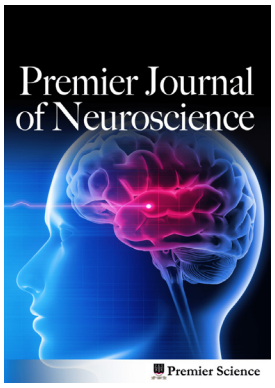


# Understanding the Silent Threat: A Review to Neurodegenerative Disorders

Amita Kajrolkar


## ABSTRACT

Neurodegenerative disorders represent a global health challenge as they lead to the progressive deterioration of central and peripheral nervous system tissue structures, accompanied by declining neurological functions. This article provides extensive details about five leading neurodegenerative disorders, consisting of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and multiple sclerosis. The paper examines both prevalence and clinical indications, in addition to pathophysiological mechanisms, followed by diagnostic procedures and limitations in early detection. The increasing aging population requires health care systems to focus on these neurological conditions as a matter of global importance. Such a review incorporates contemporary findings and recent advanced concepts when dealing with devastating conditions.


**Keywords:** Neurodegenerative disorders, Alzheimer's disease, Parkinson's disease, Diagnostic biomarkers, Protein misfolding



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Additional material is published online only. To view please visit the journal online.

Cite this as: Kajrolkar A. Understanding the Silent Threat: A Review to Neurodegenerative Disorders. Premier Journal of Neuroscience 2025;4:100012

DOI: https://doi.org/10.70389/PJN.100012

Peer Review

Received: 11 May 2025

Last revised: 19 June 2025

Accepted: 10 August 2025

Version accepted: 2

Published: 8 September 2025

Ethical approval: N/a

Consent: N/a

Funding: No industry funding

Conflicts of interest: N/a

Author contribution:
Amita Kajrolkar – Conceptualization, Writing – original draft, review and editing

Guarantor: Amita Kajrolkar

Provenance and peer-review: Commissioned and externally peer-reviewed

Data availability statement: N/a

## Introduction

Neurodegenerative disorders are a heterogeneous group of conditions characterized by progressive degeneration of the structure and function of the central and peripheral nervous systems.[1] These disorders, which include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and multiple sclerosis (MS), represent some of the most challenging medical conditions of our time.[2] The global burden of neurodegenerative disorders is substantial and growing, particularly in societies with aging populations.[3] Current estimates suggest that over 50 million people worldwide are affected by AD alone, with this number projected to triple by 2050 (Figure 1).[4]

Neurodegenerative disorders often progress silently, complicating both early detection and early treatment procedures. A prolonged subclinical progression of these diseases throughout years or decades until medical symptoms appear is linked to substantial irreversible brain damage when patients seek care.[5] This characteristic necessitates improved diagnostic tools and therapeutic approaches to protect the brain.[6] Extensive research has not yet succeeded in fully explaining the basic mechanisms that cause most neurodegenerative diseases.

Multiple disease pathological features unify various conditions through protein misfolding and aggregation along with mitochondrial dysfunction, oxidative stress, neuroinflammation, and cellular clearance abnormalities.[7] These shared pathological features offer potential therapeutic opportunities, although the disorders show clinical heterogeneity.[8]

This paper delivers an extensive investigation into major neurodegenerative disorders by analyzing their population patterns alongside clinical features, biological mechanisms, diagnostic methods, and therapeutic apprehensions. This review combines existing evidence with field developments to provide health care professionals and researchers with a modern approach to handle these destructive disorders.

## Epidemiology and Global Burden

The prevalence of neurodegenerative disorders has increased dramatically over the past decades, largely due to demographic transitions toward aging populations in many countries (Figure 2).[9] AD, the most common neurodegenerative disorder, affects approximately 10% of people aged 65 years or older and nearly 50% of those aged 85 years or older.[10] The worldwide prevalence of PD is estimated at 6.1 million individuals, with projections suggesting this number will double by 2040.[11] ALS has a global prevalence of 4–8 per 100,000 people, while HD affects approximately 5–10 per 100,000 people of European descent.[12]

