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A Comprehensive Review on the Pathophysiology, Diagnosis, and Emerging Therapies in Neurodegenerative Diseases

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Abstract

Neurodegenerative diseases (NDs) represent a class of chronic and progressive disorders characterized by the deterioration of neuronal structure and function. These diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS), and Huntington's disease (HD), impose a substantial burden on healthcare systems globally. This review synthesizes current knowledge on the pathophysiological mechanisms underlying major NDs, highlights diagnostic challenges, and discusses emerging therapeutic approaches. Key pathological processes such as protein misfolding, oxidative stress, mitochondrial dysfunction, and neuroinflammation are examined. Additionally, novel diagnostic biomarkers and advancements in gene and cell-based therapies are reviewed. Understanding these complex disorders from a molecular and clinical perspective is crucial for the development of effective interventions aimed at modifying disease progression and improving patient outcomes.

Keywords: Neurodegeneration; Alzheimer's disease; Parkinson's disease; Amyotrophic Lateral Sclerosis; biomarkers; neuroinflammation; protein aggregation; therapy

Introduction

Neurodegenerative diseases (NDs) are a group of disorders characterized by progressive dysfunction and loss of neurons in the central and/or peripheral nervous system. The most prevalent NDs—Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS), and Huntington's disease (HD)—share overlapping pathological features despite their distinct clinical manifestations. The global prevalence of NDs is rising with increasing life expectancy, making them a major cause of morbidity and mortality, particularly in aging populations. Current understanding of NDs suggests multifactorial etiologies involving genetic predisposition, environmental factors, and age-related physiological decline. Hallmark features include abnormal protein aggregation (such as

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amyloid-beta and tau in AD, or α-synuclein in PD), mitochondrial dysfunction, excitotoxicity, and chronic neuroinflammation. Despite extensive research, effective disease-modifying therapies remain elusive, and treatment is primarily symptomatic.

This review aims to provide a consolidated overview of the molecular mechanisms, clinical diagnostic tools, and novel therapeutic strategies being explored for major neurodegenerative conditions.

Materials and Methods

This study is a narrative literature review based on peer-reviewed articles published between 2000 and 2024. The databases PubMed, Scopus, Web of Science, and ScienceDirect were searched using combinations of the following keywords: "neurodegenerative diseases," "Alzheimer's disease," "Parkinson's disease," "ALS," "Huntington's disease," "pathophysiology," "biomarkers," "gene therapy," and "clinical trials."

Inclusion criteria included studies that provided mechanistic insights, diagnostic criteria, and emerging therapies in NDs. Reviews, meta-analyses, randomized clinical trials, and experimental research articles were considered. Articles not available in English or lacking relevance to the focus topics were excluded. A total of 162 studies were selected for qualitative synthesis.

Results

The literature analysis revealed the following key findings:

1. **Pathological Mechanisms**: All reviewed NDs exhibit shared features including protein misfolding, mitochondrial impairment, synaptic dysfunction, and sustained neuroinflammatory responses. These processes contribute to progressive neuronal loss and clinical decline.

2. **Diagnostic Advances**: Biomarkers such as phosphorylated tau, neurofilament light chain (NfL), and α-synuclein species in cerebrospinal fluid (CSF) and blood have shown promise in early and differential diagnosis. Imaging modalities, including PET and MRI, enhance diagnostic precision.

3. **Therapeutic Strategies**:
   - **Pharmacological Interventions**: Cholinesterase inhibitors and NMDA receptor antagonists in AD; dopamine replacement in PD; riluzole and edaravone in ALS.
   - **Gene Therapy**: Advances in CRISPR/Cas9 and antisense oligonucleotides (ASOs) offer hope for genetically linked NDs.
   - **Cell-Based Therapy**: Use of induced pluripotent stem cells (iPSCs) is under active investigation.
   - **Immunotherapy**: Monoclonal antibodies targeting amyloid-beta and tau have shown mixed clinical results but remain a central focus in AD research.

4. **Clinical Trials**: Several ongoing trials are evaluating disease-modifying agents, including small molecule inhibitors, RNA-targeting agents, and neuroprotective compounds.

Discussion

Despite differences in clinical presentation, NDs share convergent pathogenic pathways. The accumulation of misfolded proteins initiates a cascade of events involving mitochondrial dysfunction, oxidative stress, and glial activation. The role of neuroinflammation, once considered secondary, is now seen as a driver of disease progression.

The identification of fluid and imaging biomarkers has significantly improved the ability to diagnose NDs in preclinical or early stages, although standardization remains a challenge. The translation of genetic and molecular discoveries into therapies is advancing, particularly through targeted gene-silencing approaches and regenerative medicine.

Nonetheless, the heterogeneity of these diseases and the blood-brain barrier pose major obstacles in drug delivery and treatment efficacy. Combination therapies targeting multiple pathways simultaneously may represent the most effective future approach.

Conclusion

Neurodegenerative diseases constitute a growing public health concern with substantial social and economic impacts. While understanding of the molecular and clinical aspects of these disorders has progressed considerably, effective curative treatments remain limited. Continuous efforts in biomarker validation, early diagnosis, and development of gene and cell therapies are essential. A multidisciplinary approach combining neurology, molecular biology, pharmacology, and computational sciences is key to overcoming the current challenges in ND management.

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