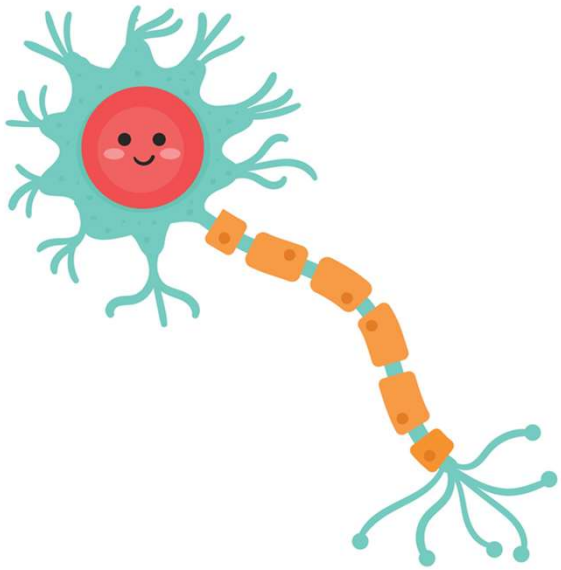
Motor Neuron disease



R2. Thanakorn Khaosuwan

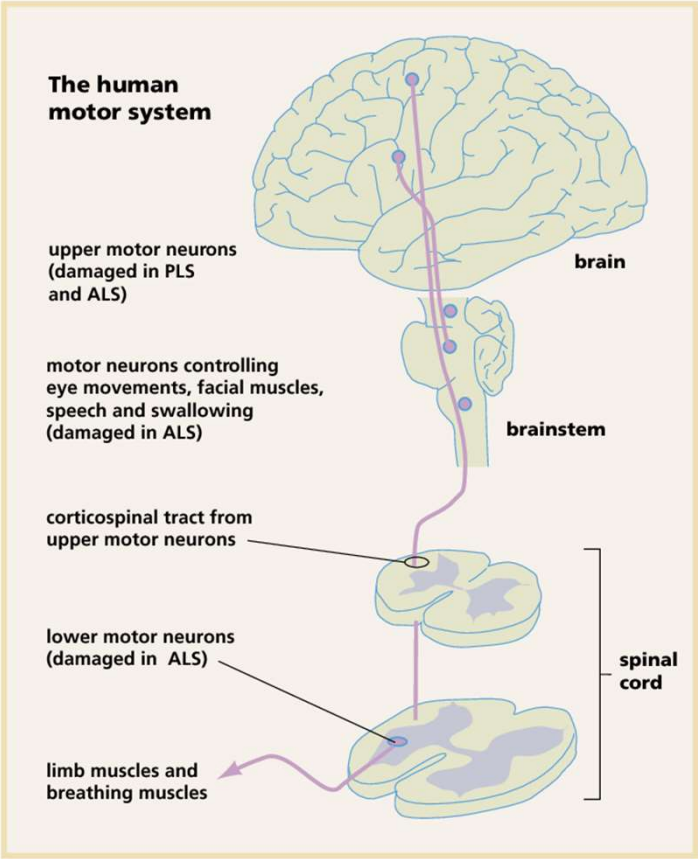
Objectives

- To recognize clinical presentations and detection of motor neuron disease
- To recognize classification, epidemiology, pathophydiology, diagnosis, genetic testing and treatments of motor neuron disease

Outline

- Motor neuron system
- Motor neuron disease
- Classification of motor neuron disease
- Epidemiology
- Pathophysiology
- Clinical presentations
- Diagnosis
- Genetic testing
- Treatment

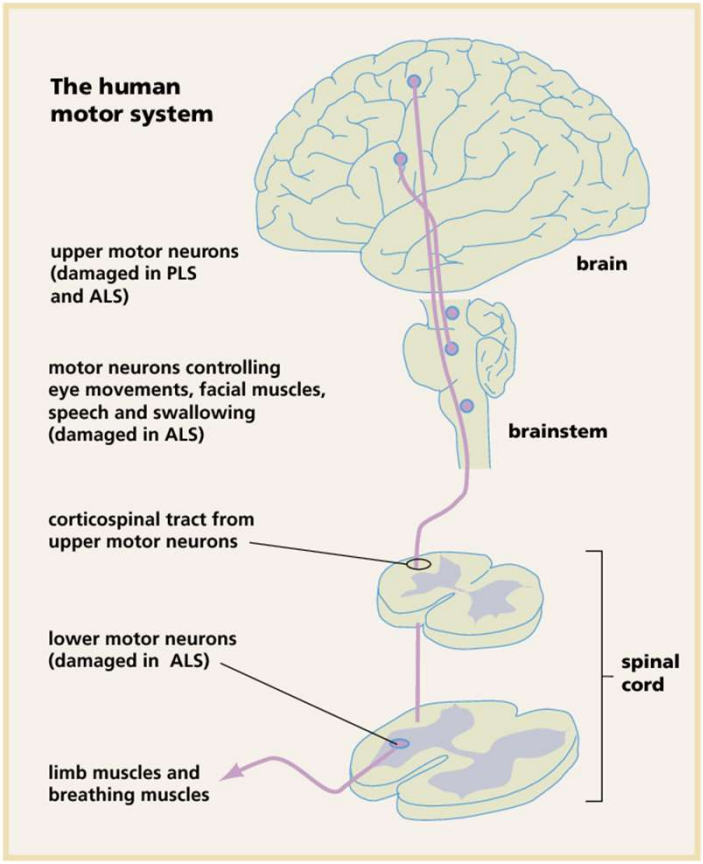
Motor neuron system



- **The motor neuron system** is composed of upper and lower motor neurons.
- **Upper motor neurons**
  - Primary motor cortex of the brain, and their axons comprise the corticobulbar tract (connecting to the brainstem) and the corticospinal tract (connecting to the spinal cord).
- **Lower motor neurons**
  - Anterior horn cells, are located in motor nuclei in the brainstem or the anterior gray matter of the spinal cord.

CONTINUUM (MINNEAP MINN) 2020;26(5, PERIPHERAL NERVE AND MOTOR NEURON DISORDERS): 1323–1347.

Motor neuron disease



- Motor neuron diseases (MND) are gradually developing disorders which results in degeneration of motor neurons in cranial nerves nuclei, spinal cord and pyramidal neurons in the motor cortex
- Mixture of UMN and LMN lesions