Neurodegenerative disorders impose substantial economic burdens on society. In the United States alone, the annual cost of caring for individuals with AD and other dementias exceeds $300 billion, with projections suggesting this figure will surpass $1 trillion by 2050.[13] These costs encompass direct health care expenditures, long-term care services, and indirect costs associated with lost productivity and informal caregiving.[14] The societal burden extends beyond financial considerations to include substantial emotional and psychological impacts on patients, families, and caregivers.[15]

Geographical and ethnic variations in the prevalence and presentation of neurodegenerative disorders highlight the complex interplay between genetic and environmental factors in their development.[16] For instance, certain genetic variants associated with increased AD risk show different frequencies across populations, while environmental exposures linked to PD risk, such as pesticide exposure, vary by region and occupation.[17,18] Such variations offer valuable insights into disease etiology and potential preventive strategies.

## Major Neurodegenerative Disorders: Clinical Presentations and Pathophysiology

### Alzheimer's Disease

AD develops as the most common neurodegenerative disease characterized by progressive memory impairment initially affecting recent memories and what they learn.

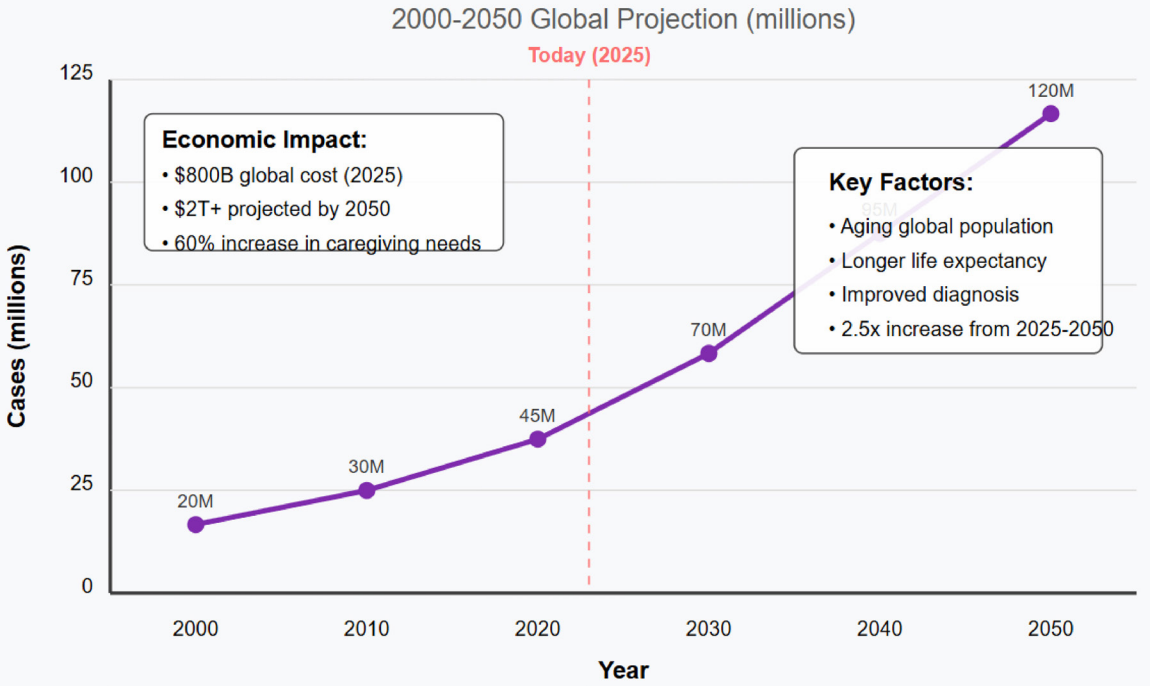


Fig 1 | Projected increase in neurodegenerative disorder cases

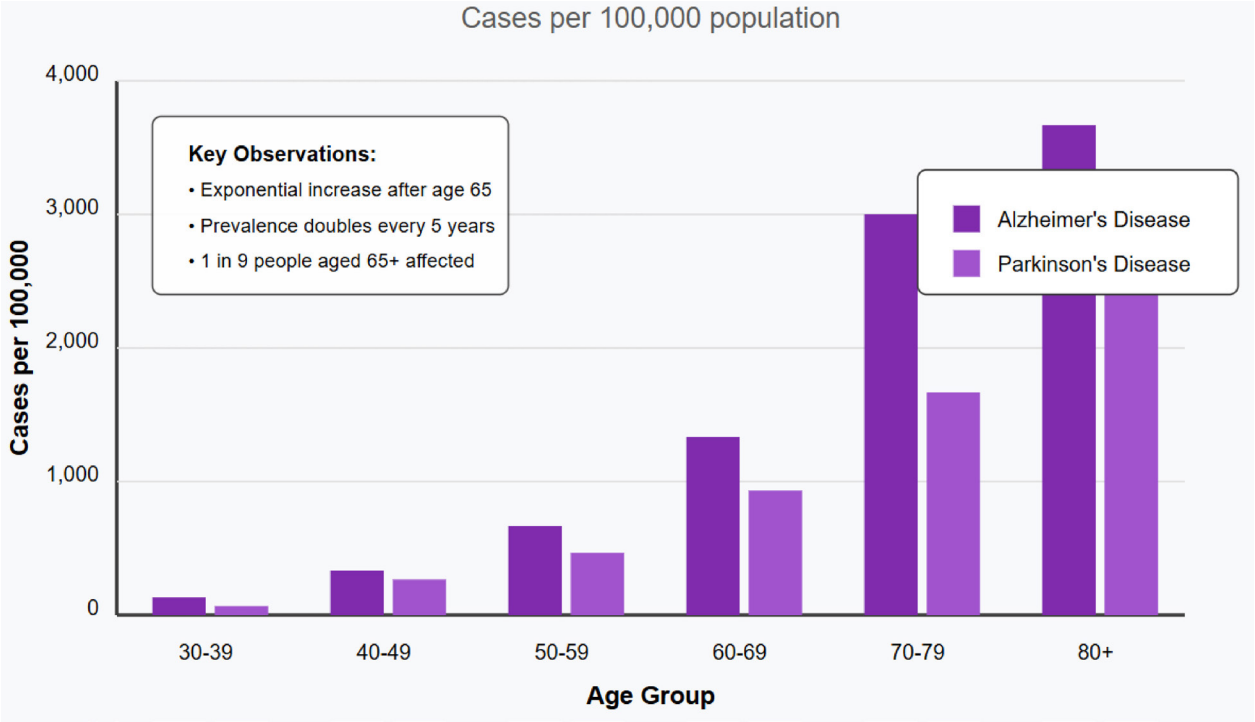


Fig 2 | Prevalence of neurodegenerative disorder by age group


DOI: https://doi.org/10.70389/PJN.100012 | Premier Journal of Neuroscience 2025;4:100012

