# Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases

Chapter 448 | Part 13: Neurologic Disorders

KEY CLINICAL POINTS

1. ALS is defined by the simultaneous involvement of upper motor neurons (UMN) and lower motor neurons (LMN).
2. Median survival is 3 to 5 years, with death typically resulting from respiratory paralysis.
3. C9orf72 mutations are a major genetic driver, accounting for ~45–50% of familial ALS (FALS).
4. Riluzole (100 mg/d) modestly extends survival; Edaravone slows the rate of progression on disability scales.
5. Sensory, bowel, bladder, and ocular motility are typically preserved in ALS.
6. MRI may show high signal intensity in corticospinal tracts (Wallerian degeneration).
7. Multifocal motor neuropathy with conduction block (MMCB) must be excluded as it is treatable.
8. Kennedy's disease (X-linked) presents with gynecomastia and reduced fertility, distinguishing it from ALS.
9. Tofersen is specifically indicated for SOD1-mediated ALS via intrathecal delivery.
10. Absence of pain or sensory changes favors a diagnosis of ALS.

## DEFINITION & CLASSIFICATION

- **Definition (Harrison's 22e):** Amyotrophic lateral sclerosis (ALS) is the most common progressive motor neuron disease.
- **Pathologic Hallmark:** Death of both lower motor neurons (LMN) and upper motor neurons (UMN).
- **LMN Component:** Includes anterior horn cells in the spinal cord and their brainstem homologues.
- **UMN Component:** Corticospinal motor neurons originating in layer five of the motor cortex.
- **Clinical Progression:** While ALS may start with only one type of neuron involved, it ultimately results in the progressive loss of both.
- **Preserved Functions:** Sensory, bowel, bladder, and ocular motility (until very late stages) are typically spared.

### Functional (Psychogenic) Disorders

- **Definition:** Also known as functional neurologic symptom disorder (FND) or conversion disorder.
- **Prevalence:** Estimated at 2–13% of patients in movement disorder clinics; more common in women.
- **Clinical Features:** Can present as tremor, tics, dystonia, myoclonus, chorea, ballism, and parkinsonism.
- **Management:** Education/explanation of diagnosis; primary treatment is psychological (e.g., cognitive-behavioral therapy) combined with physiotherapy.

### Pathology

- **Cellular Changes:** Motor neurons undergo shrinkage and accumulation of lipofuscin.
- **Cytoskeleton:** Early involvement of the motor neuron cytoskeleton; formation of 'spheroids' (neurofilament/protein accumulations) in proximal motor axons.
- **Protein Aggregates:** Ubiquitin-positive aggregates, often associated with TDP43.
- **Neuroinflammation:** Proliferation of astroglia and microglia.
- **Muscle Changes:** Denervation leads to atrophy; early stages may show reinnervation by sprouting.
- **Sclerosis:** Loss of corticospinal neurons results in thinning of tracts and fibrillary gliosis (lateral sclerosis).

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## EPIDEMIOLOGY

- **Survival:** Median survival is 3 to 5 years.
- **Progression:** Rarely reported cases of stabilization or regression.
- **Mortality:** Approximately 1 in 500 deaths in North America and Western Europe are due to ALS; death usually results from respiratory paralysis.
- **Incidence/Prevalence:** Incidence of 1–3 per 100,000; prevalence of 3–5 per 100,000.
- **Demographics:** Men are more frequently affected than women in the US and Europe.
- **Risk Factors:** Potential links to pesticides/insecticides, silica, smoking, and military service.
- **Genetics:** ~10% of cases are inherited as an autosomal dominant trait.

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## ETIOLOGY & PATHOPHYISIOLOGY

- **General Pathogenesis:** Complex process involving excitotoxicity, defective autophagy, impaired axonal transport, oxidative stress, and mitochondrial dysfunction.
- **Genetic Categories of ALS:**

1. **Protein Instability:** Mutations in SOD1, ubiquilin-1/2, and p62 lead to perturbations in protein degradation.
2. **RNA Processing/Transport:** Mutations in C9orf73, TDP43, and FUS/TLS; C9orf72 involves an intronic hexanucleotide repeat expansion (>-30 repeats) causing translation of toxic dipeptides.
3. **Axonal Cytoskeleton/Transport:** Mutations in dynactin and profilin-1.

- **Nonneuronal Involvement:** Activated microglia and astrocytes significantly influence disease course.

