflammatory response pathways. The overlapping protein patterns indicate convergent biological pathways that facilitate neurodegeneration. Novel proteomic technologies, including LC-MS/MS and TMT-based quantification, have improved biomarker identification by providing increased sensitivity and reproducibility. The cumulative data endorses proteomics as an effective instrument for identifying disease-specific molecular changes, enabling early diagnosis, and directing personalized treatment strategies in significant neurodegenerative illnesses.

Discussion

Proteomics technologies in neurodegeneration

The quest for dependable biomarkers for neurodegenerative illnesses relies on the capacity to detect intricate protein

dynamics with exceptional sensitivity and specificity [8]. Proteomic technologies, especially MS-based platforms, have transformed this field by facilitating the extensive identification, quantification, and characterization of proteins from diverse biological matrices [9]. In the context of AD, PD, and ALS, these methodologies are particularly effective for investigating disease-relevant biofluids, including cerebrospinal fluid (CSF), blood plasma, and non-invasive specimens, such as saliva and urine. MS is fundamental to neuroproteomics. Methods, including label-free quantification (LFQ), tandem mass tag (TMT) labelling, and data-independent acquisition (DIA), such as SWATH-MS, provide high-throughput and repeatable protein measurement (Figure 2) [10]. These techniques are crucial for identifying low-abundance proteins implicated in the initial stages of disease development. Moreover, innovations in liquid chromatography–MS (LC-MS/MS) have improved separation efficiency, facilitating more comprehensive proteome analysis [11, 12]. Moreover, post-translational modifications (PTMs), frequently changed in neurodegenerative diseases, can be precisely characterized by enrichment techniques combined with mass spectrometry, providing insights into dysregulated phosphorylation, ubiquitination, glycosylation, and additional modifications [13]. The alterations in PTMs are intricately associated with protein misfolding and aggregation mechanisms characteristic of AD (e.g. tau hyperphosphorylation), PD (e.g. α-synuclein ubiquitination), and ALS (e.g. TDP-43 modifications) [14]. The amalgamation of proteomics with bioinformatics and machine learning (ML) algorithms has significantly enhanced the ability to analyze high-dimensional data, pinpoint potential biomarkers, and delineate dysregulated protein networks. Public repositories and ProteomeXchange, in conjunction with neurodegenerative-specific databases, enhance data sharing and meta-analysis, hence expediting translational initiatives [15]. These improvements are poised to transform the approach from population-centric protein profiling to personalized diagnostics, thereby enhancing precision medicine in neurodegenerative treatment.

Proteomic biomarkers in AD

AD is distinguished by two principal neuropathological characteristics: The extracellular accumulation of amyloid-beta (Aβ) plaques and the intracellular aggregation of hyperphosphorylated tau protein within neurofibrillary tangles [16]. These signature proteins have historically constituted the basis for biomarker development. Aβ42 concentrations are often diminished in the CSF, signifying cerebral accumulation, whereas phosphorylated tau (p-tau) and total tau levels are increased, denoting neurofibrillary disease and axonal degeneration [17, 18]. Although these indicators are well-established in research contexts, their assessment has historically depended on invasive lumbar puncture or costly positron emission tomography (PET) imaging, restricting widespread clinical use. Table 1 presents an overview of essential proteins influencing the future of Alzheimer's diagnostics and personalized therapeutics, with each biomarker elucidating distinct facets of the disease pathogenesis.

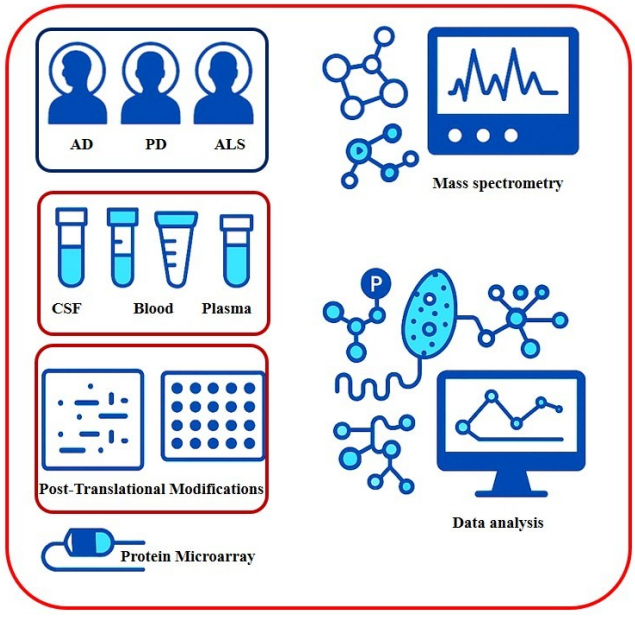

Figure 2. A schematic diagram representing the proteomics technologies in neurodegeneration