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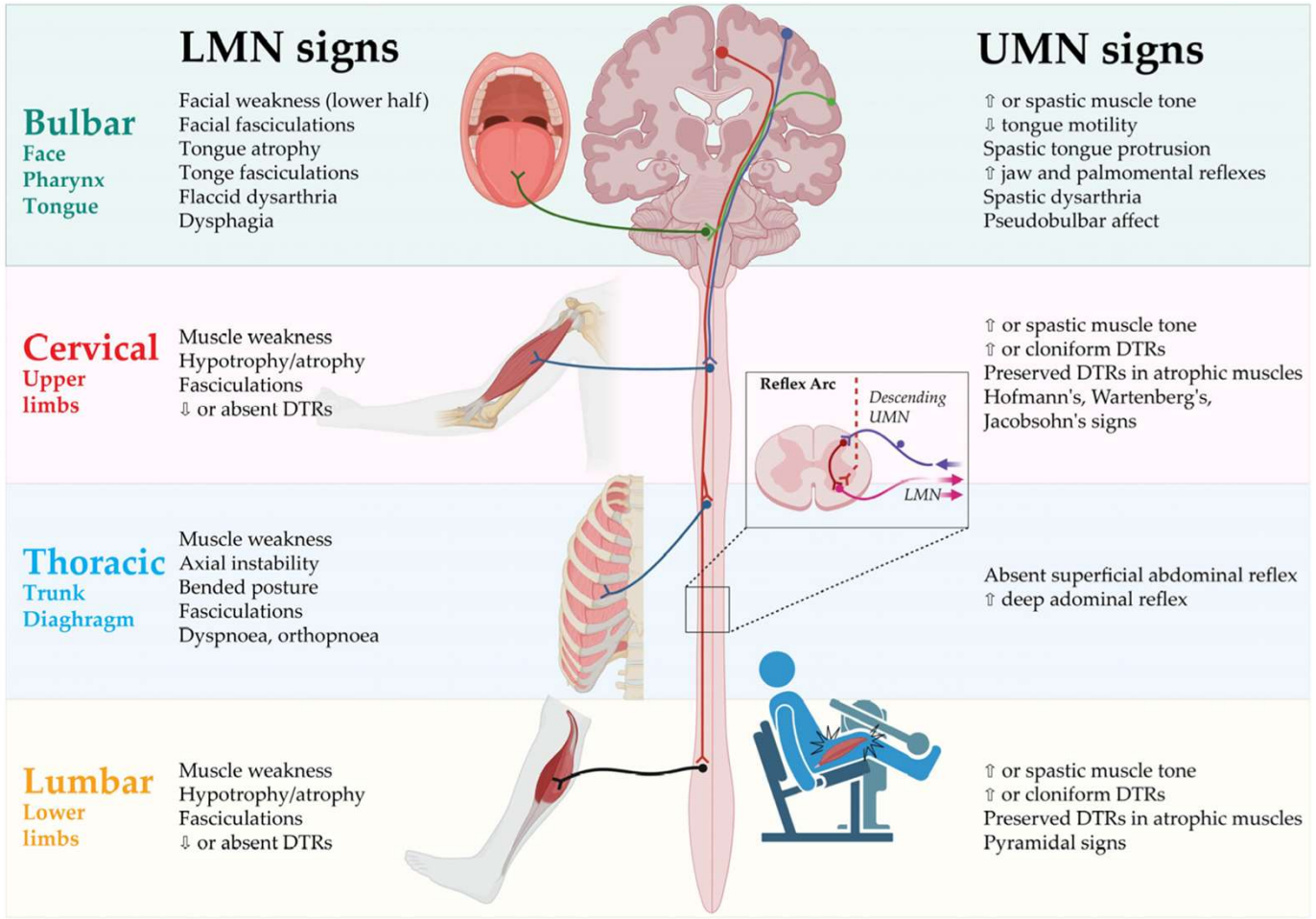


Vidovic, M.; Müschen, L.H.; Brakemeier, S.; Machetanz, G.; Naumann, M.; Castro-Gomez, S. Current State and Future Directions in the Diagnosis of Amyotrophic Lateral Sclerosis. Cells 2023, 12, 736.

Classification of Motor Neuron Diseases

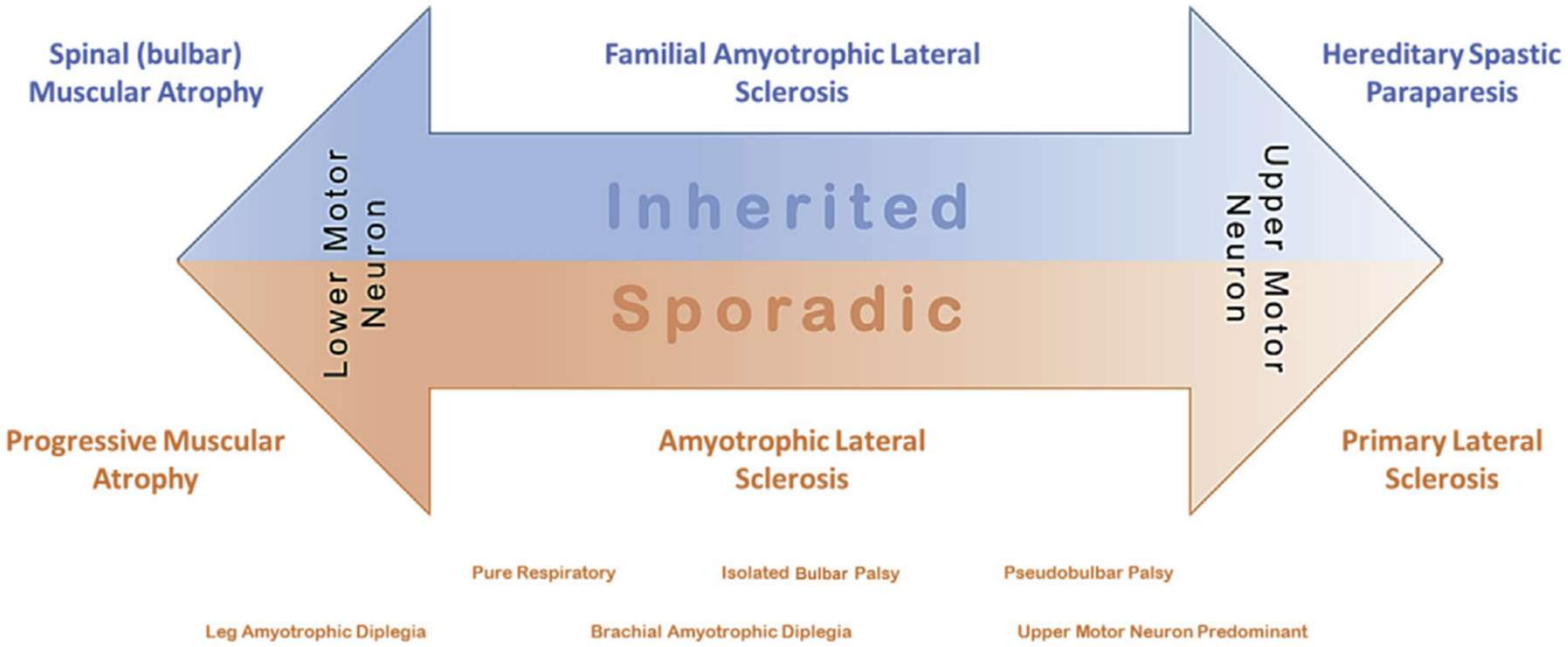


Fig. 1. The spectrum of MNDs.