### Familial ALS (FALS)

- **Clinical Status:** Clinically indistinguishable from sporadic ALS.
- **C9orf72:** Accounts for ~45–50% of FALS and 5–10% of sporadic cases.
- **SOD1:** Accounts for ~20% of FALS.
- **TDP43 & FUS/TLS:** Each account for ~5% of FALS.
- **Other Genes:** NEK1, optineurin, TBK1, KIF5A, TUBA4, PFN1 (each ~1%).
- **Special Cases:** Senataxin (slowly evolving variant); Kennedy's syndrome (X-linked; mimics ALS but involves androgen receptor).
- **ALS/FTD Link:** Over 40% of frontotemporal dementia (FTD) cases harbor C9orf72 mutations.

## CLINICAL FEATURES

- **LMN Dysfunction:**
  - Initial presentation: Insidiously developing asymmetric weakness, typically distal.
  - Cramping: Often occurs with volitional movements in the early morning.
  - Fasciculations: Spontaneous twitching of motor units (early sign).
  - Hand involvement: Predominance of extensor over flexor weakness.
- **UMN Involvement:**
  - Hyperreflexia: Hyperactivity of muscle-stretch reflexes.
  - Spasticity: Resistance to passive movements; stiffness often out of proportion to weakness.
- **Bulbar & Respiratory Symptoms:**
  - Bulbar: Difficulty with chewing, swallowing, and facial/tongue movement; dysarthria.
  - Pseudobulbar affect: Involuntary excess in weeping or laughing.
  - Respiratory: Early involvement can lead to death before other symptoms progress.
- **Progression:** Moves from asymmetric to symmetric distribution across all muscle groups.
- **Preserved Functions:** Sensory, bowel, bladder, and cognitive functions (except in cases with concurrent FTD).
- **Ocular Motility:** Spared until very late stages.

### Familial ALS (FALS) Characteristics

- **Inheritance:** Autosomal dominant.
- **Clinical Presentation:** Identical to sporadic ALS.
- **Associated Disorders:** Frequently co-occurs with Frontotemporal Dementia (FTD), especially in C9orf72 mutations.
- **Atypical Phenotypes:** Some cases show prominent amyotrophy with parkinsonism-like features (linked to tau protein mutations).

## DIFFERENTIAL DIAGNOSIS

- **Rule Out Treatable Causes (Table 448-1):**
  - **Structural Lesions:** Cervical spinal cord/foramen magnum tumors, spondylosis, or Chiari malformation.
  - **Neuropathies:** Multifocal motor neuropathy with conduction block (MMCB), motor neuropathy with paraproteinemia/cancer, and other peripheral neuropathies.
  - **Toxins/Drugs:** Lead, aluminum, strychnine, phenytoin; exposure to electricity or x-irradiation.
- **Infectious/Inflammatory:** Lyme disease (usually presents with pain/pleocytosis), viral infections (Poliomyelitis, West Nile).
- **Metabolic/Systemic:** Hyperthyroidism, vitamin deficiencies (B12, E, folate), copper/zinc deficiency, mitochondrial dysfunction.
- **Specific Mimics:**
  - **Kennedy's Disease:** X-linked; presents with gynecomastia and reduced fertility.
  - **Benign Fasciculations:** No weakness or atrophy present; excludes ALS.
  - **Chronic Traumatic Encephalopathy:** Associated with TDP43 and neurofibrillary tangles.

### Diagnostic Criteria for ALS

- **Favoring ALS:**
  - Absence of pain or sensory changes.
  - Normal bowel and bladder function.
  - Normal radiologic studies of the spine.
  - Normal CSF analysis.
- **Exclusionary Findings:**
  - Presence of motor neuronal conduction block (indicates MMCB).
  - Evidence of involvement of non-motor neurons.
  - Restriction to only UMN or only LMN.

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## DIAGNOSTIC APPROACH

1. **Initial Clinical Assessment:** Identify asymmetric weakness, hyperreflexia, and fasciculations; assess for bulbar symptoms.
2. **Rule Out Treatable Conditions (Table 448-1):**
   - Perform MRI of head/cervical spine to rule out structural lesions (tumors, spondylosis).
   - Order serum lead levels and 24-h urine for heavy metals if exposure is suspected.
   - Check thyroid function, vitamin levels, and metabolic panels.
3. **Electrophysiology:** Perform studies to identify motor neuron conduction block; presence of block suggests MMCB rather than ALS.
4. **Genetic Testing:** If family history is positive or C9orf72/SOD1 are suspected, perform a panel for ALS and FTD genes.
5. **Neuropsychological Testing:** Assess for cognitive impairment (common in ~15% of cases; higher in C9orf72 mutations).