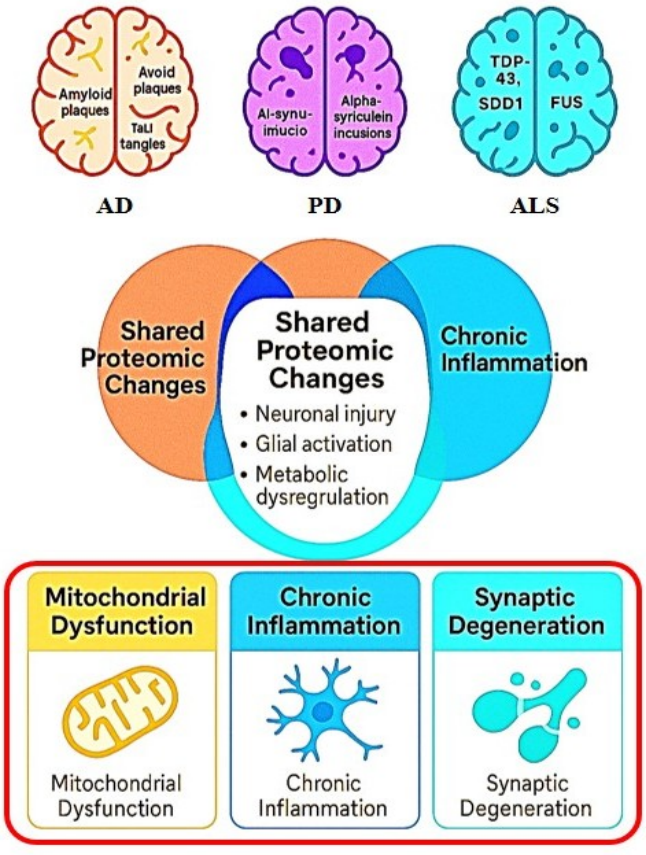

Figure 3. The proteomic landscapes of neurodegenerative diseases

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Recent advancements in proteomics have facilitated the identification of new protein candidates that elucidate more dimensions of AD pathology, encompassing synaptic failure, neuroinflammation, metabolic dysregulation, and vascular impairment [19]. Proteins, including neurogranin (a postsynaptic marker), YKL-40 (inflammation), triggering receptor expressed on myeloid cells 2 (TREM2), clusterin (CLU), and neurofilament light chain (NfL) are becoming significant biomarkers [20]. Recent advancements utilizing high-sensitivity platforms, like single-molecule arrays (Simoa), aptamer-based SOMAscan, and DIA mass spectrometry—have shown that plasma concentrations of Aβ42/40 ratios, p-tau181/p-tau217, and NfL can accurately indicate AD pathology, achieving diagnostic precision comparable to that of CSF and PET imaging [21]. Future endeavors to amalgamate these dynamic proteomic profiles with clinical and imaging data may provide more precise staging, risk classification, and personalized treatment monitoring.

Proteomic biomarkers in PD

PD, the second most prevalent neurodegenerative ailment, is clinically defined by motor symptoms, including bradykinesia, tremor, and stiffness, and pathologically by the degeneration of dopaminergic neurones in the substantia nigra and the buildup of Lewy bodies [22]. These cytoplasmic inclusions are abundant in misfolded α-synuclein, a presynaptic protein whose aggregation is pivotal to the pathophysiology of PD. Consequently, α-synuclein and its PTMs (such as phosphorylated, nitrated, and oligomeric versions) have emerged as primary possibilities in the development of proteomic biomarkers [23]. Table 2 presents a detailed summary of the molecular markers influencing the future of PD diagnosis, monitoring, and treatment, highlighting promising biomarkers for clinical and research purposes. In addition to α-synuclein, proteomic investigations have revealed extensive protein signatures linked to mitochondrial malfunction and synaptic degeneration, both essential to PD pathophysiology [24]. Mitochondrial proteins, including DJ-1 (PARK7), PINK1, and elements of the oxidative phosphorylation pathway, have been recognized as changed in CSF and blood in PD [25, 26].

