Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease and Charcot disease, is a specific disorder that involves the death of neurons.

In the United Kingdom the term motor neurone disease (MND) is commonly used, while others use that term for a group of five conditions of which ALS is the most common.

Classification

There are several forms of amyotrophic lateral sclerosis (ALS), which is a neurodegenerative disorder that affects the motor neurons in the brain and spinal cord, leading to progressive muscle weakness and atrophy.

Sporadic ALS: This is the most common form of ALS, accounting for about 90% of cases. It occurs in individuals with no family history of the disease and is thought to be caused by a combination of genetic and environmental factors.

Familial ALS: This form of ALS is inherited and accounts for about 10% of cases. It is caused by mutations in one of several genes, including the SOD1, C9orf72, FUS, TARDBP, and UBQLN2 genes.

Guamanian ALS: This is a rare form of ALS that was first identified in Guam in the 1950s. It is thought to be caused by the consumption of a toxin found in the seeds of a local plant.

Juvenile ALS: This is a rare form of ALS that occurs in individuals under the age of 25. It is usually caused by mutations in the SOD1 gene.

Progressive muscular atrophy (PMA): PMA is a type of ALS that primarily affects the lower motor neurons. It typically progresses more slowly than other forms of ALS and does not usually affect the muscles involved in breathing.

Progressive bulbar palsy (PBP): PBP is a type of ALS that primarily affects the muscles involved in speech, swallowing, and breathing. It typically progresses more slowly than other forms of ALS.

It is important to note that the different forms of ALS can have overlapping symptoms and progression, and diagnosis can be challenging.

SOD1-related amyotrophic lateral sclerosis (ALS) is a form of familial ALS that is caused by mutations in the SOD1 gene. ALS is a neurodegenerative disorder that affects the motor neurons in the brain and spinal cord, leading to progressive muscle weakness and atrophy.

The SOD1 gene encodes the protein superoxide dismutase 1, which is an antioxidant enzyme that helps to protect cells from damage caused by reactive oxygen species. Mutations in the SOD1 gene can result in a loss of function of the enzyme or a gain of toxic function, leading to the accumulation of toxic aggregates within motor neurons and eventual cell death.

SOD1-related ALS accounts for about 12% of familial ALS cases, and individuals with mutations in the

SOD1 gene typically develop symptoms of ALS in their 40s or 50s. The disease typically progresses rapidly, and most individuals with SOD1-related ALS survive for only a few years after diagnosis.

Etiology

Numerous intrinsic and extrinsic factors are involved in ALS motor neuron degeneration. One possible effector accelerating motor neuron death in ALS is damage to the blood-Central Nervous System barrier (B-CNS-B), mainly due to endothelial cell (EC) degeneration. Although mechanisms of EC damage in ALS are still unknown, vascular impairment may be initiated by various humoral inflammatory factors and other mediators. Systemic IL-6-mediated inflammation is a possible early extrinsic effector leading to the EC death causing central nervous system (CNS) barrier damage. In this review, we discuss the potential role of humoral factors in triggering EC alterations in ALS. A specific focus was on humoral IL-6 cytokine mediating EC inflammation via the trans-signaling pathway. Our preliminary in vitro studies demonstrated a proof of principle that short term exposure of human bone marrow endothelial cells to plasma from ALS patient leads to cell morphological changes, significantly upregulated IL-6R immunoexpression, and pro-inflammatory cell response. Our in-depth understanding of specific molecular mechanisms of this humoral cytokine in EC degeneration may facilitate an endothelial-IL-6-targeting therapy for restoring cell homeostasis and eventually reestablishing B-CNS-B integrity in ALS [1].

Pathology

Histology: degeneration of Anterior grey column, alpha motor neurons (in the spinal cord and in brainstem motor nuclei) (LMNs) and corticospinal tracts (UMNs). Produces mixed Upper motor neuron & Lower motor neuron findings, with a great deal of variability depending on which predominates at any given time.

Clinical

ALS is characterized by stiff muscles, muscle twitching, and gradually worsening weakness due to muscle wasting. This results in difficulty speaking, swallowing, and eventually breathing.

Recording of trapezius Motor evoked potentials (MEPs) is a valuable addition to the limb MEPs study, since it distinguishes ALS from SCM in most patients [2].