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## MANAGEMENT & TREATMENT

1. **Pharmacologic Therapy:**
   - **Riluzole:** Dose: 100 mg/d. Effect: Modestly lengthens survival.
   - **Edaravone:** Use to reduce the trajectory of worsening on disability scales.
   - **Tofersen:** Indicated for SOD1-mediated ALS; administered via intrathecal delivery to suppress mutant SOD1 expression.
2. **Supportive Care:**
   - **Respiratory Support:** Management of respiratory failure (primary cause of death).
   - **Rehabilitative Aids:** Implementation of assistive devices and physical therapy.
3. **Monitoring:**
   - Monitor for progression of bulbar symptoms and respiratory decline.
   - Assess for development of pseudobulbar affect or cognitive changes.

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## PROGNOSIS & COMPLICATIONS

- **Survival:** Median 3–5 years; death usually from respiratory failure.
- **Complications:**

- Respiratory paralysis.
- Dysphagia (difficulty swallowing) and aspiration risk.
- Pseudobulbar affect.
- Cognitive decline/Frontotemporal Dementia (especially in C9orf72 cases).

## SPECIAL POPULATIONS

- **Familial Cases:** Higher likelihood of concurrent FTD; specific genetic targets (SOD1, C9orf72).
  - **Pediatric/Juvenile:** Mutations in KIF5A or ALSIN may cause early-onset motor neuron disease.
  - **Traumatic Injury:** Chronic traumatic encephalopathy can present with ALS-like features.

## KEY PEARLS & HIGH-YIELD POINTS

- **The "Rule of Two":** ALS requires both UMN and LMN involvement; if only one is present, look for mimics.
  - **MMCB:** If conduction block is present, it is likely MMCB (treatable with IVIG/chemotherapy).
  - **C9orf72:** The most common genetic cause of FALS (~45-50%).
  - **Preservation:** Sensory, bowel, and bladder functions are almost always preserved.
  - **Tofersen:** Specifically for SOD1 mutations.
  - **Lead/Thyroid:** Always rule out these treatable causes in patients with motor neuron symptoms.

REFERENCE TABLES

TABLE 448-2

**Sporadic Motor Neuron Diseases CHRONIC Upper and lower motor neuron Predominantly upper motor neuron Predominantly...**

| DIAGNOSTIC CATEGORY | INVESTIGATION |
|---|---|
| **Structural lesions**<br>**Parasagittal or foramen magnum tumors**<br>**Cervical spondylosis**<br>**Chiari malformation of syrinx**<br>**Spinal cord arteriovenous malformation** | MRI scan of head (including foramen magnum and cervical spine) |

TABLE 448-2

**Sporadic Motor Neuron Diseases**

| CHRONIC | ENTITY |
|---|---|
| **Upper and lower motor neuron** | Amyotrophic lateral sclerosis |
| **Predominantly lower motor neuron** | Multifocal motor neuropathy with conduction block |
| | Motor neuropathy with paraproteinemia or cancer |
| | Motor predominant peripheral neuropathies |

| CHRONIC | ENTITY |
|---|---|
| **Other** | |
| **Intoxications, physical agents**<br>**Toxins—lead, aluminum, others**<br>**Drugs—strychnine, phenytoin**<br>**Electric short, x-irradiation** | 24-h urine for heavy metals<br>Serum lead level |

TABLE 448-1

) Acute Poliomyelitis Herpes zoster Coxsackie virus West Nile virus

| | |
|---|---|
| **Acute** | |
| **Poliomyelitis** | |
| **Herpes zoster** | |
| **Coxsackie virus** | |
| **West Nile virus** | |
| **Metabolic**<br>**Hypoglycemia**<br>**Hyperparathyroidism**<br>**Hyperthyroidism**<br>**D eficiency of folate, vitamin B ,**<br>**12**<br>**vitamin E**<br>**Malabsorption**<br>**Deficiency of copper, zinc**<br>**Mitochondrial dysfunction** | Fasting blood sugara<br>Routine chemistries including calciuma<br>PTH<br>Thyroid functiona<br>Vitamin B , vitamin E, folatea<br>12<br>Serum zinc, coppera<br>24-h stool fat, carotene, prothrombin time<br>Fasting lactate, pyruvate, ammonia<br>Consider mtDNA |
| **Hyperglycinuria** | Urine and serum amino acids<br>CSF amino acids |