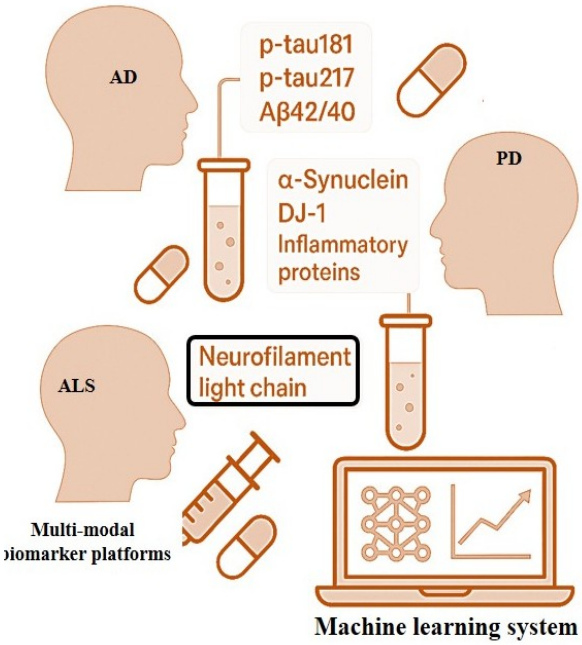

Figure 4. Integrating biomarkers and ML in neurodegenerative disease diagnosis

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Proteomic biomarkers in ALS

ALS is a persistently progressive neurodegenerative disease characterized by the destruction of upper and lower motor neurones, resulting in muscle weakness, paralysis, and ultimately, respiratory failure [27]. Proteomics has become a crucial method in this pursuit, providing dynamic, systems-level insights into the disease. Table 3 presents a detailed summary of the biomarkers essential for ALS diagnosis, progression assessment, and therapy advancement. Given that ALS is a complex disease, integrating many biomarkers from various categories may yield more robust and reliable measures for patient management and therapy approaches [28]. Neurofilament light chain (NFL) has emerged as a sensitive and dependable biomarker for the diagnosis and progression of ALS, with increased levels in both CSF and blood indicating axonal degradation [29]. Proteomic investigations have elucidated the makeup of these aggregates, identifying co-aggregated proteins including RNA-binding proteins, chaperones, and elements of the ubiquitin-proteasome and autophagy systems [30].

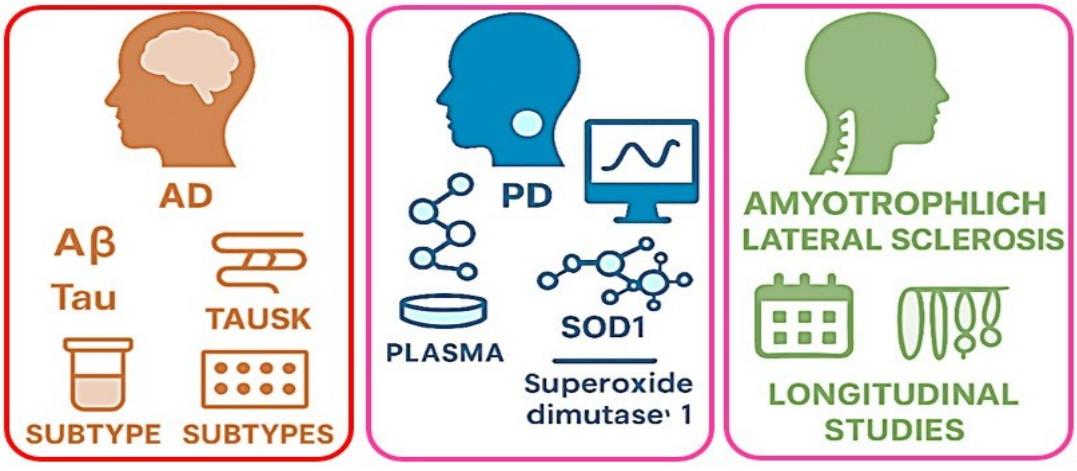

Figure 5. Modern proteomic biomarker research across neurodegenerative diseases: AD, PD, and ALS

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Table 1. Thorough examination of proteomic biomarkers identified in AD according to recent studies