Neurol Clin 33 (2015) 735–748

Classification of Motor Neuron Diseases

- Pure Lower Motor Neuron Disease
- Mixed Upper and Lower Motor Neuron Diseases
- Pure Upper Motor Neuron Diseases

Neurol Clin 33 (2015) 735–748

Classification of Motor Neuron Diseases

Pure Lower Motor Neuron Disease

Heritable disease

- Spinobulbar muscular atrophy (SMA)
- Spinobulbar muscular atrophy (SBMA) or Kennedy's disease

Sporadic disease

- Progressive muscular atrophy (PMA)

Neurol Clin 33 (2015) 735–748

Classification of Motor Neuron Diseases

Mixed Upper and Lower Motor Neuron Diseases

- Amyotrophic lateral sclerosis (ALS)
  - Both familial and sporadic ALS

Neurol Clin 33 (2015) 735–748

Classification of Motor Neuron Diseases

Pure Upper Motor Neuron Diseases

- Hereditary spastic paraplegia (HSP)
- Primary Lateral Sclerosis (PLS)

Neurol Clin 33 (2015) 735–748

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic Lateral Sclerosis (ALS)

- Fatal neurodegenerative and the most frequent motor neuron disease
- Primarily characterized by progressive weakness of voluntary muscles due to degenerating motor neurons in the brain, brainstem and spinal cord
- Non-motor symptoms, such as behavioral and cognitive impairment, and even manifest as an overlap syndrome with signs of frontotemporal dementia (FTD), known as ALS-FTD

Vidovic, M.; Müschen, L.H.; Brakemeier, S.; Machetanz, G.; Naumann, M.; Castro-Gomez, S. Current State and Future Directions in the Diagnosis of Amyotrophic Lateral Sclerosis. Cells 2023, 12, 736.

Amyotrophic Lateral Sclerosis (ALS)

Epidemiology

- The worldwide prevalence and incidence : 4.42 per 100000 population and 1.59 per 100000 person years
- Highest in western Europe and lowest in South Asia
- The prevalence and incidence of ALS is higher in men than in women

BMJ 2023;383:075037

Clinical of ALS

Amyotrophic Lateral Sclerosis (ALS)

- The clinical hallmarks of ALS are related to the impairment of voluntary muscles
- Progressive weakness of the limbs, speech and swallowing dysfunction and respiratory failure with concomitant signs, such as muscle atrophy, fasciculations and increased muscle tone.

Vidovic, M.; Müschen, L.H.; Brakemeier, S.; Machetanz, G.; Naumann, M.; Castro-Gomez, S. Current State and Future Directions in the Diagnosis of Amyotrophic Lateral Sclerosis. Cells 2023, 12, 736.

Clinical of ALS

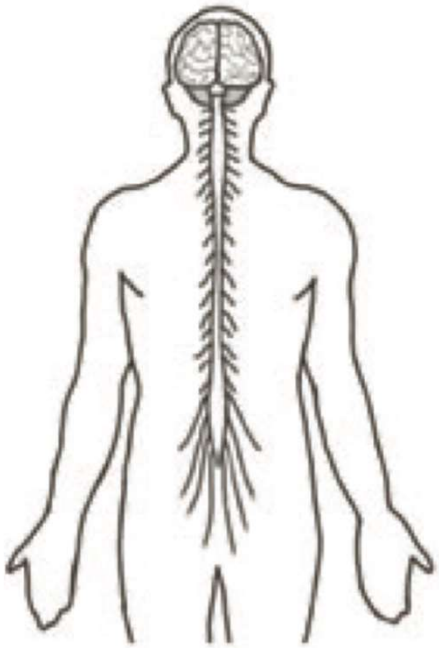
Frontotemperal dementia

Personality change
Behavioral abnormalities
Language dysfunction
Memory impairment

