Amyotrophic Lateral Sclerosis (ALS)

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1 How to study ALS

To study ALS, I would begin with a 5 minute video to get a quick overview and lay the mental foundation for the future topics such as: Khan academy ALS video.

The textbooks I recommend for further research or reference is:

- (PT Specific) Physical rehabilitation - O'Sullivan[1]

- Neuromuscular disorders by Amato[2]
- Umphred's neurological rehabilitation[3]
- Continuum by AAN[4]

Lastly, I would then recommend going into true evidence based practice by using scientific articles to find up to date information on the topic.

2 introduction

What does "Amyotrophic Lateral Sclerosis" even mean?

- a –> no
- myo –> muscle
- Trophic –> Nourishment Thus Amyotrophic means "no muscle nourishment"

Amyotrophic lateral sclerosis (ALS), AKA Lou Gehrig's disease, is the most common and devastatingly fatal motor neuron disease (MND) among adults[1]. ALS is characterized by the degeneration and loss of motor neurons in the spinal cord, brainstem, and brain, resulting in UMN and LMN clinical signs and symptoms[1]. Recently, ALS is being recategorized as a multisystem disorder/syndrome with variable pathological involvement of extra-motor networks and connections, in addition to the LMNs and UMNs[1]

3 Epidemiology

> **Note**
>
> see Wolfson et al. (2023)[5] for updated 2023 global metrics

3.1 Age

ALS can occur at any age but onset generally occurs in the mid-to-late 50s[1].

3.2 Gender

Most studies have found that the disease affects men slightly more than women, with an approximate ratio of 1.7:1. After age 65, the gender difference decreases[1].

3.3 Family History

About 5% to 10% of individuals have a family history of ALS (familial ALS, [FALS])[1]. Familial ALS is phenotypically and genetically heterogeneous[1].

Most cases of FALS are autosomal dominant[1]. Regardless, recessive and X-linked forms have been described[1]. For example, the rare juvenileonset ALS is reported to be inherited in an autosomal recessive pattern[1].

3.3.1 FALS Categorization

FALS is categorized by mode of inheritance and further subcategorized by specific gene or chromosomal locus@osullivanPhysicalRehabilitation2019.

The very large majority of adult individuals with ALS have no family history of the disease (sporadic ALS)[1].

> **Note**
>
> A very small percentage of individuals with sporadic ALS do have a mutation in SOD1

Over 20 chromosomal regions and a number of identified genes have been linked to ALS. 20% of hereditary ALS cases are attributed to one of 100+ mutations in superoxide dismutase 1 (SOD1)[1]. ~50% of individuals with an SOD1 ALS variant are symptomatic by 46yrs, and 90% are symptomatic by 70 years of age[1].

3.4 Onset

- ~70% to 80% of individuals develop limb-onset ALS, with initial involvement in the extremities[1].
- 20% to 30% develop bulbar-onset ALS, with initial involvement in the bulbar muscles[1].
- Bulbar-onset ALS is more common in middle-aged women, and initial symptoms may include difficulty speaking, chewing, or swallowing[1]

Table 1: Motor Neuron Diseases (MNDs)[1]

Subtype	Nervous system pathology
ALS	Degeneration of the corticospinal tracts, neurons in the motor cortex and brainstem, and anterior horn cells in the spinal cord
Primary lateral sclerosis	Degeneration of upper motor neurons

Subtype	Nervous system pathology
Progressive bulbar palsy	Degeneration of motor neurons of cranial nerves IX to XII
Progressive muscular atrophy	Loss or chromatolysis of motor neurons of the spinal cord and brainstem

4 Etiology

Etiology for ALS is unknown, apart from the few hereditary cases[1]. Current theories attribute ALS to be the summation of multiple mechanisms including: oxidative stress, aberrant RNA processing, exogenous neurotoxicity, excitotoxicity, impaired axonal transportation, axonal dysfunction, mitochondrial disruption, protein misfolding, protein aggregation, apoptosis, and lifestyle factors that contribute to neuronal degeneration[1].

4.1 Disease-Causing mutations

4.1.1 SOD1 Mutation

Mutations in SOD1 gene impact Superoxide dismutases (SOD) function, resulting in a *hypothesized* accumulation of free radicals that can lead to neurodegeneration[1].

Most mutations in FALS have shown only modest reductions in enzyme activity[1]. Leading researchers to believe that a mutant SOD1 protein may have actively toxic properties[1].

4.2 Glutamate

A deficiency in EAAT2 results in excess glutamate in the motor cortex and spinal cord[1]. Excess glutamate has been theorized to result in neurodegeneration via excitotoxicity[1]

4.3 Neurofilament clumping

A histopathologic characteristic of ALS is neurofilament proteins clumping into spheroids[1].

4.4 Autoimmune reaction

Several studies have demonstrated an autoimmune reaction contributing to the etiology of ALS[1].

- Wolfgang et al., (1973) found serum factors that were toxic to anterior horn motor neurons in patients with ALS[1]
- Smith et al., (1992) identified antibodies to calcium channels in ALS patients[1]

4.5 Neurotrophic Factor Deficiency

Some researchers hypothesize that a deficiency in neurotrophic factors: "Neurotrophic Hormone Deficiency Theory"[1]. Studies on isolated motor neurons have demonstrated that neurotrophic factors are important in motor neuron survival[1]. Although there is a theoretical link, results from post-mortem studies have been inconclusive[1].

4.6 Other Theories

Other theories have been devised to explain the onset of ALS, but these have limited or indirect evidence[1].

- Exogenous or environmental factors[1]
- Apoptosis[1]
- Viral infection[1]

References

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