Protein Class	Biomarker	Biological Role/Function	Clinical Relevance	Potential as Biomarker	Ref.
Amyloid proteins	Aβ42 and Aβ40	Form amyloid plaques; implicated in neurotoxic mechanisms	Key proteins indicative of AD pathogenesis, major targets for pharmacological interventions	Extensively utilized in CSF and plasma for the diagnosis of AD and the monitoring of its progression	[55]
	Aβ oligomers	Neurotoxic variants of Aβ; implicated in synaptic impairment	Suggestive of initial amyloid pathology	Prospective biomarker for the early identification and therapeutic monitoring	[56]
Tau proteins	p-tau	Forms neurofibrillary tangles; affects microtubule stability.	Robust correlation with cognitive deterioration and neurodegeneration	Extremely sensitive in CSF for identifying early AD and evaluating progression	[57]
	Total tau	General tau protein levels elevate in response to neuronal damage	Marker of axonal injury associated with cognitive deterioration	Biomarker for illness surveillance and prognostic assessment	[58]
Synaptic proteins	Neurogranin (Ng)	Engaged in synaptic plasticity and signaling	Linked to synapse impairment in the initial stages of AD	Robust association with cognitive decline in early AD	[59]
	Synaptotagmin-1 (Syt1)	Engaged in neurotransmitter secretion and synaptic vesicle amalgamation	Early declines in AD are associated with synapse loss	Prospective biomarker for early diagnosis and assessment of treatment efficacy	[60]
Inflammatory proteins	YKL-40	Chitinase-like protein associated with glial activation and neuroinflammation	Increased levels in CSF and plasma during neuroinflammation in AD	Possible indicator of neuroinflammation and disease advancement	[61]
	CRP	Acute-phase reactant implicated in systemic inflammation	Increased in plasma in AD, indicating systemic inflammation.	Valuable for assessing disease severity and neuroinflammation	[62]
Neurofilament proteins	NfL	Neuronal structural element, indicator of axonal injury	Robust indicator of neurodegeneration, heightened in both AD and other neurodegenerative disorders	Extremely sensitive for monitoring neurodegeneration and disease advancement	[63]
Mitochondrial proteins	Mitochondrial complex I proteins	Crucial function in oxidative phosphorylation and energy synthesis	Mitochondrial malfunction identified in AD, associated with neuronal deterioration	Preliminary evidence of mitochondrial malfunction, prospective therapeutic target	[64]
Chaperones	CLU	Engaged in protein folding and the elimination of misfolded proteins	Contributes to amyloid plaque development and neuroinflammation	Possibility for both early detection and as a therapeutic objective	[65]
Vascular proteins	Endothelin-1 (ET-1)	Modulates vascular constriction and endothelial activity	Associated with compromised blood-brain barrier and cerebrovascular alterations in AD	Possible sign of cerebrovascular impairment in AD	[66]

Abbreviations: AD: Alzheimer's disease; PD: Parkinson's disease; ALS: Amyotrophic lateral sclerosis.

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Comparative proteomics across AD, PD, and ALS

The proteome profiles of AD, PD, and ALS illustrate their unique clinical characteristics and shared molecular abnormalities [31]. Comparative proteome investigations of several neurodegenerative illnesses offer a robust framework for elucidating disease-specific signatures, common pathogenic mechanisms, and the prospects for distinct biomarker development. Although each condition is conventionally characterized by distinct protein aggregates—amyloid-β and tau in AD, α-synuclein in PD, and TDP-43/SOD1/FUS in ALS—emerging data underscores shared proteomic characteristics that contribute to overarching neurodegenerative mechanisms (Figure 3) [32]. Comparative investigations consistently demonstrate a fundamental array of common proteome