Limb onset

UMN signs
Weakness
Babinski's sign
Hoffman's sign
Spacicity

LMN signs
Weakness
Muscle atrophy
Fasciculations

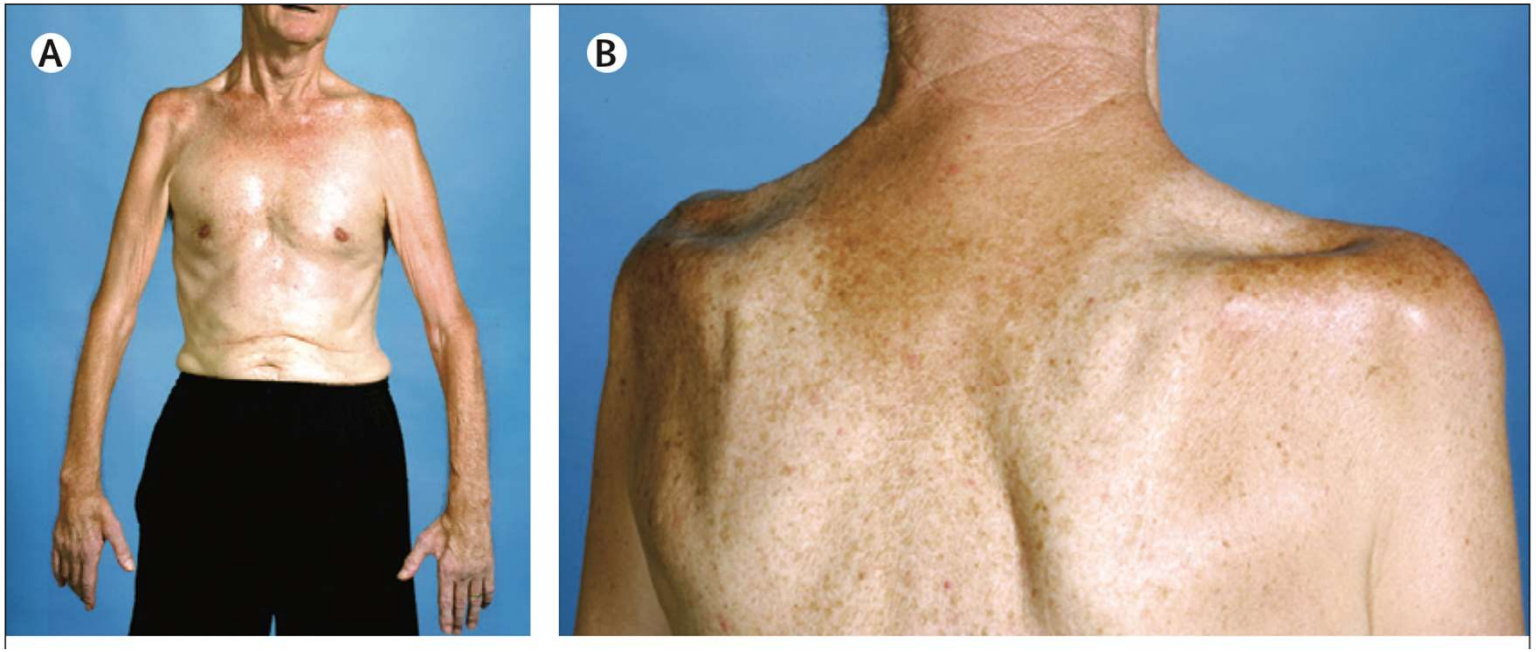


Bulbar onset

UMN signs
Slow speech
Palmomental reflex
Jaw jerk reflex

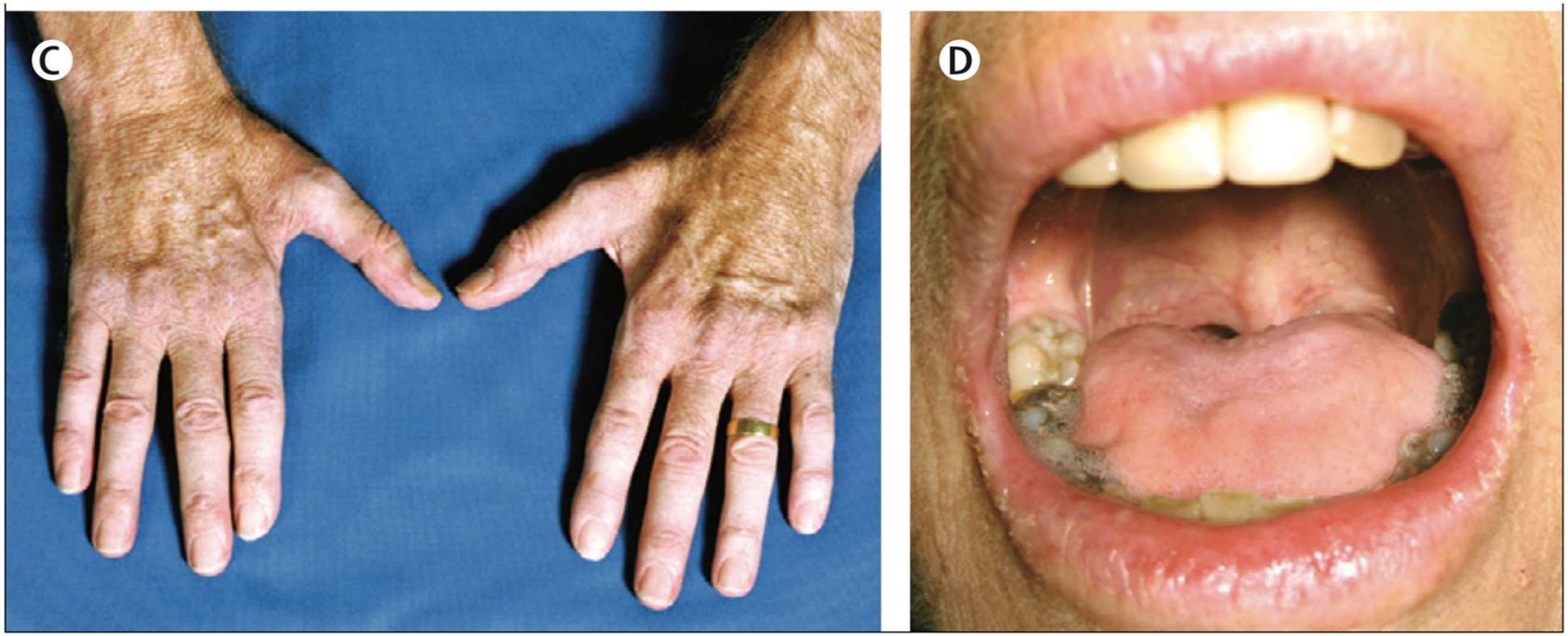
LMN signs
Facial weakness
Low palatal elevation
Dysarthria
Tongue fasciculations
Tongue atrophy

IMAJ 2019; 21: 438–443



(A) Proximal and symmetrical upper limb wasting results in an inability to lift arms against gravity ("man-in-the- barrel" or flail-arm variant ALS)
(B) Recessions above and below the scapular spine, indicating wasting of supraspinatus and infraspinatus muscles, as well as substantial loss of deltoid muscle. As a consequence, the glenohumeral joint becomes prominent, and prone to subluxation.

Lancet 2011; 377: 942–55



(C) Disproportionate wasting of the thenar muscles combined with the first dorsal interossei, the so-called “split-hand”, is a typical feature in ALS.
(D) Substantial wasting of tongue muscles in bulbar-onset ALS.

Lancet 2011; 377: 942–55

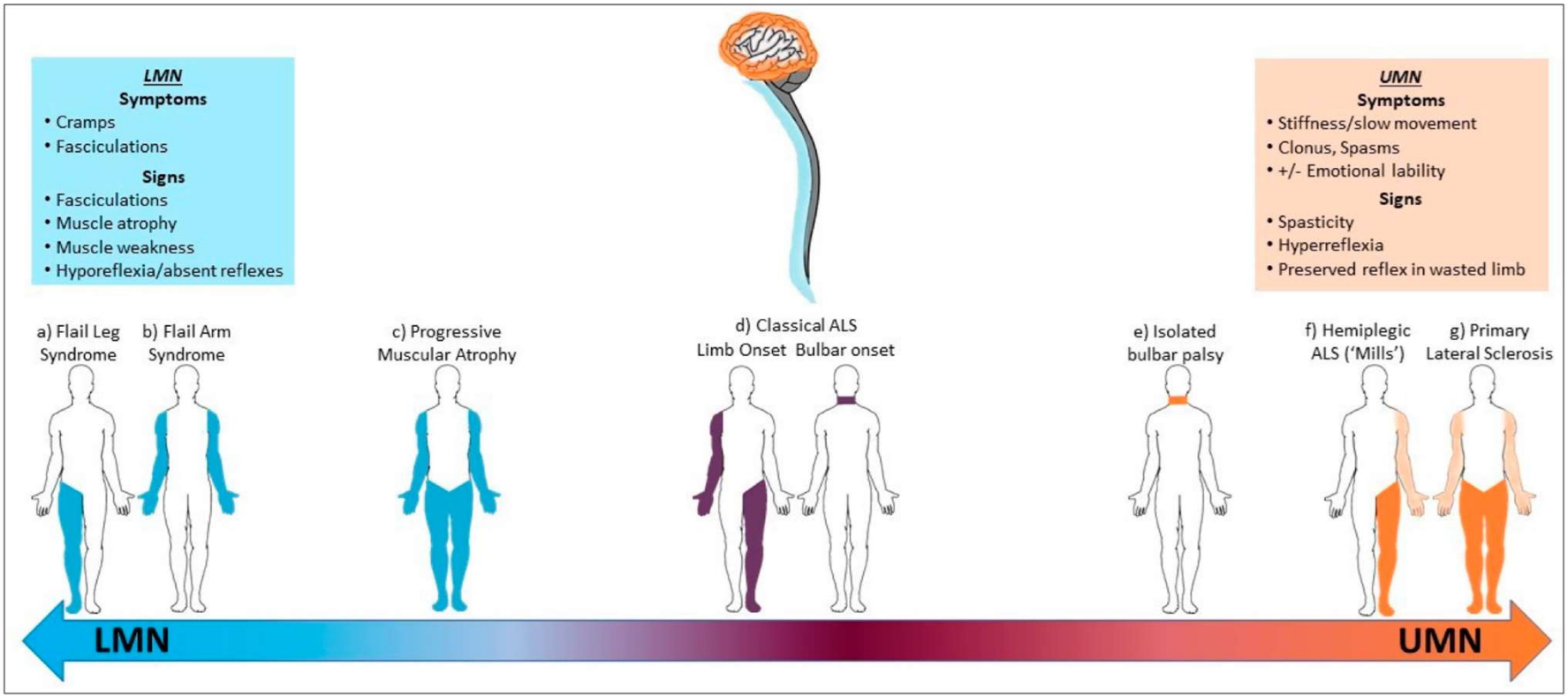


Figure 2. Pattern of motor involvement across the ALS clinical phenotypes. Blue, LMN involvement; Orange, UMN involvement; Purple, mixed (UMN/LMN) involvement.

Dharmadasa,T.Cortical Excitability across the ALS Clinical Motor Phenotypes. Brain Sci. 2021, 11, 715.

