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REVIEW ARTICLE

Review of Biomarkers for Neurodegenerative Diseases: Progress and Challenges

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ABSTRACT

An increasing worldwide health burden is a result of the enormous obstacles associated with diagnosing, treating, and managing neurodegenerative disorders. Important indicators of abnormal processes in the central nervous system, biomarkers have become more promising for tracking the effectiveness of treatment, enabling early diagnosis, and comprehending the course of disease. The present state of biomarkers in neurodegenerative illnesses is thoroughly assessed in this study, with an emphasis on developments, constraints, and potential future applications. We examine in detail the contributions and difficulties of five important groups of biomarkers: biochemical, imaging, genetic, inflammatory, and clinical. These include disorders like amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's disease. Protein aggregates (Aβ42, tau, α-synuclein), metabolites, and neurofilament light chain (NfL) are examples of biochemical biomarkers that provide information on pathophysiological changes unique to a particular illness. Early diagnosis and illness monitoring are facilitated by the visualisation of structural and molecular changes made possible by imaging biomarkers such as PET, MRI, and SPECT. Genetic biomarkers provide insight into illness risk and family aggregation, ranging from uncommon mutations to common variations. Neuroinflammatory processes are reflected in inflammatory biomarkers such chemokines and cytokines, which suggests a role for these processes in the development of illness. Clinical biomarkers include behavioural, motor, and cognitive tests that help characterise and monitor illness. Their clinical translation is hampered, meanwhile, by issues with standardisation, specificity, and variability. The urgent need for coordinated efforts to validate and create reliable biomarker panels for precise neurodegenerative disease diagnosis, prognosis, and targeted treatment interventions is emphasised by this study.

Keywords: *Biomarkers, Neurodegenerative diseases, Diagnosis, Imaging, Treatment*

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INTRODUCTION

A class of crippling illnesses known as neurodegenerative diseases, which are marked by the gradual malfunction and death of neurons, pose an ever-greater threat to the world's healthcare systems. A considerable burden is placed on carers and society at large by these diseases, which relentlessly impair cognitive, motor, and sensory functions. These conditions include Huntington's disease (HD), Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and others [1].

The slow but unabated loss of certain groups of neurons in the central nervous system (CNS) is the defining characteristic of neurodegenerative disorders. While the build-up of tau neurofibrillary tangles and amyloid-beta (Aβ) plaques causes cognitive decline and memory impairment in AD, the death of dopaminergic neurons in the substantia nigra causes motor dysfunction and tremors in PD [2][3].

The complex biology of neurodegenerative illnesses and the absence of reliable early diagnostic techniques represent one of the biggest management problems. When symptoms become evident and permanent brain damage has occurred, the diagnosis is frequently made. As a result, there is a pressing need for sensitive and trustworthy diagnostic instruments that can identify these illnesses in their early stages and enable prompt therapies that may be able to stop the disease from progressing [4].

The search for these diagnostic instruments has recently focused on biomarkers, which are quantifiable markers of pathological processes, normal biological processes, or reactions to an exposure or

intervention [5]. Biomarkers have the ability to shed light on the pathophysiology of disease, support early diagnosis, track the course of the illness, evaluate the effectiveness of treatment, and maybe even help with the creation of personalised medicine strategies.

In the context of neurodegenerative disorders, a number of biomarker classes have been the subject of extensive inquiry; these classes each provide distinct insights into the processes and course of the diseases. Aβ42, tau, α-synuclein, and neurofilament light chain (NfL) are examples of biochemical biomarkers that have demonstrated potential in AD, PD, and ALS because they represent the pathological alterations in protein aggregation, neuronal damage, and axonal degeneration [6][7].

Thanks to developments in imaging technologies, such as single-photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance imaging (MRI), scientists can now see structural, functional, and molecular changes in the central nervous system. When paired with volumetric MRI, amyloid and tau PET tracers have shown to be useful instruments for studying AD pathology and disease progression [8][9].

Mutations and polymorphisms are examples of genetic biomarkers that greatly influence phenotypic variability and disease vulnerability. For example, mutations in the genes APP, PSEN1, and PSEN2 are linked to familial types of AD, providing insight into the genetic basis of the illness [10].

Furthermore, there has been an increase in interest in inflammatory biomarkers, which represent the neuroinflammatory processes in neurodegenerative illnesses. Neuroinflammation plays a critical role in the course of AD, PD, and ALS, as evidenced by changes in cytokines, chemokines, and microglial activation markers [11].