Table 2. Proteomic biomarkers reported in PD

Protein Class	Biomarker	Biological Role/ Function	Clinical Relevance	Potential as Biomarker	Ref.
α-Synuclein & aggregates	α-Synuclein (α-Syn)	Engaged in the control of synaptic vesicles, the release of dopamine, and the process of neurodegeneration	Principal protein associated with PD, constituting Lewy bodies within neurones	Biomarker for the diagnosis of PD, monitoring disease progression, and serving as a treatment target	[67]
	Oligomeric α-Syn	Neurotoxic variant of α-synuclein associated with synaptic impairment	Manifesting in the initial phases of PD, it correlates with cognitive deterioration.	Prospective biomarker for early identification and treatment assessment	[68]
Mitochondrial proteins	Parkin	E3 ubiquitin ligase, implicated in mitochondrial quality regulation	Mutations in the Parkin gene result in early-onset PD	Parkin deficiency noted in familial PD, beneficial for genetic and sporadic PD research.	[69]
	DJ-1	Safeguards cells against oxidative stress and modulates mitochondrial activity	Increased in early PD, linked to neuroprotection and oxidative stress	Promising biomarker for the early detection and monitoring of neurodegeneration	[70]
Neuroinflammatory markers	YKL-40	Chitinase-like protein associated with neuroinflammation and glial activation	Increased levels in CSF and plasma in PD, correlated with neuroinflammation	Possible indicator of glial activation and disease advancement	[71]
	CRP	Acute-phase reactant, associated with systemic inflammation	Elevated CRP levels indicate systemic and neuroinflammation in PD	Utilized for the surveillance of inflammation-associated PD advancement	[71]
Neurofilament proteins	NfL	Structural protein, a sensitive marker of axonal injury	Increased levels in CSF and blood, signifying neuronal injury and neurodegeneration	Extensively utilised to assess disease advancement and evaluate treatment efficacy	[72]
Synaptic proteins	Synaptotagmin-1 (Syt1)	Engaged in neurotransmitter secretion and synaptic vesicle amalgamation	Reduction in PD indicates synaptic impairment and neurodegeneration	Possible early biomarker for cognitive and motor impairment in PD	[73]
	VAMP2 (Synaptobrevin-2)	An essential vesicular protein implicated in the fusion of synaptic vesicles	Impaired vesicular release and dopaminergic signaling in PD	Beneficial for assessing dopaminergic activity and synaptic impairment	[74]
Cytoskeletal proteins	TUBB3 (β-III Tubulin)	Element of microtubules, crucial to cytoskeletal architecture and neuronal activity	Modified expression in PD, associated with axonal degradation and neuronal loss	Biomarker for neuronal injury and structural alterations in PD pathogenesis	[75]
Chaperone proteins	HSP70	Engaged in protein folding, stabilization, and degradation	Defensive function against misfolded proteins in PD, linked to cellular stress	Prospective therapeutic target for mitigating neurodegeneration in PD	[76]
Vascular proteins	Endothelin-1 (ET-1)	Modulates vasoconstriction and the integrity of the blood-brain barrier	Elevated ET-1 levels in PD, associated with cerebrovascular impairment	Marker of vascular alterations and cerebrovascular well-being in PD	[66]
Lipid metabolism	Ceramides	Engaged in lipid signaling, apoptosis, and cellular membrane architecture	Modified lipid metabolism identified in PD, associated with neurodegeneration	Possible biomarker for early-stage PD, specifically with lipid dysregulation.	[77]
Proteasomal proteins	Ubiquitin-proteasome system components	Decomposes misfolded or damaged proteins, sustains cellular homeostasis	Impairment in PD contributes to protein aggregation and the formation of Lewy bodies	Beneficial for assessing cellular stress and proteostasis failure associated with PD	[78]

Abbreviations: AD: Alzheimer's disease; PD: Parkinson's disease; ALS: Amyotrophic lateral sclerosis.

Table 3. Proteomic biomarkers reported in ALS

Protein Class	Biomarker	Biological Role/ Function	Clinical Relevance	Potential as Biomarker	Ref.
Neurofilament proteins	NfL	Structural protein; marker of axonal injury and neurodegeneration	Increased levels in CSF, plasma, and serum; significantly correlated with the course of ALS	Commonly employed for diagnosing ALS, tracking disease progression, and assessing therapy outcomes	[79]
	NfH	Component of the neurofilament network; indicative of axonal damage	Increased levels are associated with disease severity and the loss of motor neurones	Utilized in both the diagnostic and longitudinal assessment of ALS development.	[80]
Motor neuron markers	TDP-43	DNA/RNA-binding protein; participates in RNA processing and stability	Mislocalized in ALS, it forms cytoplasmic clumps in afflicted motor neurones.	Principal pathology characteristic of ALS; prospective diagnostic and prognostic biomarker	[81]
	FUS	RNA-binding protein implicated in mRNA splicing and control	Mutations linked to familial ALS; protein aggregation in impacted neurones	Principal indicator for familial ALS; may assist in distinguishing disease subtypes	[82]
Mitochondrial proteins	SOD1	Enzyme that facilitates the transformation of superoxide radicals into hydrogen peroxide	Mutations in SOD1 result in familial ALS, compromising oxidative stress response and mitochondrial function.	Promising therapeutic target and diagnostic biomarker for familial ALS	[83]
	Mfn2	Regulates mitochondrial fusion, essential for preserving mitochondrial integrity.	Modified in ALS, associated with mitochondrial impairment and neurodegeneration	Possible biomarker for mitochondrial dysfunction in ALS pathogenesis	[84]
Chaperone proteins	HSP70	Engaged in protein folding, stabilization, and degradation.	Increased in ALS patients; function in safeguarding cells against stress-related injury	Marker of cellular distress and possible target for therapeutic intervention	[76]
Cytoskeletal proteins	Vimentin	Intermediate filament responsible for preserving cellular morphology and stability	Increased in ALS; linked to glial activation and neuroinflammation.	Valuable for assessing glial participation and neuroinflammation in ALS	[85]
Inflammatory markers	YKL-40	Chitinase-like protein implicated in inflammation and glial activation	Increased levels in CSF and plasma in ALS patients; correlated with disease severity.	Possible indicator of neuroinflammation and disease advancement	[86]
	CRP	Acute-phase reactant, associated with systemic inflammation	Elevated CRP levels associated with systemic inflammation and the progression of ALS	Utilized for assessing inflammation and the severity of disease	[87]
Ubiquitin-proteasome system	Ubiquitin	Labelling protein for proteasomal breakdown	Compromised proteasomal function in ALS, leading to protein aggregation	Increased ubiquitin levels in ALS are associated with proteostasis disruption and neurodegeneration	[88]
Vascular proteins	Endothelin-1 (ET-1)	Modulate vascular constriction and endothelial activity	Elevated ET-1 levels are associated with vascular impairment in ALS.	Prospective biomarker for cerebrovascular impairment and the advancement of ALS	[66]
Exosome proteins	Exosomal TDP-43	Discharged from neurones and glial cells, implicated in protein aggregation	The presence of TDP-43 in exosomes corresponds with the severity of ALS	Non-invasive biomarker for assessing disease progression	[89]
Lipid metabolism	Ceramides	Engaged in cellular signaling, programmed cell death, and membrane stability	Dysregulated lipid metabolism in ALS, associated with neurodegeneration	Possible early biomarker for ALS, specifically in lipid dysregulation and cellular apoptosis pathways	[90]