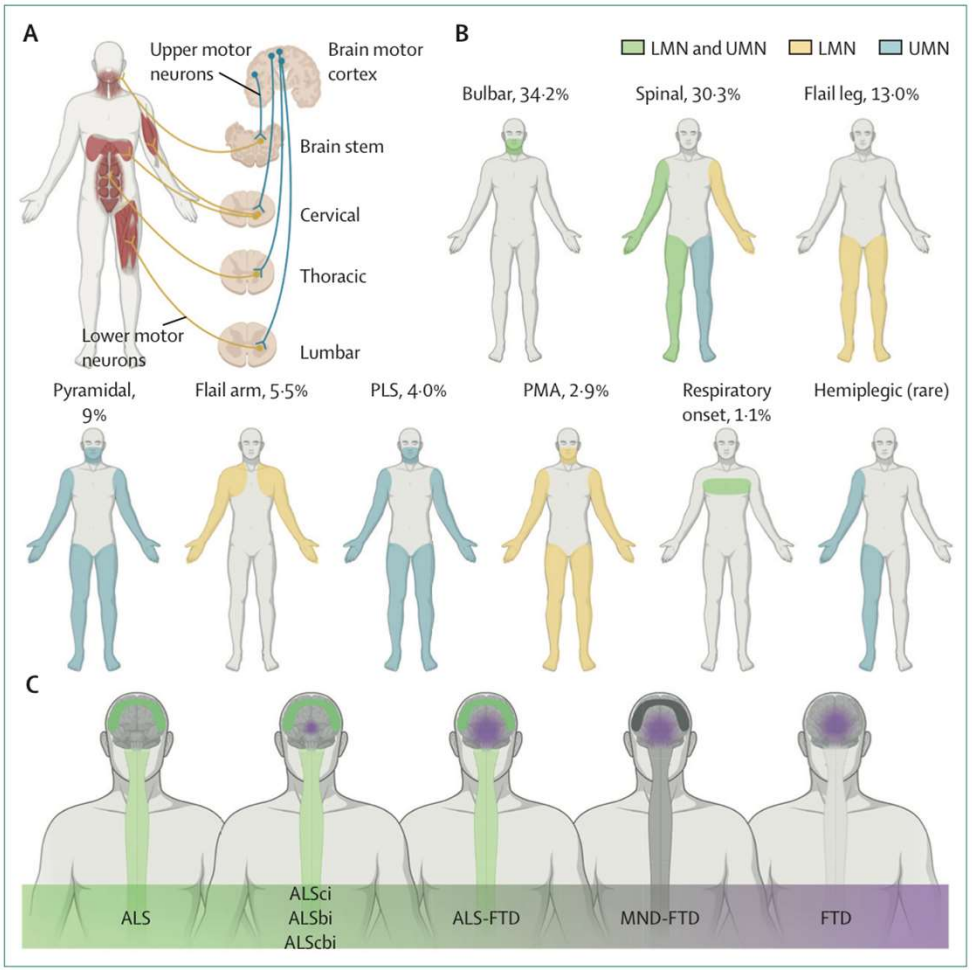


Figure 1: **Amyotrophic lateral sclerosis phenotypic variation and spectrum with frontotemporal dementia**

Lancet 2022; 400: 1363–80

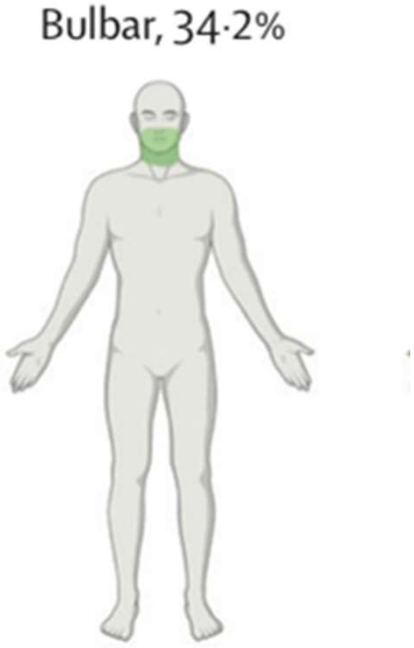
Spinal-Onset ALS

- Focal weakness in distal muscle groups of the limbs and simultaneous UMN and LMN involvement.
- Distal segments of the upper or lower limbs are affected in a focal manner at the onset of the disease.
- UMN dysfunction is not always easily identified in wasted or atrophic muscles of the limbs, particularly in the early stages of the disease

Vidovic, M.; Müschen, L.H.; Brakemeier, S.; Machetanz, G.; Naumann, M.; Castro-Gomez, S. Current State and Future Directions in the Diagnosis of Amyotrophic Lateral Sclerosis. Cells 2023, 12, 736.

Bulbar-Onset ALS

- Initial motor dysfunction in the bulbar region.
- Speech difficulties and frequent choking with concomitant hypersalivation are the cardinal presenting symptoms.
- Both LMN and UMN impairment are present, causing tongue wasting with fasciculations, facial spasticity and pseudobulbar affect in the early stages of the disease.
- Propagation to other spinal regions is evident later in the disease's course



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Progressive Muscular Atrophy (PMA)

- Clinically isolated LMN impairment of the anterior horn cells and brainstem motor nuclei.
- Subclinical UMN impairment can be detected in the early stages of the disease
- Although PMA tends to have a slower disease progression than classical ALS
- 20 to 30% of the patients may develop ALS with clinically evident UMN impairment within 5 to 10 years from the disease's onset.

Vidovic, M.; Müschen, L.H.; Brakemeier, S.; Machetanz, G.; Naumann, M.; Castro-Gomez, S. Current State and Future Directions in the Diagnosis of Amyotrophic Lateral Sclerosis. Cells 2023, 12, 736.

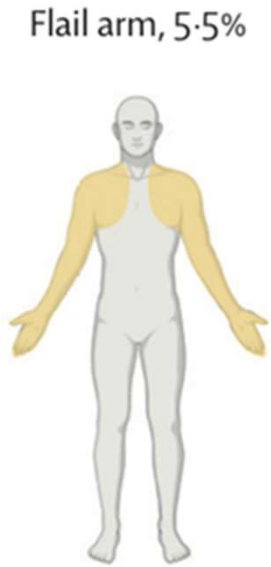
Primary Lateral Sclerosis (PLS)

- Progressive isolated UMN dysfunction detectable in at least two regions (thoracic region will not be considered) for at least two years.

Vidovic, M.; Müschen, L.H.; Brakemeier, S.; Machetanz, G.; Naumann, M.; Castro-Gomez, S. Current State and Future Directions in the Diagnosis of Amyotrophic Lateral Sclerosis. Cells 2023, 12, 736.

