NOTES
MOTOR NEURON DISEASES

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Group of degenerative motor neuron diseases
  - Progressive muscle weakness, disability

CAUSES
- Mainly genetic

SIGNS & SYMPTOMS

- Muscle weakness, fatigue → disability

DIAGNOSIS

OTHER DIAGNOSTICS
- History, physical examination (upper, lower motor neuron signs)
- Muscle biopsy
- Electromyography (EMG)

TREATMENT

MEDICATIONS
- Emerging disease-modifying agents (limited efficacy)

OTHER INTERVENTIONS
- Primarily supportive care

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

osms.it/amyotrophic-lateral-sclerosis

PATHOLOGY & CAUSES

- Progressive, degenerative motor neuron disease; upper, lower motor neuron signs
  - AKA Lou Gehrig's disease
- Genetic associations in familial ALS provide insight to pathogenesis
- Protein aggregation → neuronal injury, death → retrograde neuronal degeneration → gliosis
- *Superoxide dismutase 1 (SOD1)*: antioxidant protein encoded on chromosome 9; 20% of familial ALS
  - Gain-of-function mutation → misfolding → protein aggregation → direct neuronal injury, unfolded protein response → death
  - Interference with organelle autophagy, proteasome function
  - Interference with axonal transport, mitochondrial function
  - Further protein sequestration within protein aggregate
- *C9orf72*: protein of unknown significance; 40% of familial ALS

- Hexanucleotide repeat expansion → long 5' end of RNA transcript → abnormal transcription, novel protein production → aggregation
- Unknown specific pathogenesis
- Accumulated, novel proteins; dead neurons

- *TDP-43, FUS*: RNA-binding genes
  - Abnormal RNA processing → abnormal protein accumulation → neuronal injury
  - Pathway not completely known
- Inflammatory response
  - Cerebral inflammatory response primarily mediated by microglia, astrocytes
  - Natural killer, peripheral T-cells, monocytes infiltrate, contribute to inflammation
  - Microglial response → nitric oxide, oxygen radical, cytokine, glutamate release → motor neuron cell death
  - *SOD1* mutations especially susceptible to pathologic inflammatory response

TYPES

Progressive motor atrophy

- Predominant lower motor neuron degeneration

Primary lateral sclerosis

- Predominant upper motor neuron degeneration

Progressive bulbar palsy (AKA bulbar ALS)

- Affected cranial nerves → abnormal deglutition, phonation → ventilator support required
- Poor prognosis
  - Mortality rate > 50% at two years

CAUSES

- May be sporadic
- Familial (5–10%)
  - Multiple genes (e.g. *SOD1*)

RISK FACTORS

- Family history, age, cigarette smoking

COMPLICATIONS

- Frontotemporal lobar dementia (FTLD)
  - Disinhibition, compulsivity, loss of empathy
  - *Pseudobulbar affect (PBA)*: common; inappropriate, labile, expressive emotions (e.g. crying, yawning)
- Neuromuscular respiratory failure
- Dysphagia → pneumonia

SIGNS & SYMPTOMS

- Early symptoms
  - Asymmetric hand weakness → dropping of objects (e.g. glasses of water)
  - Cramping of upper extremities (common)
  - Dysarthria, dysphagia, dysphonia develop later
- Atrophy → ↓ strength → ↓ muscle bulk, abnormal tone → fasciculations
  - Weakness → inability to ambulate → wheelchair use
- Late symptoms
  - Respiratory weakness → dyspnea → respiratory infection
  - Recurrent bouts of cough, fever, chill → pneumonia

DIAGNOSIS

LAB RESULTS

- ↑ creatinine kinase (due to muscle atrophy)
- Heavy-metal levels, lyme disease
  - Negative

OTHER DIAGNOSTICS

- El Escorial criteria (all three required)
  - Evidence of lower motor neuron (LMN) disease by clinical/electrophysiologic/neuropathic examination
  - Evidence of upper motor neuron (UMN) disease by clinical examination
  - Progressive spread of signs/symptoms within/outside of body region, as determined by history/examination
- Family history

- Neurological
  - Upper, lower motor neuron signs
- Psychiatric
  - Mental status examination → apathy, disinhibition, PBA in FTLD individuals

EMG

- Helps differentiate from other neuromuscular junction diseases
- Acute denervation
  - Fibrillations of muscle fibers → active denervation → improper neuronal discharge → small-amplitude baseline variance
- Chronic denervation
  - Large amplitude, long duration, complex motor potentials
  - Denervation injury → ↑ muscle fiber recruitment, ↓ neuronal innervation

TREATMENT

MEDICATIONS

Disease-modifying agents

- New to market, mild/modest benefit
- Riluzole
  - Indicated for mild-moderate disease of < five year duration
  - *Mechanism of action*: ↓ any excitotoxic interplay by glutamate in neuronal toxicity → ↓ rate of neuron degeneration, symptom progression
- Edaravone
  - *Mechanism of action*: free-radical scavenger → ↓ oxidative stress → ↓ rate of neuronal death, symptom progression
- Symptom management
  - *Muscle spasms*: quinine
  - *Muscle spasticity*: muscle relaxants

OTHER INTERVENTIONS

- Nothing curative, management of symptom progression, severity
- Symptom management
  - *Multidisciplinary approach*: neurologists, physical therapists, speech therapists, dietitians
  - *Respiratory management*: ↓ aspiration event → ↓ rate of progression to tracheostomy, ventilator-dependence
  - Respiratory evaluation every three months after diagnosis

Figure 82.1 Amyotrophic lateral sclerosis is also known as Lou Gehrig's disease. Gehrig played for the Yankee's and died of ALS at the age of 37.