The "amyloid cascade hypothesis" has long dominated AD research, proposing that Aβ accumulation represents the initiating event in AD pathogenesis, triggering a sequence of downstream events including tau protein pathology, synaptic dysfunction, neuroinflammation, and ultimately neuronal death.[19] However, recent clinical trial failures targeting Aβ have prompted a reevaluation of this hypothesis and a greater focus on alternative or complementary mechanisms.[20] The emergence of tau-focused theories, metabolic dysfunction models, and the recognition of mixed pathologies has expanded our understanding of AD's complex etiology.[21]

Longitudinal brain scans reveal that AD-related changes appear decades before patients start showing symptoms.[22] During the early phases of AD, a person experiences growing levels of amyloid beta in the brain, followed by tau pathology and associated brain atrophy.[23] This new information guides us to start disease treatment at an early stage.[24]

### Parkinson's Disease

PD is characterized by progressive motor symptoms including bradykinesia, rigidity, resting tremor, and postural instability.[25] Nonmotor symptoms, which often precede motor manifestations, include olfactory dysfunction, sleep disorders, autonomic dysfunction, and neuropsychiatric features such as depression and cognitive impairment.[26] The pathological hallmark of PD is the degeneration of dopaminergic neurons in the substantia nigra pars compacta, coupled with the presence of intraneuronal inclusions known as Lewy bodies, which contain aggregated α-synuclein protein.[27]

The actual manner by which dopamine neurons deteriorate in PD remains unclear, but several biological processes, including damage to mitochondria and activation of the immune system, play major roles. PD is now recognized as a condition that affects multiple body systems because α-synuclein first harms cells beyond the brain before spreading to brain regions over time.