Flail-Arm-Syndrome

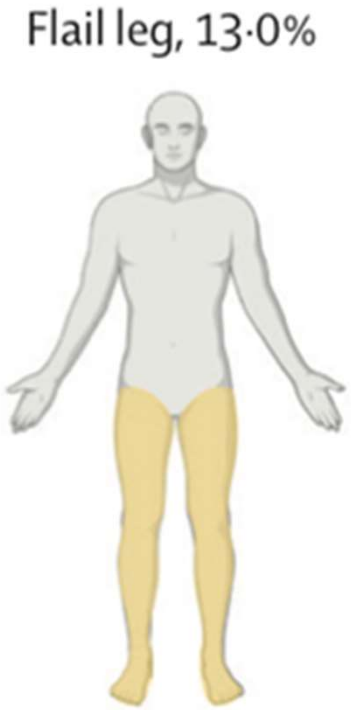
- Also known as Vulpian Bernhardt's type
- Progressive, proximal and symmetrical weakness of both upper limbs caused by LMN impairment is predominantly apparent.
- Motor symptoms in bulbar muscles or lower limbs are unaffected from 12 to 20 months after the onset of upper limb symptoms.
- Represents a rather benign phenotype with a median survival time of 4 years and a 10 year survival rate of 17%.



Vidovic, M.; Müschen, L.H.; Brakemeier, S.; Machetanz, G.; Naumann, M.; Castro-Gomez, S. Current State and Future Directions in the Diagnosis of Amyotrophic Lateral Sclerosis. Cells 2023, 12, 736.

Flail-Leg-Syndrome

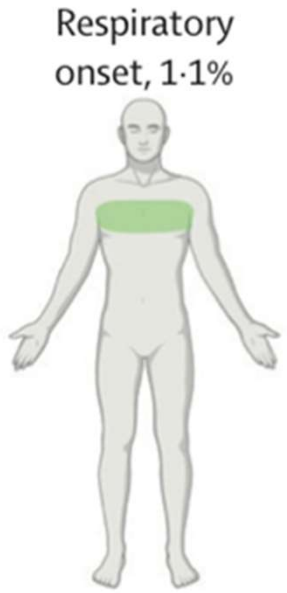
- Progressive and symmetrical weakness of both lower limbs, whereas distal muscle groups are typically affected and LMN involvement outweighs UMN involvement.
- Other segments are clinically spared for a mean of 16 months after the disease's onset.
- Unlike FAS, FLS has a similar prognosis as spinal-onset ALS, with a median survival time of 3 years and a 10-year survival rate of 13%.



Vidovic, M.; Müschen, L.H.; Brakemeier, S.; Machetanz, G.; Naumann, M.; Castro-Gomez, S. Current State and Future Directions in the Diagnosis of Amyotrophic Lateral Sclerosis. Cells 2023, 12, 736.

Axial or Respiratory-Onset ALS

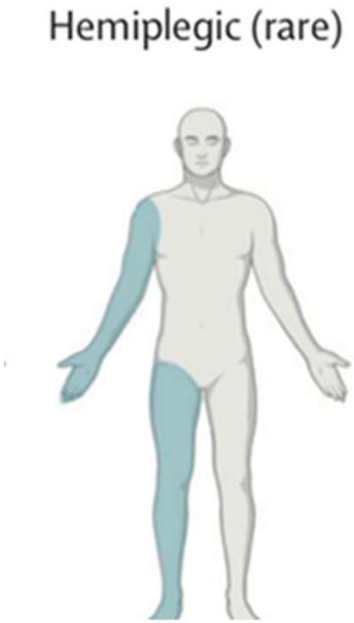
- Presents itself with weakness of trunk muscles.
- Typically, paravertebral muscles are affected, resulting in bent posture, axial instability and dropped head syndrome.
- In respiratory-onset ALS patients suffer from dyspnoea and orthopnoea at the beginning of the disease, caused by weakness of the respiratory muscles and the diaphragm, which is also anatomically related to the thoracic region.
- The prognosis is poor due to early respiratory failure and complications such as pneumonia.



Vidovic, M.; Müschen, L.H.; Brakemeier, S.; Machetanz, G.; Naumann, M.; Castro-Gomez, S. Current State and Future Directions in the Diagnosis of Amyotrophic Lateral Sclerosis. Cells 2023, 12, 736.

Hemiplegic ALS (Mill's Syndrome)

- Very rare phenotype is defined by slowly progressive, unilateral muscle weakness in the limbs alongside clinically predominant UMN signs, such as pathological deep tendon reflexes (DTR) and pyramidal tract signs.
- The onset may either occur in the upper limbs with subsequent descending propagation to the lower limbs or vice versa.



Vidovic, M.; Müschen, L.H.; Brakemeier, S.; Machetanz, G.; Naumann, M.; Castro-Gomez, S. Current State and Future Directions in the Diagnosis of Amyotrophic Lateral Sclerosis. Cells 2023, 12, 736.

***Panel 1*: Definitions of amyotrophic lateral sclerosis motor signs and phenotypes**

Lower motor neurons (LMN)
- Brainstem cranial motor nerve nuclei or anterior horn cells
- LMN dysfunction is characterised by muscle weakness, atrophy, and fasciculations

Upper motor neurons (UMN)
- Betz cells in layer V of the primary motor cortex
- UMN dysfunction is characterised by increased and pathological reflexes (including Hoffmann's sign, Babinski, and snout), pathological spread of reflexes, preserved reflexes in a weak limb, and spasticity

Bulbar amyotrophic lateral sclerosis
- Phenotype presents with weakness starting in the muscles controlling speaking and swallowing
- Both LMN and UMN signs are present

Pseudobulbar palsy
- A non-classical subset of bulbar onset, characterised by prominent bulbar features, predominantly from UMN signs, which slowly spread to limbs

Pseudobulbar affect
- Uncontrollable emotional outbursts, including laughing, crying, and excessive yawning

Classical amyotrophic lateral sclerosis
- Phenotype presents with muscle weakness starting in the limbs; both LMN and UMN signs are present

Cervical-onset amyotrophic lateral sclerosis
- A subset of classical amyotrophic lateral sclerosis with weakness commencing in the upper limbs, especially hand weakness

Lumbar-onset amyotrophic lateral sclerosis
- A subset of classical amyotrophic lateral sclerosis with weakness commencing in the lower limbs, especially foot drop

Flail arm
- Prominent LMN dysfunction initially causing proximal muscle weakness greater than distal muscle weakness in the arms
- Unlike progressive muscular atrophy, patients with flail arm do manifest progressive UMN dysfunction; this entity can also be referred to as brachial amyotrophic diplegia

Flail leg:
- LMN dysfunction causing muscle weakness in the legs; unlike progressive muscular atrophy, this phenotype does not generalise or generalises very slowly

Primary lateral sclerosis*:
- UMN dysfunction causing weakness in muscles controlling limbs, swallowing, and speaking
- Less commonly causes respiratory dysfunction

Pyramidal:
- Like primary lateral sclerosis but additionally eventually exhibiting LMN signs

Progressive muscular atrophy*:
- LMN dysfunction causing weakness in muscles controlling limbs, swallowing, speaking, and respiratory function

Respiratory onset
- LMN and UMN dysfunction causing weakness commencing in the respiratory muscles

Hemiplegic
- Predominantly UMN dysfunction causing muscle weakness in one side of the body

Cachexia
- Unexplained weight and muscle loss

*This Seminar considers primary lateral sclerosis and progressive muscular atrophy on the spectra of amyotrophic lateral sclerosis phenotypes, although they can also be considered as separate clinical entities.

Lancet 2022; 400: 1363–80

Diagnostic Criteria

Table 1. The revised El Escorial criteria (2000) and the Awaji criteria (2008).