Damage to the cerebral tissue structural connectivity associated with amyotrophic lateral sclerosis (ALS), which extends beyond the motor pathways, can be visualised by diffusion tensor imaging (DTI). The effective translation of DTI metrics as biomarker requires its application across multiple MRI scanners and patient cohorts.

A large-scale study overcomes the challenges associated with processing and analysis of multiplatform, multicentre DTI data, and effectively demonstrates the anatomical fingerprint patterns of changes in a DTI metric that reflect distinct ALS disease stages. This success paves the way for the use of DTI-based metrics as read-out in natural history, prognostic stratification and multisite disease-modifying studies in ALS [3].

Speech decline

Although speech declines rapidly in some individuals with amyotrophic lateral sclerosis (ALS), longitudinal changes in speech have rarely been characterized. The study objectives were to model the rate of decline in speaking rate and speech intelligibility as a function of disease onset site, sex, and age at onset in 166 individuals with ALS; and estimate time to speech loss from symptom onset. We also examined the association between clinical (speaking rate/intelligibility) measures and patient-reported measures of ALS progression (ALSFRS-R). Speech measures declined faster in the bulbar-onset group than in the spinal-onset group. The rate of decline was not significantly affected by sex and age. Functional speech was still maintained at 60 months since disease onset for most patients with spinal onset. However, the time to speech loss was 23 months based on speaking rate < 120 (w/m) and 32 months based on speech intelligibility < 85% in individuals with ALS-bulbar onset. Speech measures were more responsive to functional decline than were the patient-reported measures. The findings of this study will inform future work directed toward improving speech prognosis in ALS, which is critical for determining the appropriate timing of interventions, providing appropriate counseling for patients, and evaluating functional changes during clinical trials [4)].

Diagnosis

Peripheral nerve imaging is a potentially powerful technique to distinguish multifocal motor neuropathy (MMN) from ALS [5)].

Findings suggest that elevated serum neurofilament light chain (NfL) levels in ALS are driven by Upper Motor Neuron degeneration and the disease progression rate and are independently associated with survival at time of diagnosis [6)].

Differential diagnosis

Amyotrophic lateral sclerosis (ALS) may be mimicked by disorders affecting the different levels of the motor system from cortex to muscle. Clinical heterogeneity is a feature of both ALS and related syndromes allowing for a large differential diagnosis. During the initial stage of a motor disorder false positive and false negative diagnoses of ALS are possible. Examples of disorders that should not be misdiagnosed as ALS, because their prognosis and treatment differ, are multifocal motor neuropathy, Kennedy's bulbospinal atrophy, cervical myelopathy, hyperthyroidism and hyperparathyroidism. Syndromes remote from polio and radiation treatments should be recognised. Eventually, frontier forms of ALS with signs restricted to either the upper or lower motor neurons deserve particular attention. Electrodiagnosis is pivotal to disclose signs and extension of the peripheral motor neuron, to detect and quantify cortico-spinal involvement, to search for specific signs of conditions that mimic ALS. Until specific markers become available, clinical evaluation supported by electrodiagnosis and other ancillary tests are crucial to provide with the correct diagnosis, prognosis and treatment [7)].

One of the most common differential diagnoses from ALS are cervical myelopathies (CM), especially the degenerative ones (DCM)

Treatment

Amyotrophic lateral sclerosis treatment.

Research

Dysfunctional astrocytes may contribute to Amyotrophic lateral sclerosis and glial cell line-derived neurotrophic factor (GDNF) can be protective. Baloh et al. showed that human neural progenitor cells transduced with GDNF (CNS10-NPC-GDNF) differentiated to astrocytes protected spinal motor neurons and were safe in animal models. CNS10-NPC-GDNF were transplanted unilaterally into the lumbar spinal cord of 18 ALS participants in a phase 1/2a study (NCT02943850). The primary endpoint of safety at 1 year was met, with no negative effect of the transplant on motor function in the treated leg compared with the untreated leg. Tissue analysis of 13 participants who died of disease progression showed graft survival and GDNF production. Benign neuromas near delivery sites were common incidental findings at post-mortem. This study shows that one administration of engineered neural progenitors can provide new support cells and GDNF delivery to the ALS patient spinal cord for up to 42 months post-transplantation [8].

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