Neurodegenerative disease diagnosis and monitoring also heavily depends on clinical indicators, such as motor, behavioural, and cognitive tests. Evaluation of cognitive impairment and disease development in AD is aided by standardised tests such as the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) [12][13].

Even with the encouraging advances in biomarker research, there are still major obstacles to overcome. Widespread clinical application of biomarkers is hampered by individual variation in biomarker levels, lack of specificity for some disorders, and requirement for standardisation across populations and laboratories [14].

Aiming to critically assess the current state of biomarkers for neurodegenerative diseases in light of these complications, this review will cover the biomarkers' advances, drawbacks, and the urgent need for coordinated efforts to validate and establish trustworthy biomarker panels for efficient disease management and therapeutic interventions. This study aims to shed light on the advancements and difficulties faced in the use of biomarkers as vital instruments in the battle against neurodegenerative illnesses through a thorough examination.

Section 1: Biochemical Biomarkers in Neurodegenerative Diseases

The potential for biochemical indicators to provide light on the pathophysiological mechanisms behind neurodegenerative illnesses is enormous. These biomarkers provide insight into the complex alterations taking place inside the central nervous system (CNS) as a disease progresses. They include a broad range of molecules, such as proteins, metabolites, and other molecular entities [1].

The biochemical indicators linked to neuronal injury and protein aggregation have been researched the most. Two important clinical hallmarks of Alzheimer's disease (AD) are the intracellular buildup of hyperphosphorylated tau protein and the development of amyloid-beta (Aβ) plaques [2]. These proteins have become important biochemical indicators for AD diagnosis and follow-up, especially Aβ42 and different types of tau (phosphorylated tau, total tau) [3].

Aβ42 levels in AD patients' blood and cerebrospinal fluid (CSF) have often been shown to be different from those in healthy controls [4]. Moreover, elevated levels of both the total and phosphorylated tau proteins are correlated with the severity and development of the illness and are suggestive of neuronal damage [5]. When combined, these indicators show improved predictive value and diagnostic accuracy, helping to differentiate AD from other types of dementia and monitor the course of the illness [6].

Parkinson's disease (PD) is typified by the degeneration of dopaminergic neurons in the substantia nigra. Certain molecular indicators, specifically α-synuclein, are also linked to PD. Aggregation of α-synuclein into Lewy bodies is a pathogenic feature of Parkinson's disease [7]. Increased concentrations of α-synuclein species, particularly in oligomeric forms, have been seen in CSF samples from individuals with Parkinson's disease (PD), indicating potential as a biomarker for early PD diagnosis and tracking the disease's development [8].

Furthermore, axonal damage and neuronal degeneration have been linked to neurofilament light chain (NfL), a structural protein that is widely expressed in neurons, in a number of neurodegenerative

illnesses, including AD, PD, and amyotrophic lateral sclerosis (ALS) [9]. Research has repeatedly shown that individuals with neurodegenerative illnesses have higher levels of NfL in their blood and CSF, which is indicative of axonal damage and disease severity [10].

Beyond protein-based indicators, biochemical biomarkers are being investigated. Analysing the metabolites in biological samples, or "metabolomic profiling," provides a thorough understanding of the metabolic changes that occur in neurodegenerative disorders. Alzheimer's disease, Parkinson's disease, and other neurodegenerative diseases have been linked to changes in metabolites related to energy metabolism, lipid homeostasis, and neurotransmitter pathways [11]. For example, disturbances in the metabolism of fats, specifically changes in the amounts of ceramide and sphingomyelin, have been noted in AD, suggesting their involvement in the degeneration of neurons [12].

Biochemical biomarkers have enormous promise, but a number of obstacles stand in the way of their clinical use and general acceptance. Individual differences in biomarker levels and the absence of standard operating procedures for sample collection, processing, and analysis lead to inconsistent results that compromise the reliability of biomarkers [13]. Furthermore, the specificity of certain biomarkers is also a source of worry since changes in certain proteins can be seen in a variety of neurodegenerative diseases, which reduces the diagnostic precision of these biomarkers [14].

Moreover, a major area of ongoing study is the hunt for less intrusive techniques for detecting biomarkers in readily accessible bodily fluids like blood or saliva. This endeavour seeks to address the drawbacks of invasive CSF collection and streamline routine clinical use [15].

Section 2: Imaging Biomarkers in Neurodegenerative Diseases

Because imaging methods make it possible to see structural, functional, and molecular alterations inside the central nervous system (CNS), they have revolutionised our understanding of and ability to diagnose neurodegenerative illnesses. Among the primary modalities used to detect and track disease-related changes in the brain are single-photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance imaging (MRI) [1].