Clinically definite ALS	Clinical or electrophysiological * evidence of UMN and LMN involvement in bulbar region and ≥2 spinal regions *or* Clinical or electrophysiological * evidence of UMN and LMN involvement in 3 spinal regions
Clinically probable ALS	Clinical or electrophysiological * evidence of UMN and LMN involvement in ≥2 regions with UMN signs rostral to LMN signs
Clinically probable Laboratory-supported ALS ♦	Clinical evidence of UMN and LMN involvement in 1 region *or* Clinical evidence of isolated UMN involvement in 1 region with electrophysiological evidence of LMN involvement in ≥2 regions
Clinically possible ALS	Clinical or electrophysiological * evidence of UMN and LMN involvement in 1 region *or* Evidence of isolated UMN involvement ≥2 regions *or* Evidence of LMN involvement rostral to UMN involvement

Diagnostic Criteria

Table 2. The Gold Coast criteria (2020).

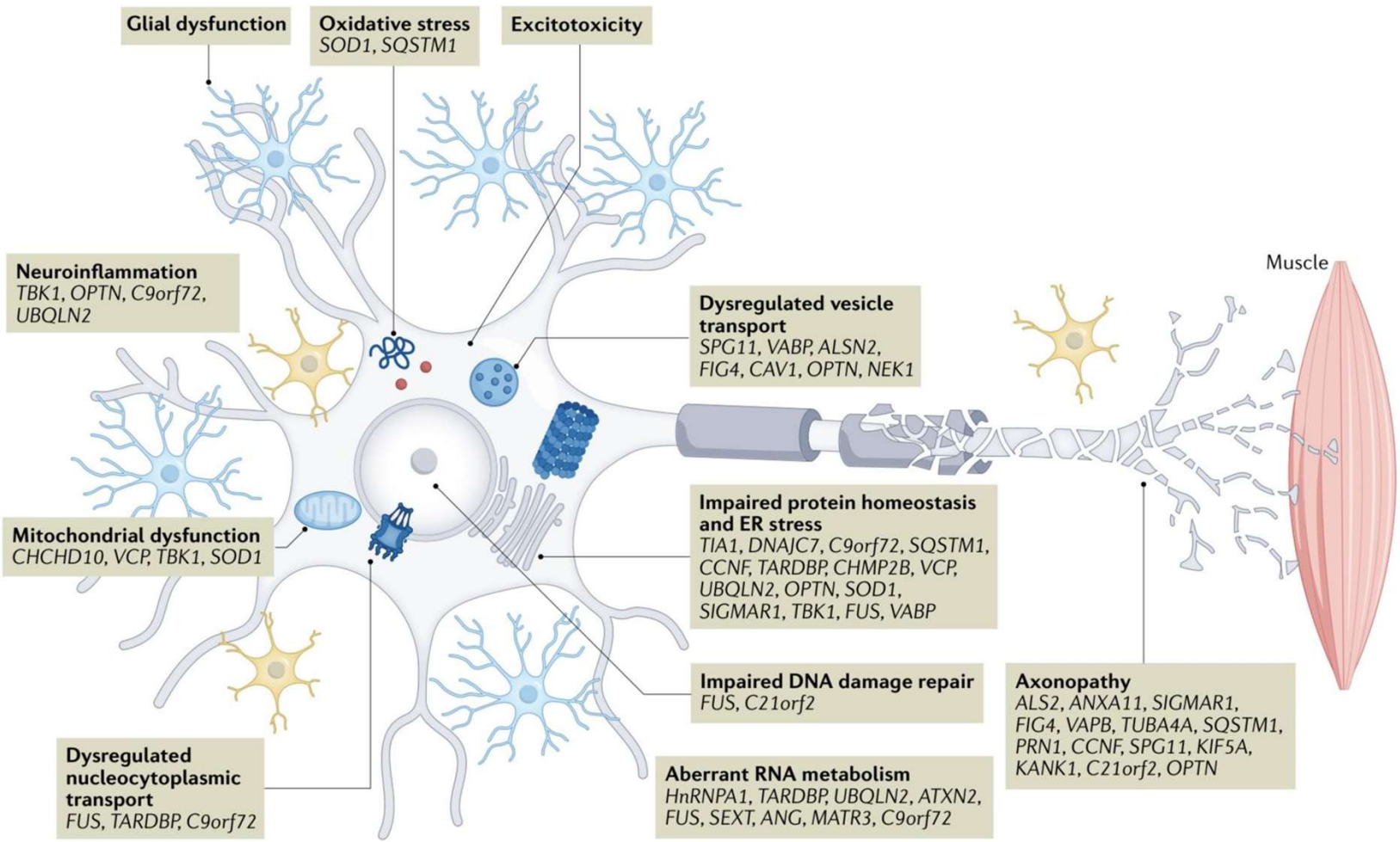
Progressive motor impairment *and* Clinical or electrophysiological UMN and LMN involvement in ≥1 region *or* only LMN involvement in ≥2 regions *and* Exclusion of other diseases

UMN: upper motor neuron; LMN: lower motor neuron.

Studies evaluating the feasibility of the Gold Coast criteria to date have shown an increase in diagnostic sensitivity with largely preserved high specificity

Vidovic, M.; Müschen, L.H.; Brakemeier, S.; Machetanz, G.; Naumann, M.; Castro-Gomez, S. Current State and Future Directions in the Diagnosis of Amyotrophic Lateral Sclerosis. Cells 2023, 12, 736.

Pathophysiology



Mead, R.J., Shan, N., Reiser, H.J. et al. Amyotrophic lateral sclerosis: a neurodegenerative disorder poised for successful therapeutic translation. Nat Rev Drug Discov 22, 185–212 (2023).

