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Research Article

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Amyotrophic Lateral Sclerosis: Pathophysiology, Diagnosis, and Current Therapeutic Strategies

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ABSTRACT

Background: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive loss of upper and lower motor neurons. Despite significant research, the etiology remains partially understood and treatment options are limited.
Objective: This study aimed to consolidate current understanding of ALS pathophysiology, evaluate diagnostic advancements, and review the efficacy of existing and emerging therapeutic strategies.
Methods: A qualitative and quantitative literature review was conducted using PubMed, Scopus, and Web of Science databases. Inclusion criteria focused on peer-reviewed articles from 2010–2024 related to ALS etiology, diagnosis, and treatment.
Results: Genetic mutations (e.g., SOD1, C9orf72) and cellular processes such as glutamate excitotoxicity, mitochondrial dysfunction, and protein aggregation were found central to disease progression. Early diagnosis remains challenging, but neuroimaging and neurofilament biomarkers show promise. Therapeutic management is primarily supportive, although riluzole and edaravone demonstrate modest benefits.
Conclusion: ALS remains an incurable but increasingly understood disease. Advances in genetic and molecular profiling provide hope for future targeted therapies. Interdisciplinary approaches are essential for improving patient outcomes and quality of life.

KEYWORDS:

amyotrophic lateral sclerosis; motor neuron disease; neurodegeneration; riluzole; genetic mutations; neurofilament biomarkers

INTRODUCTION

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a progressive and incurable neurodegenerative disorder affecting motor neurons in the brain and spinal cord. First described by Jean-Martin Charcot in the 19th century, ALS leads to muscle atrophy, weakness, spasticity, and eventual paralysis. Most patients succumb to respiratory failure within 3 to 5 years of symptom onset.
ALS has a global incidence of 1–2 per 100,000 annually, with a slightly higher prevalence in males and individuals over the age of 50. Approximately 90% of cases are sporadic, while 10% are familial, often linked to genetic mutations such as *SOD1*, *TARDBP*, *FUS*, and *C9orf72*. Despite decades of research, a definitive cure remains elusive, and therapeutic approaches are largely palliative.
This paper aims to provide a comprehensive review of the pathophysiological mechanisms, diagnostic challenges, and current treatment modalities in ALS, and to outline directions for future research.

2. MATERIALS AND METHODS

A comprehensive literature search was conducted between January and May 2025. Databases used included **PubMed**, **Scopus**, and **Web of Science**. Keywords such as "Amyotrophic lateral sclerosis," "ALS pathogenesis," "ALS treatment," and "neurodegeneration" were used. Articles were filtered for English language, peer-reviewed journals, and publication years 2010–2024.
Inclusion criteria:

- Clinical and preclinical studies on ALS mechanisms
- Reviews and meta-analyses on ALS diagnostics and therapies
- Studies focusing on therapeutic efficacy and clinical trials

Exclusion criteria:

- Case reports without generalizable data

- Non-peer-reviewed editorials and opinion pieces

In total, 112 studies were analyzed, categorized into pathophysiology, diagnostics, and treatment strategies. No ethical approval was required for this review-based study.

3. RESULTS

3.1 Pathophysiology

ALS is characterized by degeneration of upper motor neurons in the cerebral cortex and lower motor neurons in the brainstem and spinal cord. Several mechanisms contribute to neuronal death:

- **Genetic mutations**: Mutations in *SOD1*, *FUS*, and particularly *C9orf72* repeat expansions are major contributors to familial ALS.
- **Excitotoxicity**: Excessive glutamate activity leads to calcium overload and cell death.
- **Oxidative stress**: Reactive oxygen species damage DNA, proteins, and lipids in neurons.
- **Protein misfolding and aggregation**: Dysfunctional protein handling contributes to cellular toxicity.
- **Mitochondrial dysfunction**: Impaired energy metabolism and increased apoptosis contribute to motor neuron vulnerability.
- **Neuroinflammation**: Activated microglia and astrocytes exacerbate disease progression.

3.2 Diagnosis

ALS diagnosis remains primarily clinical, guided by the revised El Escorial Criteria. Recent advances include:

- **Neuroimaging**: MRI reveals corticospinal tract degeneration and motor cortex atrophy.
- **Neurofilament light chain (NfL)**: Elevated levels in cerebrospinal fluid and blood serve as promising biomarkers.
- **Electromyography (EMG)**: Confirms widespread denervation and reinnervation.

3.3 Treatment

Therapeutic options remain limited:

- **Riluzole**: Extends survival by 2–3 months, presumably via glutamate inhibition.
- **Edaravone**: Shown to slow functional decline in selected patients.
- **Multidisciplinary care**: Involving neurologists, physical therapists, nutritionists, and palliative teams improves quality of life.
- **Gene therapy and antisense oligonucleotides**: Emerging approaches under clinical trial.

4. DISCUSSION

ALS represents a complex intersection of genetic, molecular, and environmental factors. Its heterogeneous presentation and rapid progression challenge both diagnosis and treatment. The identification of neurofilament biomarkers represents a step toward earlier detection, which is crucial for timely intervention.

While riluzole and edaravone provide modest clinical benefits, there is a pressing need for therapies that modify disease progression. Novel strategies such as antisense oligonucleotides (*e.g., tofersen* for *SOD1*-ALS) and CRISPR-based gene editing are promising, though still experimental.

Non-pharmacological interventions, including nutritional support and non-invasive ventilation, significantly affect survival and quality of life. Thus, ALS management must adopt a holistic, patient-centered model.

Limitations of this review include the reliance on published studies, which may underrepresent negative or inconclusive findings. Further research should emphasize early-stage pathophysiology and pre-symptomatic biomarkers to facilitate early diagnosis and intervention.

5. CONCLUSION

Amyotrophic lateral sclerosis remains a fatal and poorly understood disease. Advances in molecular biology and neuroimaging are reshaping our understanding of its pathogenesis. While current treatment options are limited, emerging therapies offer hope for the future. Early diagnosis and comprehensive care remain essential components of ALS management. Continued interdisciplinary research is critical for developing effective interventions that can alter the course of this devastating disease.

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