Abbreviations: AD: Alzheimer's disease; PD: Parkinson's disease; ALS: Amyotrophic lateral sclerosis.

Table 4. Summary of proteomic biomarkers by validation stage

Stage	Biomarker	Associated Disease(s)	Specimen Source	Validation Evidence	Clinical Relevance
Clinical readiness	NfL	AD, PD, and ALS	CSF and plasma	Validated in large multi-center cohorts	Established indicator of neurodegeneration and disease advancement
Clinical readiness	Phosphorylated tau (p-tau181, and p-tau217)	AD	CSF and plasma	Multiple longitudinal studies	Diagnostic and prognostic value in AD
Validation phase	α-synuclein (total/oligomeric)	PD	CSF and plasma	Moderate cohort studies	Promising diagnostic biomarker; standardization of the assay is required
Validation phase	TDP-43	ALS	CSF and brain tissue	Limited cohort validation	Prospective diagnostic and pathogenic biomarker
Discovery phase	Neurogranin and SNAP-25	AD and PD	CSF and brain tissue	Exploratory proteomic analyses	Indicate synaptic dysfunction; necessitate extensive validation
Discovery phase	Complement proteins (C1q, C3, and C4)	AD and ALS	Plasma and CSF	Small-sample studies	Neuroinflammation indicators; translational phase awaiting

Abbreviations: AD: Alzheimer's disease; PD: Parkinson's disease; ALS: Amyotrophic lateral sclerosis.

changes associated with neuronal damage, glial activation, and metabolic dysfunction. NfL, an indicator of axonal injury, is raised in AD, PD, and ALS, and correlates with the severity and course of each condition [33]. Markers of neuroinflammation, including YKL-40, TREM2, and complement proteins (e.g. C1q, C3), are present in the CSF and plasma proteomes of all three illnesses, indicating a shared inflammatory environment [20]. Neuroinflammation, indicated by elevated proteomic levels of microglial and astrocytic markers (e.g. GFAP, CHI3L1, and complement factors), is another unifying theme [34]. Persistent stimulation of innate immune responses leads to brain injury and the progression of neurodegenerative diseases. Synaptic dysfunction and loss are prevalent in AD, PD, and ALS, as demonstrated by reduced levels of synaptic vesicle proteins (SNAP-25, and synaptophysin), postsynaptic scaffolding proteins (PSD-95, and neurogranin), and neurotransmitter regulators [35].