TABLE 448-3

Genetic Motor Neuron Diseases DISEASE I. Selected Upper and Lower Motor Neurons (Familial ALS) + Frontotemporal Dementia

| DISEASE | GENE SYMBOL | GENE NAME | INHERITANCE | U.S. FREQUENCY % FALS | USUAL ONSET | PROTEIN FUNCTION |
|---|---|---|---|---|---|---|
| **I. Selected Upper and Lower Motor Neurons (Familial ALS) + Frontotemporal Dementia (FTD)** | | | | | | |
| | C9ORF72 | Chromosome 9 open reading frame 72 | AD | 45% (6–10% SALS) | Adult | Regulates vesicle trafficking |
| **ALS** | SOD1 | Cu/Zn superoxide dismutase 1 | AD | 20% (2% SALS) | Adult | Protein antioxidant |

| DISEASE | GENE SYMBOL | GENE NAME | INHERITANCE | U.S. FREQUENCY % FALS | USUAL ONSET | PROTEIN FUNCTION |
|---|---|---|---|---|---|---|
| | TARDBP | TAR DNA binding protein | AD | 5% | Adult | DNA, RNA binding |
| **ALS/ALS-FTD** | FUS/TLS | Fused in sarcoma/ translocated in liposarcoma | AD | 5% | Adult | DNA, RNA binding |
| | CCNF | E3 ubiquitin ligase cyclin F | AD | 2% | Adult | Mediates ubiquitination |
| **ALS** | NEK1 | NMA-related kinase | AR | 2% | Adult | Microtubules, nuclear transport |
| | TBK1 | Tank binding kinase 1 | AD | 2% | Adult | Regulates autophagy, inflammation |
| **ALS** | KIF5A | Kinesin family member 5A | AD | 1–2% | Early adult | Microtubule motor |
| | PFN1 | Profilin 1 | AD | ~1% | Adult | Involved in actin polymerization |
| **ALS/ALS-FTD** | OPTN | Optineurin | AD/AR | ~1% | Adult | Attenuates NF-κB |
| | SPG11 | Spastic paraplegia 11 | AR | ~1% | Adult | Vesicle trafficking |
| **ALS** | SETX | Senataxin | AD | ~1% | Late juvenile | DNA helicase |
| | VCP | Valosin-containing protein | AD | ~ 1% | Adult | ATPase |
| **ALS-FTD** | UBQLN2 | Ubiquilin 2 | XR | <1% | Adult or juvenile | Protein degradation |

| DISEASE | GENE SYMBOL | GENE NAME | INHERITANCE | U.S. FREQUENCY % FALS | USUAL ONSET | PROTEIN FUNCTION |
|---|---|---|---|---|---|---|
| | CHMP2B | Chromatin modifying protein 2B | AD | <1% | Adult | Chromatin binding protein |
| **ALS-FTD** | MAPT | Microtubule Associated Protein Tau | AD | <1% | Adult | Cytoskeletal protein |
| | ALS2 | Alsin | AR | <1% | Juvenile | GEF signaling |
| **ALS-FTD** | CHMP2B | Chromatin modifying protein 2B | AD | <1% | Adult | Chromatin binding protein |
| **Spinal muscular atrophies** | SMN | Survival motor neuron | AR | 1/10,000 live births | Infancy | RNA metabolism |
| | HEXB | Hexosaminidase B | AR | | Childhood | Ganglioside recycling |
| | GM2A | GM2-activator protein | AR | | Childhood | Ganglioside recycling |
| | HEXA | Hexosaminidase A | AR | | Childhood | Ganglioside recycling |
| **X-linked spinobulbar muscular atrophy** | AR | Androgen receptor | XR | | Adult | Nuclear signaling |
| **SPG3A** | ATL1 | Atlastin | AD | 10% AD FSP | Childhood | GTPase—vesicle recycling |
| | SPAST | Spastin | AD | 50–60% AD FSP | Early adulthood | ATPase family—microtubule associate |
| **SPG10** | KIF5A | Kinesin heavy chain isoform 5A | AD | 10% AD FSP | Second–third decade | Motor-associated protein |

| DISEASE | GENE SYMBOL | GENE NAME | INHERITANCE | U.S. FREQUENCY % FALS | USUAL ONSET | PROTEIN FUNCTION |
|---|---|---|---|---|---|---|
| | REEP1 | Receptor Expression Enhancing Protein 1 | AD | 10% AD FSP | Early | Mitochondrial protein |
| **SPG5** | CYP7B1 | Cytochrome P450 | AR | 5–10% AR FSP | Variable | Degrades endogenous substances |
| | SPG7 | Paraplegin | AR | 5–10% AR FSP | Variable | Mitochondrial protein |