Using molecular imaging techniques like PET, one may visualise the typical brain alterations caused by the buildup of tau and amyloid-beta (Aβ) clumps in Alzheimer's disease (AD). By binding to Aβ plaques, amyloid PET tracers such as florbetaben, flutemetamol, and florbetapir enable the in vivo assessment of amyloid load in AD patients [2]. Similarly, pathogenic tau aggregates are the focus of tau PET tracers like AV-1451, also called flortaucipir, which help to visualise tau deposition and monitor the course of the illness [3].

Moreover, structural MRI is essential for evaluating changes in regional volumes and brain atrophy, which sheds light on neurodegeneration linked to illness. Volumetric analyses, in particular assessments of cortical and hippocampus thickness, function as imaging biomarkers in AD, exhibiting associations with the severity of the illness and cognitive impairment [4]. Furthermore, research on functional MRI (fMRI) clarifies changes in brain connectivity and malfunctioning of neural networks in neurodegenerative illnesses, providing important understanding of the underlying processes of these diseases [5].

The hallmark motor symptoms of Parkinson's disease (PD) are caused by a loss of dopaminergic neurons in the substantia nigra. Presynaptic dopamine function may be visualised and quantified by dopamine transporter (DAT) imaging utilising SPECT or PET tracers, such as ^123I-FP-CIT and ^18F-FDOPA. This technique helps with the differential diagnosis of parkinsonian disorders and helps track the evolution of the illness [6].

Additionally, methods for molecular imaging that target aggregates of alpha-synuclein similar to those found in Lewy bodies are being developed and have the potential to increase the specificity and accuracy of PD diagnosis [7]. The early diagnosis and tracking of Parkinson's disease development would be revolutionised by the capacity to identify these abnormal protein aggregates in vivo.

Imaging biomarkers are essential for understanding the pathophysiology of several neurodegenerative illnesses, not just Alzheimer's and Parkinson's disease. For example, diffusion tensor imaging (DTI) and functional magnetic resonance imaging (MRI) help to explain white matter abnormalities and dysfunction of the motor network in ALS, offering information on the course and prognosis of the illness [8].

Imaging biomarkers are not yet widely used in clinical practice, despite tremendous progress. Significant obstacles include interpretational uncertainty, limited accessibility to modern imaging equipment, and cost limits. Furthermore, it is still difficult to standardise imaging techniques and interpretation standards among various platforms and centres, which has an effect on the repeatability and dependability of imaging results [9].

Furthermore, problems with imaging biomarkers' specificity and capacity to differentiate between various neurodegenerative illnesses that could have similar imaging characteristics must be resolved for the practical translation of these biomarkers. It may be possible to increase diagnostic precision and clarify disease-specific patterns by using multimodal imaging strategies and integrating several imaging modalities [10].

Section 3: Genetic Biomarkers in Neurodegenerative Diseases

The pathophysiology and course of a number of neurodegenerative illnesses are significantly influenced by genetic variables, which also provide information on disease susceptibility, phenotypic diversity, and family aggregation. The likelihood and development of various illnesses are greatly increased by mutations, polymorphisms, and changes in certain genes [1].

A tiny proportion of Alzheimer's disease (AD) patients are linked to uncommon autosomal dominant mutations in genes such presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid precursor protein (APP). These mutations contribute to early-onset familial types of AD by directly influencing amyloid processing and increasing the synthesis of amyloid-beta peptides [2]. Nonetheless, the great majority of AD cases are thought to be sporadic, and the vulnerability to the illness is influenced by a complex interaction between genetic and environmental variables [3].

Common genetic variations have been found to be risk factors for late-onset AD, in addition to uncommon family instances. The biggest genetic risk factor for late-onset AD is variations in the apolipoprotein E (APOE) gene, namely the ε4 allele [4]. The APOE ε4 variant carries a higher risk and an earlier age of onset, which can affect the severity and course of the illness [5].

Similarly, phenotypic diversity and illness risk in Parkinson's disease (PD) are greatly influenced by hereditary variables. Alpha-synuclein aggregation, mitochondrial dysfunction, and protein degradation pathways have all been linked to family forms of Parkinson's disease (PD) through mutations in genes such SNCA (encoding alpha-synuclein), LRRK2, PARKIN, and PINK1 [6][7].

Furthermore, common genetic variations linked to illness vulnerability have been found through genetic investigations on Parkinson's disease. Changes in the GBA gene, which codes for the lysosomal enzyme glucocerebrosidase, are a significant risk factor for instances of Parkinson's disease (PD) that occur sporadically as well as in families [8]. The confluence of molecular processes and genetic pathways behind the pathophysiology of Parkinson's disease is clarified by these genetic discoveries.

