AMYOTROPHIC LATERAL SCLEROSIS – PATHOGENESIS, CLINICAL FEATURES, AND DIAGNOSTIC STRATEGIES

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Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neurodegenerative disorder characterized by the selective degeneration of upper and lower motor neurons in the brain and spinal cord. The disease leads to progressive muscle weakness, atrophy, paralysis, and ultimately respiratory failure. This article reviews current knowledge regarding the molecular mechanisms, genetic factors, clinical manifestations, and diagnostic approaches to ALS.

Keywords: amyotrophic lateral sclerosis, ALS, motor neuron disease, TDP-43, SOD1, C9orf72, excitotoxicity, neurodegeneration.

Introduction

ALS is the most common form of motor neuron disease, with an incidence of approximately 1–2 cases per 100,000 people per year. The majority of cases are sporadic, while about 5–10% are familial. Median survival is 3–5 years from symptom onset, although survival varies considerably. Despite decades of research, the exact cause of ALS remains incompletely understood.

Molecular and Cellular Pathogenesis

The pathological hallmark of ALS is the progressive loss of motor neurons in the motor cortex, brainstem, and anterior horns of the spinal cord. Several interrelated mechanisms contribute to motor neuron degeneration:

Glutamate-mediated excitotoxicity causes sustained calcium influx and neuronal injury due to impaired astrocytic glutamate uptake. Mitochondrial dysfunction results in impaired energy production and increased formation of reactive oxygen species (ROS), promoting oxidative stress and neuronal apoptosis. Protein misfolding and aggregation, especially involving TDP-43, SOD1, and FUS proteins, disrupt normal cellular processes and lead to cytotoxic inclusion bodies.

Additional mechanisms include impaired axonal transport, neuroinflammation mediated by activated microglia and astrocytes, dysfunction of the ubiquitin–proteasome system, and endoplasmic reticulum stress. These processes interact in a complex network that ultimately leads to irreversible neuronal loss.

Genetic Factors

More than 30 genes have been associated with ALS. The most common genetic abnormalities involve mutations in C9orf72, SOD1, TARDBP (encoding TDP-43), and FUS. These mutations affect RNA metabolism, protein homeostasis, mitochondrial

function, and cytoskeletal stability. Genetic testing has become increasingly important for diagnosis, prognosis, and inclusion in targeted clinical trials.

Clinical Manifestations

ALS typically presents in middle or late adulthood. Initial symptoms may include focal muscle weakness, cramps, and fasciculations. The disease can begin in the limbs (limb-onset ALS) or with speech and swallowing difficulties (bulbar-onset ALS). As the disease progresses, patients develop spasticity, hyperreflexia, muscle atrophy, and respiratory muscle weakness.

Non-motor symptoms such as cognitive impairment, behavioral changes, and frontotemporal dementia occur in a significant subset of patients, reflecting the multisystem nature of the disease.

Diagnostic Strategies

The diagnosis of ALS is primarily clinical and based on the demonstration of both upper and lower motor neuron signs in multiple body regions, as defined by the revised El Escorial and Awaji criteria. Electromyography (EMG) is essential to detect widespread denervation and reinnervation. Magnetic resonance imaging (MRI) is used to exclude alternative diagnoses.

Biomarkers such as neurofilament light and heavy chains in cerebrospinal fluid and blood have emerged as promising tools for early diagnosis and disease monitoring.

Differential Diagnosis

Several conditions can mimic ALS, including cervical myelopathy, multifocal motor neuropathy, myopathies, myasthenia gravis, and structural brain or spinal cord lesions. Careful diagnostic evaluation is required to avoid misdiagnosis.

Prognosis and Complications

Disease progression is relentless in most cases, leading to severe disability and respiratory failure. Prognostic factors include age at onset, site of onset, rate of progression, and respiratory function at diagnosis.

Conclusion

ALS is a devastating neurodegenerative disease characterized by complex molecular mechanisms and heterogeneous clinical presentation. Advances in genetics and biomarker research are improving early diagnosis and opening new avenues for targeted therapies.

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