PRIMEVIEW

AMYOTROPHIC LATERAL SCLEROSIS

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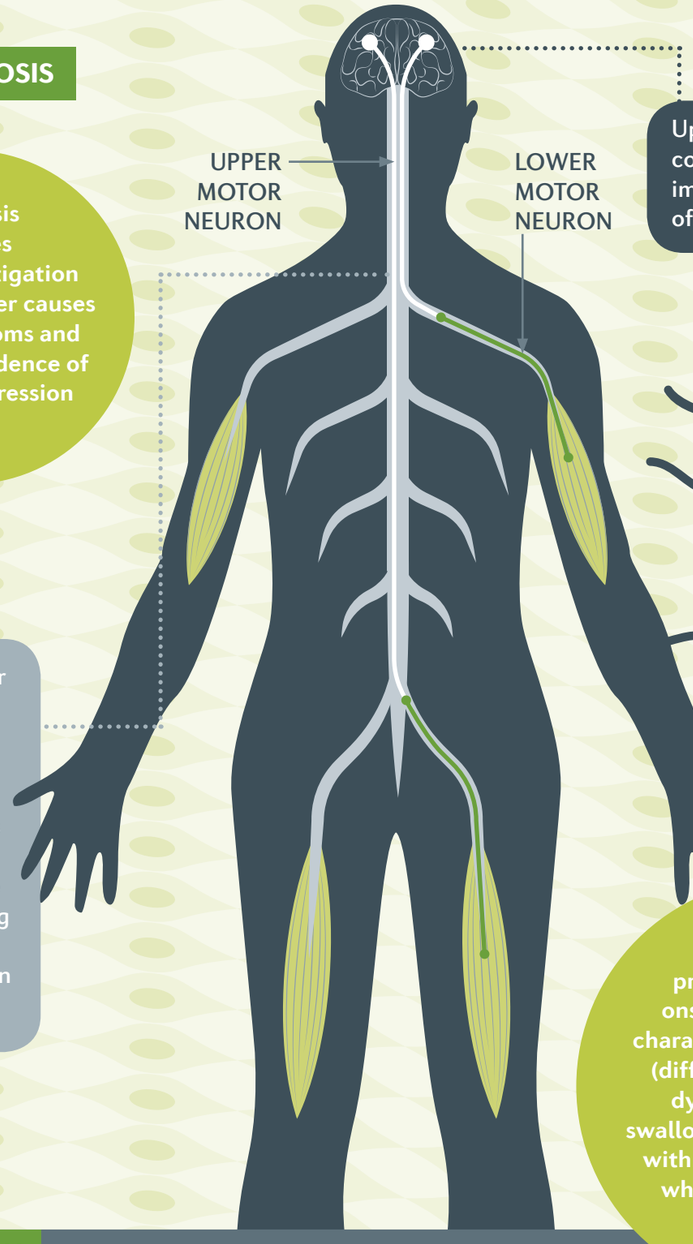
Amyotrophic lateral sclerosis (ALS; also known as motor neuron disease) is a rare, neurodegenerative disease that is characterized by the degeneration of upper and lower motor neurons, leading to muscle weakness and paralysis.

MECHANISMS

ALS can be classified as either sporadic or familial. Familial ALS has been associated with mutations in >30 genes, but mutations in four genes — *C9orf72*, *TARDBP*, *SOD1* and *FUS* — account for >70% of cases. Proteins encoded by these genes are involved in several aspects of motor neuron function, including protein homeostasis, DNA repair, RNA metabolism, vesicle transport, mitochondrial function and glial cell function. Several of these mechanisms probably interact to contribute to the degeneration of motor neurons in ALS. In general, the proteins encoded by these genes are ubiquitously expressed, so why these mutations lead to the selective degeneration of motor neurons, and not other cell types, is unknown. The pathological hallmark of ALS is the accumulation of intraneuronal protein aggregates, which, in most individuals, contain TAR DNA-binding protein 43. However, other proteins can form aggregates, including superoxide dismutase 1 and neurofilament. Whether these protein aggregates or the protein complexes that precede their formation are toxic to neurons is poorly understood.

DIAGNOSIS

Diagnosis includes clinical investigation to rule out other causes of the symptoms and to identify evidence of disease progression



Symptoms of upper motor neuron degeneration include spasticity and muscle weakness, whereas fasciculations (twitching), muscle cramps and wasting are indicative of lower motor neuron degeneration

Up to 50% of patients develop cognitive and/or behavioural impairments during the course of the disease

Some forms of ALS share a genetic overlap with neuropsychiatric conditions, such as schizophrenia

EPIDEMIOLOGY

In Europe, incidence is in the range of 2–3 cases per 100,000 individuals; incidence is lower in east Asia (0.8 cases per 100,000 individuals) and south Asia (0.7 cases per 100,000 individuals). The phenotype of ALS varies between populations. For example, the age at onset of symptoms and diagnosis is higher in Europe than in Asia or South America. In addition, the proportion of individuals with bulbar-onset disease is much lower in Asia than in Europe and patient survival is lower in Europe (24 months from the onset of disease) than in central Asia (48 months).

One-third of patients present with bulbar-onset disease, which is characterized by dysarthria (difficulty speaking) and dysphagia (difficulty swallowing); the rest present with spinal-onset disease, which is characterized by limb muscle weakness

The gross macroscopic features of ALS include atrophy of skeletal muscle and the motor cortex, and sclerosis of the pyramidal tracts

MANAGEMENT

Few randomized controlled trials assessing symptomatic therapies in patients with ALS have been conducted; accordingly, many therapies are based on the management of other diseases. For example, anticholinergic drugs can be used to treat sialorrhoea (hypersalivation), baclofen can be used to treat spasticity and muscle relaxants can be used to treat cramps. The management of dysphagia includes dietary changes, swallowing manoeuvres and exercise and, if severe, use of a gastrostomy tube. Other available symptomatic treatments include speech therapy for dysarthria and noninvasive ventilation for respiratory failure.

Two disease-modifying therapies — riluzole and edaravone — have been approved by the US FDA

OUTLOOK

One barrier to the development of effective treatments for ALS is the poor understanding of how the pathology of disease affects the overall integrity and function of brain networks. Improvements in model systems to study ALS and better ways to study the disease in humans will enhance our understanding of ALS and enable us to target therapies to specific aspects of the pathophysiology.

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