Moreover, mutations in genes including SOD1, C9orf72, TARDBP, and FUS contribute to familial and sporadic types of amyotrophic lateral sclerosis (ALS), demonstrating genetic variability [9]. These genes' mutations impair cellular processes related to protein aggregation, oxidative stress, and RNA processing, which exacerbates the motor neuron degeneration seen in ALS [10].

Although genetic biomarkers provide important information on the genesis and susceptibility of diseases, their practical application in forecasting the start and course of diseases is still lacking. Due to the multifaceted character of neurodegenerative illnesses and their inadequate penetrance, genetic markers have little prognostic utility, particularly in sporadic instances [11].

Genetic testing for mutations linked to illness also presents ethical, counselling, and privacy issues that should be carefully considered in clinical practice. Informed consent and genetic counselling are essential for educating people and families about the meaning of the results of genetic testing, especially when there is family aggregation [12].

However, genetic indicators have the potential to help identify high-risk groups for clinical trials, help at-risk individuals receive early treatments, and enable individualised approaches to treatment and illness management. Next-generation sequencing technology and genome-wide association studies (GWAS) are driving research into targeted therapeutics and precision medicine methods by revealing new genetic variations linked to neurodegenerative illnesses [13].

Section 4: Inflammatory Biomarkers in Neurodegenerative Diseases

Due to the intricate interaction of cellular and molecular processes driving neuronal dysfunction and degeneration, inflammation plays a critical role in the development and progression of a number of neurodegenerative disorders [1]. Inflammatory biomarkers offer information on immunological dysregulation in the central nervous system (CNS) linked to dementia. These biomarkers include chemokines, cytokines, and indicators of microglial activation.

Neuroinflammation is a common characteristic of Alzheimer's disease (AD), which is accompanied by the build-up of neurofibrillary tangles and amyloid-beta (Aβ) plaques. The neuroinflammatory milieu in AD is influenced by dysregulated microglial activation and the production of pro-inflammatory cytokines such interleukin-1β (IL-1β), tumour necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) [2]. These

cytokines have been found to be elevated in the brains, peripheral blood, and cerebrospinal fluid (CSF) of AD patients, and their levels are correlated with the severity of the illness and cognitive loss [3].
Similar to this, neuroinflammation and microglial activation are important aspects of the pathophysiology of Parkinson's disease (PD). Dopaminergic neuron degeneration in the substantia nigra is a result of dysregulated immunological responses and the production of inflammatory mediators such as TNF-α, interleukin-1 (IL-1), and interferon-gamma (IFN-γ) [4]. Neuroinflammation has been linked to the course of Parkinson's disease (PD) as evidenced by the increased levels of these inflammatory markers seen in the brains and CSF of these individuals [5].
Furthermore, motor neuron degeneration in amyotrophic lateral sclerosis (ALS) is facilitated by a persistent inflammatory response in the central nervous system. The CSF and peripheral blood of ALS patients have been found to contain altered levels of cytokines and chemokines, including interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-1α (MIP-1α), suggesting the involvement of inflammatory processes in the pathophysiology of the disease [6].
There is still much to learn about the reciprocal link between neuroinflammation and neurodegeneration. Although inflammation may initially act as a defence mechanism against insults to the neurons, persistent and dysregulated inflammation can worsen damage to the neurons and accelerate the course of the illness [7].
Furthermore, there is growing evidence that peripheral immunological dysregulation plays a role in neurodegenerative disorders. Peripheral immune cells enter the central nervous system (CNS) as a result of disruption of the blood-brain barrier and systemic immune activation, which exacerbates neuroinflammatory responses [8].
However, because inflammatory processes are dynamic and varied, it might be difficult to interpret the results of inflammatory biomarkers in neurodegenerative illnesses. Biomarker levels vary across people, between disease stages, and between disease subtypes, which complicates the clinical relevance and interpretation of these markers [9].
Furthermore, the specificity of inflammatory biomarkers for specific neurodegenerative disorders is also a matter of concern, despite the fact that they provide insights into disease processes. Their diagnostic utility is limited by the overlap of inflammatory profiles and shared inflammatory pathways among many illnesses [10].
Notwithstanding these obstacles, addressing neuroinflammation is a potentially effective treatment approach for neurodegenerative illnesses. Potential options for altering illness include the exploration of anti-inflammatory therapy and immunomodulatory medicines that attempt to modulate inflammatory responses [11]. Research on inflammatory pathways, such as TNF-α suppression or microglial modulation, has shown promise in preclinical and clinical settings for modifying the course of illness and enhancing therapeutic outcomes [12].
To sum up, inflammatory biomarkers in neurodegenerative illnesses offer important new understandings of the dysregulated immune responses in the central nervous system that affect the aetiology and course of the disease. But in order to fully use their potential for diagnostic, prognostic, and therapeutic reasons, more research efforts are required to address issues with variability, specificity, and interpretation difficulty. A potential treatment approach that offers hope for altering the course of neurodegenerative diseases involves targeting neuroinflammatory pathways.