### Amyotrophic Lateral Sclerosis

The degeneration of upper and lower motor neurons manifests as increasing muscle weakness, together with muscle atrophy and spasticity, which results in ALS.[28] The condition begins with unbalanced weakness in a single limb that expands to multiple areas until it reaches the respiratory muscles, leading to respiratory failure.[29] The disease's variable clinical forms, length of survival, and rate of progression show its extensive multifaceted nature.[30]

The pathophysiology of ALS involves multiple mechanisms, including protein aggregation (particularly TDP-43), oxidative stress, excitotoxicity, mitochondrial dysfunction, impaired axonal transport, and neuroinflammation.[31] Approximately 10% of ALS cases are familial, with mutations identified in several genes, including SOD1, C9orf72, TARDBP, and FUS.[32] The remaining 90% of cases are classified as sporadic, although genetic factors are increasingly recognized as contributing to these cases as well.[33]

The concept that ALS exists within the same clinical and pathological spectrum as frontotemporal dementia (FTD) has become widely accepted among experts because 15% of ALS patients fulfill FTD diagnostic requirements, while 50% display some level of cognitive or behavioral impairments.[34] Both conditions share similar genetic backgrounds through C9orf72 expansion inheritance and TDP-43 pathology.[35]

### Huntington's Disease

HD is an autosomal dominant neurodegenerative disorder in which an expanded CAG repeat sequence within the huntingtin gene on chromosome 4 leads to the disease development.[36] The disease manifests via the three distinct symptom groups, including chorea, cognitive deficits, and psychiatric disorders with depression, together with irritability and apathy.[37] The length of CAG repeats produces an opposite correspondence to age at symptom appearance, where prolonged repeats may trigger premature disease presentation.[38]

Mutant huntingtin protein (mHTT) drives HD pathophysiology through improper protein folding and formation of harmful aggregates that disturb cellular operations at multiple points.[39] The disease manifestations stem principally from mHTT-induced toxic damage to medium spiny striatal neurons.[40] Cellular disturbances caused by mHTT include transcriptional disorganization, impaired mitochondrial function, defective axonal cargo transport, synaptic dysfunction, and proteostasis breakdown.[41]

Different animal models exist today to study important aspects of human HD because of the hereditary nature of this disease, and these models help scientists understand HD mechanisms and test new treatments.[42] Recent gene-silencing approaches such as antisense oligonucleotides and RNA interference show potential for reducing mHTT production to modify the disease course.[43]

### Multiple Sclerosis

Information of the central nervous system that causes demyelination leads to different neurological symptoms, depending on where the lesions develop.[44] MS patients typically present with visual disturbances, motor weakness, sensory symptoms, coordination problems, and a decline in brain functions.[45] Disease progression follows three distinct patterns: relapsing-remitting, secondary progressive, primary progressive, or progressive-relapsing.[46]

The MS pathophysiology encompasses three key sets of mechanisms, comprising autoimmune reactions, inflammation, and neurodegeneration.[47]

New findings about how MS develops have shown that B cells participate in immune functions unrelated to antibodies, while revealing the presence of innate cells and nervous system-specific inflammation patterns and early brain cell degeneration processes.[48] Such insights led to improved MS therapy strategies for managing immune system elements (Table 1).[49]