UPPER & LOWER MOTOR NEURON SIGNS

	TONE	STRENGTH	DEEP TENDON REFLEXES (DTR)	OTHER
UPPER MOTOR	↑ spasticity	↓	↑	Babinski sign[1], pathologic deep tendon reflexes (DTRs)[2], pseudobulbar affect (PBA)
LOWER MOTOR	↓ flaccid	↓	↓/absent	Fasciculations

1 - Reflex great toe extension, fanning of other digits on lateral stimulation of plantar foot
2 - Cross-adduction at hip adductors

SPINAL MUSCULAR ATROPHY

osms.it/spinal-muscular-atrophy

PATHOLOGY & CAUSES

- Genetically-mediated degenerative neurologic disease of childhood
  - Lower motor neuron weakness, muscular atrophy
- Survival of motor neuron-1 (*SMN1*) loss-of-function mutation → ↓ motor neuron survival → loss of alpha motor neurons (even *in utero*) → degeneration of anterior horn cells → denervated skeletal muscle → hypotonia, muscle atrophy

CAUSES

SMN1 loss-of-function mutation

- Autosomal recessive
- Encoded on chromosome 5q
- Multiple physiologic roles
  - *Spliceosome assembly*: ↓ nuclear expression of *SMN1* in spinal muscular atrophy (SMA)
  - *Inhibition of caspase system*: ↓ *SMN1* expression → disinhibition of caspase → ↑ caspase expression → cellular apoptosis
  - Unclear role in alpha motor neuron (patho)physiology

SMN2 pseudogene point mutation

- Encodes similar protein as *SMN1*
  - *Difference*: exon 7 (c.840C>T)
  - ↑ susceptibility for protein degradation → ↓ functional protein at baseline
- *SMN1* deficient → *SMN2* responsible for SMN protein production → poor production of viable protein → motor neuron cell death
  - Copy number variation correlates with clinical presentation

RISK FACTORS

- Family history

COMPLICATIONS

- Sleep disturbance
- Cardiac arrhythmias (esp. SMA 1, 2, 3)
- Restrictive respiratory disease (esp. SMA 0,1)
  - Diaphragmatic involvement → respiratory collapse
- Dysphagia → aspiration → pneumonia
- Poor ambulation → delayed gastric emptying → gastrointestinal (GI) reflux, constipation

SIGNS & SYMPTOMS

- Lower motor neuron signs
  - Proximal limb severity (more common than distal), ↓ muscle strength, tone; ↓/absent DTRs, muscle atrophy, fasciculations

DIAGNOSIS

OTHER DIAGNOSTICS

- Neurological
  - Fasciculations; ↓ muscle strength, tone; DTRs
- Muscle testing
  - EMG
  - Abnormal spontaneous activity, fibrillations, positive sharp waves
- Muscle biopsy
  - Large zones of severely atrophic myofibers
  - Remaining innervated fibers → unchanged/hypertrophied size

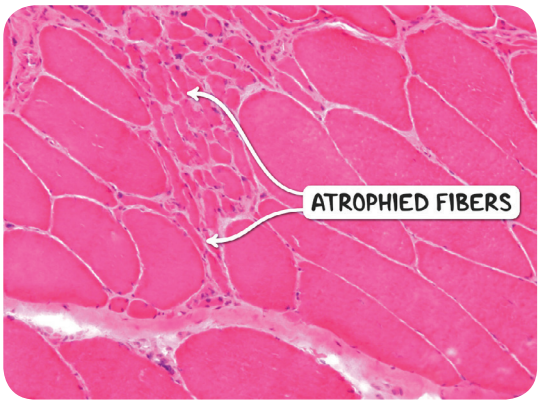

Figure 82.2 A muscle biopsy demonstrating neurogenic atrophy as would be seen in motor neurone diseases like spinal muscular atrophy. Denervated muscle fiber bundles are small and atrophied whilst those that remain innervated retain their normal size.

TREATMENT

MEDICATIONS

Experimental disease-modifying therapy

- Nusinersen
  - Antisense oligonucleotide → binds SMN2 mRNA → ↓ exon 7 splicing → ↑ levels of functional SMN protein
  - Limited effectiveness

OTHER INTERVENTIONS

- Pulmonary
  - Secretion management → ↓ aspiration events → ↓ pneumonia
  - Ventilator support (SMA 0,1)
- Nutrition, GI
  - Manage food consistency → ↓ aspiration
  - Gastrostomy tube placement in SMA 1
  - Encourage ambulation → ↓ gastric emptying time → ↓ constipation, GI reflux
- Orthopedic, musculoskeletal
  - Physical therapy
  - Spinal bracing → ↓ scoliosis → ↓ incidence of restrictive lung disease

TYPES OF SPINAL MUSCULAR ATROPHY

TYPE	AGE OF ONSET	LIFE EXPECTANCY	DEFINING CHARACTERISTICS
0	Prenatal	< 6 months	↓ fetal movement in pregnancy, facial diplegia, congenital heart defects, arthrogryposis
1	< 6 months	< 2 years	Furrowed brow, paradoxical breathing, bell-shaped chest, frog-leg posturing; poor suck, swallowing reflexes
2	6–18 months	10–40 years	Sparing of face/eye muscles, tongue atrophy, minipolymyoclonus[1], scoliosis
3	> 18 months	Unchanged	Legs more likely than arms to display onset of motor symptoms, respiratory muscle weakness, scoliosis
4	> 5 months	Unchanged	Achieves all motor milestones, less severe

1 - Fine tremor-like variant of myoclonus, commonly affects distal limbs