Section 5: Clinical Biomarkers in Neurodegenerative Diseases

Clinical biomarkers in neurodegenerative illnesses comprise a range of measures that are employed in diagnosis, tracking the course of the disease, and analysing the effectiveness of treatment. These biomarkers mainly comprise behavioural, motor, and cognitive evaluations, which help with the clinical characterisation of different neurodegenerative diseases [1].
Cognitive tests are essential clinical indicators for Alzheimer's disease (AD) diagnosis and disease progression tracking. Two commonly used standardised tests that evaluate several cognitive domains, such as memory, attention, language, and executive function, are the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) [2]. These evaluations help distinguish between pathological cognitive impairment and normal ageing by offering a quantifiable measure of cognitive decline.
Furthermore, memory, language, and orientation are assessed using neuropsychological tests that concentrate on certain cognitive domains, such as the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), which provides comprehensive cognitive profiles in AD patients [3]. These examinations support monitoring the course of the illness and evaluating the effectiveness of proposed treatments.

Clinical biomarkers for Parkinson's disease (PD) mostly focus on motor evaluations, taking into account the cardinal motor symptoms, which include bradykinesia, tremors, stiffness, and postural instability [4]. To evaluate motor function and impairment in individuals with Parkinson's disease (PD), the Unified Parkinson's Disease Rating Scale (UPDRS) and its revised version, the Movement Disorder Society-sponsored revision of the UPDRS (MDS-UPDRS), are commonly used [5]. These tests offer a consistent framework for assessing the onset of motor symptoms and how they develop over time.

Clinical biomarkers in Parkinson's disease (PD) also include evaluations of non-motor symptoms such as mood disorders, autonomic dysfunction, and cognitive impairment. Characterising non-motor symptoms and their effect on patients' quality of life is made easier by measures like the Beck Depression Inventory (BDI) and the Non-Motor Symptoms Scale (NMSS) [6].

Clinical biomarkers for amyotrophic lateral sclerosis (ALS) mainly assess motor function and disease progression. A number of daily functional domains are evaluated by the revised ALS Functional Rating Scale (ALSFRS-R), including bulbar, limb, and respiratory function [7]. This scale helps monitor functional deterioration in people with ALS and offers a standard measurement of the disease's development.

Since respiratory muscle loss has a major influence on the prognosis of ALS, respiratory function tests, especially forced vital capacity (FVC) measurements, are valuable clinical indicators [8]. Keeping an eye on changes in respiratory function helps doctors decide whether to intervene quickly and what respiratory support treatments are best for individuals with ALS.

Nevertheless, there are a few drawbacks to clinical biomarkers in neurodegenerative illnesses, notwithstanding their usefulness. Due to the subjective evaluations that these biomarkers rely on, there might be variations depending on patient compliance and examiner experience [9]. Timely diagnosis and care is further complicated by certain evaluations' insensitivity to small changes un the early stages of the disease.

Furthermore, the variability in symptom presentation and pace of progression across individuals resulting from the variety of neurodegenerative diseases influences the validity and applicability of clinical biomarkers [10].

To get over these restrictions and improve the sensitivity and specificity of clinical biomarkers, attempts are being made to augment clinical evaluations with objective and quantitative measurements, such as digital biomarkers utilising wearable technology or neuroimaging-based indicators [11]. Personalised care techniques can be enabled by using new technology for longitudinal evaluations and remote monitoring. This has the potential to capture changes in disease development in real time.

In summary, clinical biomarkers in neurodegenerative diseases—which mainly include motor and cognitive evaluations—are essential for diagnosis, tracking the course of the disease, and assessing the efficacy of treatment. Clinical biomarkers have inherent limits associated to subjectivity and illness heterogeneity; nonetheless, continuous improvements in technology-driven methodologies and objective measuring instruments are intended to enhance the precision and consistency of clinical biomarkers. The therapy of neurodegenerative diseases can benefit from the improvement of clinical biomarkers through the integration of digital technology and multimodal evaluations.

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