**Table 1 | Major neurodegenerative disorders: a summary**

| Disorder | Key Clinical Features | Primary Pathophysiological Mechanisms | Typical Age of Onset | Genetic Factors | Key Diagnostic Markers |
|---|---|---|---|---|---|
| AD | Cognitive decline, memory impairment, behavioral alterations | Amyloid plaques, tau tangles, synaptic loss | Late-onset (65+), early-onset (before 65) | APP, PSEN1, PSEN2 genes; APOE ε4 | Amyloid positron emission tomography (PET), Tau PET, cerebrospinal fluid (CSF) Aβ42, tau |
| PD | Tremor, rigidity, bradykinesia, postural instability | Lewy body formation, α-synuclein accumulation, dopamine neuron loss | 60+ years | SNCA, LRRK2, PARK7, PINK1, PRKN | DaTscan, clinical features |
| HD | Chorea, cognitive decline, psychiatric symptoms | CAG repeat expansion in HTT gene, mHTT aggregation | 30–50 years | HTT gene mutation (autosomal dominant) | Genetic testing (CAG repeat length) |
| ALS | Muscle weakness, atrophy, fasciculations, respiratory failure | TDP-43 and FUS protein aggregation, motor neuron death | 50–70 years | SOD1, C9orf72, TARDBP, FUS | EMG, nerve conduction studies, clinical symptoms |
| FTD | Behavioral changes, language impairment, executive dysfunction | TDP-43 or tau protein accumulation, neuronal loss | 45–65 years | MAPT, GRN, C9orf72 | Neuropsychological testing, imaging, genetic testing |

## Diagnostic Approaches and Biomarkers

The diagnosis of neurodegenerative disorders traditionally involves clinical assessment, supported by neuroimaging, laboratory tests, and occasionally genetic testing.[50] However, the substantial overlap in clinical presentations between different disorders and the subtlety of early symptoms create significant diagnostic challenges.[51] Moreover, definitive diagnosis for many conditions, particularly AD and PD, has historically required post-mortem neuropathological examination, highlighting the limitations of current clinical diagnostic approaches.[52]

Recent advances in biomarker development have transformed the diagnostic landscape for several neurodegenerative disorders.[53] For AD, CSF measurements of Aβ42, total tau, and phosphorylated tau demonstrate high sensitivity and specificity for underlying AD pathology.[54] The development of PET ligands binding to amyloid and tau has further enhanced the ability to visualize pathology in vivo.[55] These biomarkers have been incorporated into research diagnostic criteria and are increasingly used in clinical practice and therapeutic trials.[56]

For PD, diagnostic biomarkers remain less well-established, although several promising approaches are under investigation.[57] These include imaging of the dopaminergic system using single-photon emission computed tomography or PET, measurement of α-synuclein in CSF or peripheral tissues, and assessment of nonmotor symptoms such as REM sleep behavior disorder, which may precede motor symptoms by years.[58] For ALS, neurophysiological studies such as electromyography and nerve conduction studies play a crucial role in diagnosis, while neurofilament levels in CSF and blood are emerging as valuable biomarkers of disease activity and progression.[59]

Many neurodegenerative disorders are now recognized to have preclinical or prodromal stages, where pathological changes progress without noticeable symptoms.[60] Recognition of individuals in this stage allows the greatest chance for disease-modifying treatments that prevent severe neuronal destruction.[61] This approach has been particularly developed for AD, with research frameworks defining preclinical and prodromal stages based on biomarker profiles (Table 2).[62]

## Challenges in Early Detection

Despite advances in biomarker development, several challenges remain for early neurodegenerative disorder detection.[63] The invasive nature of lumbar puncture CSF sample collection and the high cost of PET imaging limit their practicality in widespread screening programs.[64] These factors drive researchers to find less invasive blood-based biomarkers that enable greater screening capability.[65]

Recent technological advances now allow the sensitive detection of pathological proteins such as Aβ, tau, and neurofilament light chain in blood samples.[66]

**Table 2 | Current and emerging biomarkers**

| Disorder | Traditional Biomarkers | Emerging Biomarkers | Advantages | Limitations |
|---|---|---|---|---|
| AD | CSF Aβ42, tau, p-tau, PET imaging | Blood-based Aβ, tau, neurofilament light (NfL), p-tau variants | Less invasive (blood tests), earlier detection | Variable sensitivity and specificity (blood tests), availability, cost |
| PD | DaTscan, clinical markers | α-synuclein in CSF/blood, NfL, imaging of Lewy pathology | Less invasive | Sensitivity, specificity, and full validation of these are being explored |
| ALS | EMG, nerve conduction | NfL, pNFH (phosphorylated neurofilament heavy), TDP-43 CSF | Can aid in earlier diagnosis | Cost, standardization across labs needed |
| FTD | Imaging (MRI), Clinical markers | NfL, pNFH, CSF progranulin, plasma progranulin | Easier, faster methods than some CSF-based analysis | Variable results depending on disease subtype |