Bioinformatics and systems biology approaches

With the increasing volume and complexity of proteomic data in neurodegenerative illnesses, bioinformatics and systems biology have become essential for converting raw data into significant biological and clinical insights [36]. These computational methodologies facilitate the amalgamation of multi-omics data, elucidate intricate molecular connections, and prioritize the most pertinent biomarkers for diagnosis, prognosis, and therapeutic intervention. In the realm of AD, PD, and ALS, such instruments are crucial for elucidating the molecular heterogeneity and intersecting pathophysiology of these disorders [31]. Protein-protein interaction (PPI) networks, developed utilizing databases, such as STRING or BioGRID, can pinpoint critical regulatory nodes or subnetworks enriched in synaptic, inflammatory, or mitochondrial pathways throughout AD, PD, and ALS [37]. System-level techniques, including weighted gene co-expression network analysis (WGCNA), categorize proteins into modules according to associated expression patterns and associate them with clinical features or disease phases [37]. Simultaneously, ML techniques are progressively employed for biomarker identification and categorization. Advanced methodologies, including integrated multi-omics ML models (e.g. employing autoencoders or ensemble classifiers), have demonstrated potential in forecasting the progression from mild cognitive impairment to AD, as well as in stratifying PD subtypes based on proteomic profiles [37].

Proteomic databases: Resources, like PRIDE (Proteomics Identifications Database), PeptideAtlas, and CPTAC provide repositories for both raw and processed proteomic data [38]. These enable meta-analyses and cross-validation of biomarker candidates.

Neuro-specific tools: Platforms, such as NeuroMMSig and Harmonizome amalgamate multi-omics data concentrated on neurological disorders, whereas AlzData and Agora offer access to AD-specific molecular datasets, encompassing proteomics, transcriptomics, and genetic information [39].

Pathway and network analysis tools: Instruments, like Cytoscape, Database for Annotation, Visualization, and Integrated Discovery (DAVID), Gene Set Enrichment Analysis (GSEA), and Ingenuity Pathway Analysis (IPA) facilitate the visualization and enrichment analysis of protein networks and pathways [40]. Platforms, such as iLINCS, OmicsNet, and NetworkAnalyst are extensively utilized for the integration of genomic and transcriptomic data [41].

ML and AI frameworks: Software libraries, like scikit-learn, TensorFlow, and AutoML frameworks facilitate ML applications in proteomics, encompassing feature selection and disease prediction [42]. Integrating proteomics within a systems biology paradigm enables researchers to progress from isolated protein indicators to comprehensive signatures that embody the dynamic and interrelated characteristics of neurodegeneration [36].

Clinical translation and diagnostic applications: The primary objective of proteomic biomarker discovery in AD, PD, and ALS is to facilitate early and precise diagnosis while informing personalized treatment approaches (Figure 4). Although many potential biomarkers have been identified by high-throughput proteome analysis, their progression from laboratory to clinical use is a complicated, multi-phase process [43]. This process entails stringent validation, regulatory endorsement, and strategic incorporation into clinical practice, frequently as components of companion diagnostic systems.

Validation and standardization of biomarkers: Prior to the application of a proteomic biomarker in clinical environments, it must complete a multi-phase validation (like analytical, clinical, and standardization) process to guarantee accuracy, repeatability, and clinical significance [44].

Regulatory considerations and clinical trials: The regulatory framework for biomarker approval is overseen by authorities, such as the Food and Drug Administration (FDA) (United States), European Medicines Agency (EMA) (Europe), and Pharmaceuticals and Medical Devices Agency (PMDA) (Japan), each imposing rigorous standards for diagnostic and prognostic instruments [45]. Proteomic biomarkers must exhibit clinical value, signifying that they provide actionable insights that impact patient care or therapy choices.

Companion diagnostics and personalized therapy: The advancement of precision medicine in neurology depends on the capacity to align patients with treatments according to their molecular profiles. Proteomic biomarkers are pivotal to this initiative, serving as companion diagnostics that forecast therapy response, track disease progression, and detect adverse effects (Figure 5). In AD, CSF and plasma levels of p-tau181, p-tau217, and Aβ42/40 ratios are increasingly utilized to identify individuals with underlying amyloid pathology—those most likely to benefit from anti-amyloid medications, such as aducanumab or lecanemab [46]. These markers are set to become essential for commencing such treatments, thereby synchronizing diagnostics with therapeutic decision-making. In PD, initiatives are under progress to establish biomarkers that forecast responses to dopaminergic treatments, or mitochondrial-targeted medicines [47].

Current research landscape on proteomic biomarkers in AD, PD and ALS

Recent improvements in proteomics have resulted in substantial gains in the identification and characterization of biomarkers linked to AD [21]. Research has progressed beyond traditional markers, like Aβ and tau to identify new candidates. A thorough proteome investigation combining Aβ and tau imaging with CSF proteomics discovered 127 differentially abundant proteins throughout the AD spectrum, with glial-associated proteins, such as SMOC1 and ITGAM identified as significant predictors of Aβ pathology [48]. Simultaneously, analyses of blood-based proteomic biomarkers highlight the growing efficacy of plasma Aβ and phosphorylated tau as less invasive instruments for early identification. CSF-based research has identified five molecular subtypes of AD: Hyperplasticity, innate immune activation, blood-brain barrier dysfunction, RNA dysregulation, and choroid plexus dysfunction, each associated with distinct genetic profiles, highlighting the complexity of AD pathogenesis [49].

Challenges and future perspectives

Technical and biological obstacles

Technical obstacles continue to pose a significant impediment to the regular clinical application of proteomic biomarkers. High-throughput platforms, such as MS have exceptional sensitivity and specificity; yet, they are deficient in standardization for sample preparation, instrument calibration, and data analysis protocols. Interlaboratory variability and restricted repeatability hinder cross-study comparisons [50]. Biological problems arise from the intrinsic complexity and variability of neurodegenerative disorders. The proteomic profile may differ markedly based on disease stage, comorbidities, and

genetic predisposition [51]. Proteins of interest may undergo degradation, modification, or masking, affecting their detection and interpretation. As biomarker testing becomes more accessible, ethical considerations are increasingly salient.

Progress in single-cell and spatial proteomics

Recent advancements in single-cell and spatial proteomics are set to transform our comprehension of neurodegeneration with unparalleled precision. Single-cell proteomics facilitates the quantification of protein expression in individual cells, circumventing the averaging effects inherent in bulk tissue analysis [52]. This is especially significant in neurodegenerative illnesses, because pathology is frequently unique to cell types and spatially confined. Single-cell investigations can reveal distinct protein signatures in neurones, astrocytes, microglia, and oligodendrocytes across different disease phases. Spatial proteomics holds significant potential for elucidating disease propagation pathways and investigating neuroimmune interactions, including microglial responses next to degenerating neurons [52]. Collectively, these approaches will improve biomarker specificity and contextual significance, facilitating more precise disease modelling and therapeutic target validation.

AI-assisted interpretation

Artificial intelligence (AI) and ML algorithms will assume a progressively significant role in analyzing intricate proteome datasets, discerning nuanced patterns, and forecasting specific disease trajectories [53]. Nonetheless, meticulous consideration must be given to the transparency, reproducibility, and therapeutic application of these models. Despite considerable obstacles, the domain of proteomic biomarker research in neurodegenerative illnesses is progressing swiftly. With technical enhancement, advanced biological comprehension, and ethical consideration, proteomics is poised to become fundamental to next-generation neurology—providing earlier detection, more precise diagnoses, and genuinely personalized treatment approaches for patients with AD, PD, ALS, and associated disorders [54]. This evaluation ranks proteomic biomarkers based on their validation status, offering a translational roadmap that connects discovery research with clinical use (Table 4). This paradigm emphasizes the advancements made in developing reliable biomarkers like NfL and p-tau217, as well as the urgent necessity to propel emergent candidates through standardized validation processes.

Conclusion

This paper presents a comparative and translational proteomics paradigm for AD, PD, and ALS, emphasizing shared patterns of protein dysregulation and delineating the practical obstacles in converting biomarker candidates into clinically reliable tools. This comprehensive viewpoint enhances our comprehension of neurodegenerative pathomechanisms and offers a framework for future initiatives to connect discovery with treatment implementation. Progress in high-resolution mass spectrometry, bioinformatics, and multi-omics integration has revealed numerous potential biomarkers in brain tissues, encompassing traditional markers, such as Aβ and tau in AD, as well as novel candidates in synaptic, inflammatory, and mitochondrial pathways in PD and ALS. The shift to stage-specific, longitudinal, and multi-biomarker profiles is essential for accurately reflecting the dynamic biology of neurodegeneration. Nonetheless, obstacles persist, encompassing technological unpredictability, biological intricacy, and ethical considerations surrounding early diagnosis. The advent of single-cell and spatial proteomics, alongside ML and systems biology methodologies, is expanding the limits of possibility, providing cell-type resolution, anatomical accuracy, and predictive capability. The successful clinical implementation of proteomic biomarkers will depend on rigorous validation, equitable accessibility, regulatory compliance, and incorporation into personalized medicine frameworks. The collaboration between proteomics and novel therapeutic approaches offers the potential for early intervention and a change from reactive care to proactive neuroprotection.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results, and manuscript drafting. Each author approved the submission of the final version of the manuscript.

Conflict of interest

The authors declared no conflict of interests.

Acknowledgements

All authors thank the SIMATS, Chennai, India, for the constant support.

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