DOI: https://doi.org/10.70389/PJN.100012 | Premier Journal of Neuroscience 2025;4:100012

These developments hold promise for more accessible biomarker testing, although further validation and standardization are required before routine clinical implementation.[67] The integration of multiple biomarkers, including imaging, fluid biomarkers, cognitive assessments, and digital markers derived from wearable devices, may provide more comprehensive and accurate early detection strategies.[68]

The challenge of early detection originated from differentiating pathological brain changes from normal aging alterations in individuals undergoing neurodegeneration.[69] The structural, along with functional, brain variations associated with healthy aging can cause diagnostic challenges by producing similar findings to early dementia indicators.[70] This problem particularly affects elderly patients who frequently present with various brain diseases that affect the interpretation of biomarkers and diagnosis steps.[71]

The heterogeneity of disease presentation and variable progression rates complicates the work of early detection teams.[72] Despite sharing the same underlying pathology, patients show different clinical paths because their genetic profiles differ, as well as their lifestyle patterns, health histories, and brain protection capacity.[73] Developing individualized biomarker methods continues as a major scientific hurdle.[74]

### Future Directions and Emerging Concepts

Emerging concepts are now revolutionizing how we understand, detect, and manage neurodegenerative disorders.[75] The recognition of substantial overlap between different disorders at clinical, pathological, and genetic levels has led to more nuanced views of these conditions as existing along spectrums rather than as discrete entities.[76] This perspective is exemplified by the ALS-FTD continuum and the frequent coexistence of multiple pathologies in older individuals with dementia.[77]

The role of nonneuronal cells, especially glial cells and the neurovascular unit, in driving neurodegenerative processes is gaining greater focus.[78] Microglia, astrocytes, and oligodendrocytes are now recognized as active participants in disease pathogenesis rather than passive bystanders, opening new avenues for therapeutic targeting.[79] Similarly, the contribution of vascular factors to neurodegeneration is increasingly appreciated, particularly in AD, where cerebrovascular pathology frequently coexists with typical AD pathology.[80]

Environmental elements together with lifestyle choices significantly influence both neurodegenerative risk levels and disease progression pace.[81] Mounting scientific evidence indicates that elements like physical and cognitive activities, dietary patterns, sleeping habits, and cardiovascular risk factor management directly influence neurodegenerative risk assessment.[82] Consequently, health care providers utilize this evidence to design preventive care methods focused on these modifiable risk factors in high-risk patient groups.[83]

Finally, advances in technology, particularly artificial intelligence and machine learning, are transforming approaches to diagnosing and predicting neurodegenerative disorders.[84] These computational methods can integrate diverse data types, including imaging, genetic, proteomic, and clinical information, to identify patterns and relationships not apparent through traditional analytical approaches.[85] Such technologies hold promise for enhancing diagnostic accuracy, predicting disease trajectories, and personalizing treatment approaches.[86]

### Conclusion

Neurodegenerative disorders present significant challenges for patients alongside their caregivers and both health care institutions and wider community structures. The current understanding of their pathophysiology and advances in diagnostic biomarker development have led to important progress, but major detection and intervention challenges still exist for early disease identification. Advances in disease detection will become possible through integrated clinical, genetic, and biochemical uses of imaging technologies that help develop disease-modifying therapeutic approaches. Multiple studies are producing refined knowledge about the heterogeneous nature of these disorders that affect several neural connections and different brain cell types to enable the creation of individualized strategies for intervention. A growing worldwide problem with neurodegenerative diseases requires urgent research and complete approaches that focus on both patient care and disease treatment during the next several decades.

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