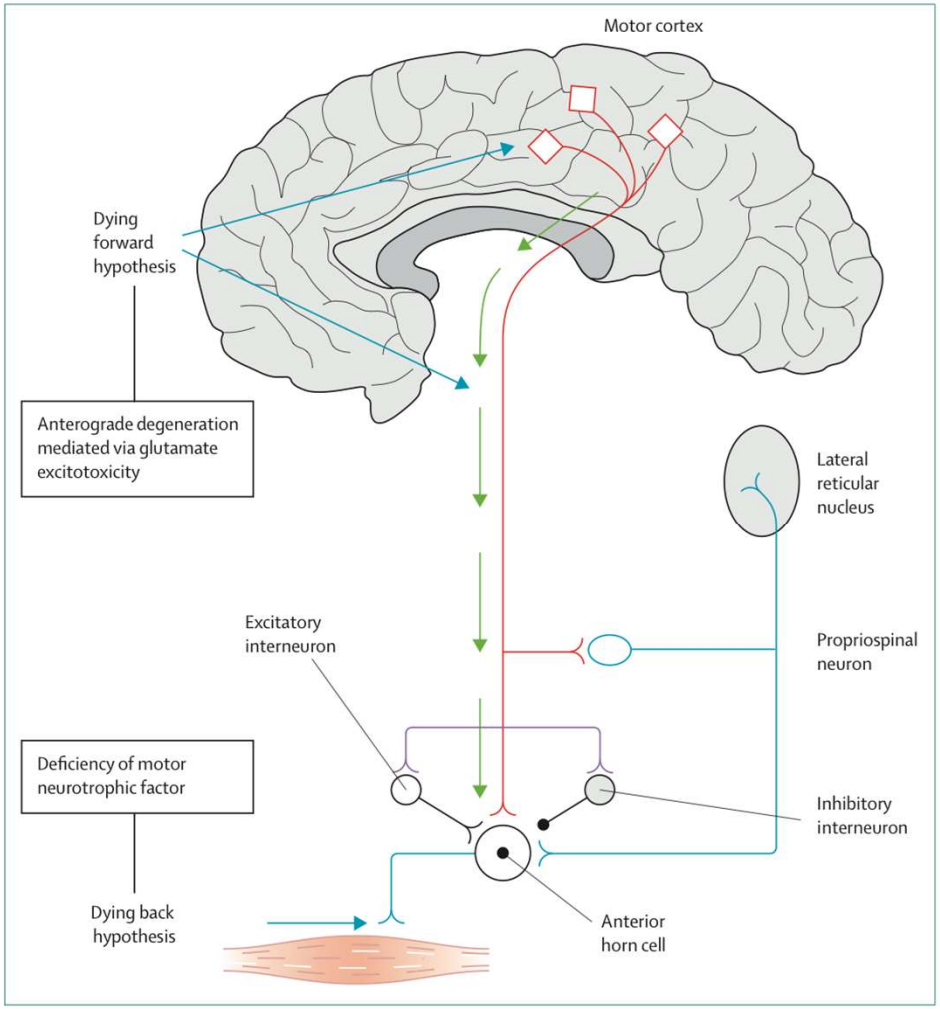


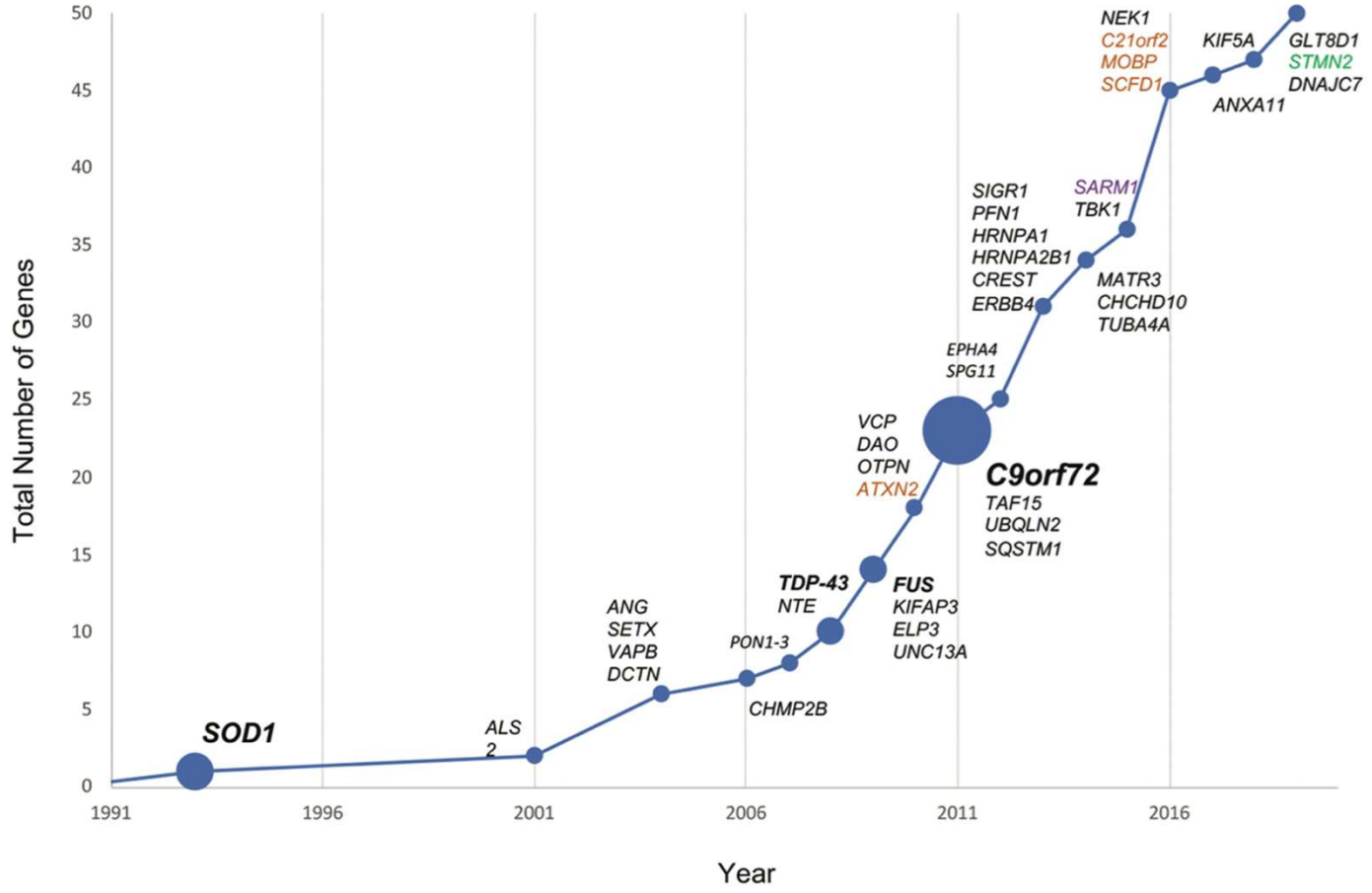
***Figure 3*: The "dying-forward" and "dying-back" hypotheses**

Lancet 2011; 377: 942–55

Molecular pathomechanisms

- Most common neuropathological signature of ALS is cytoplasmic aggregation of TDP-43 protein, a protein encoded by TARDBP(found in 97% of cases of sporadic ALS)
- Other aggregating proteins, such as SOD1 and FUS, are found in patients with SOD1 mutation and FUS mutations
- Patients with C9ORF72 (chromosome 9, open reading frame 72) hexanucleotide repeat expansions have accumulations of dipeptide.

BMJ 2023;383:075037



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Mutations involving in the ALS pathogenesis and progression.

Mutation	Description	Role in ALS
SOD1	Superoxide dismutase enzyme breaks down superoxide radicals such as hydrogen peroxide and molecular oxygen [3,4,5,11,50].	Toxic gain mutations in this gene is causing formation of SOD1 aggregates in the neuron cells [3,4,5,11,50].
TARDBP	TAR DNA Binding Protein encodes DNA binding protein 43 kDa (TDP-43) involving in the protein synthesis in the neuron cells. Also, responsible for RNA stability [3,4,5,11,50].	Mutation causes in the formation of TDP-43 aggregates in the motor neurons [3,4,5,11,50].
FUS	FUS RNA Binding Protein is involving in the protein synthesis in the cell nucleus. FUS regulates transcription and alternative splicing [3,4,5,11,50].	Mutation causes impairment in the mRNA transport which results in the protein aggregates in the motor neurons [3,4,5,11,50].
C9ORF72	C9orf72 protein is most abundant in neurons, cerebral cortex and motor neurons. It is responsible for transcription, mRNA processing and transportation [3,4,5,11,50].	GGGGCC repeats in C9orf72 were found ~40% familial cases and ~7% sporadic cases. Mutation results in the RNA toxicity [3,4,5,11,50].
CHCHD10	Gene encodes a small protein found in the mitochondrial intermembrane space and involving in the oxidative phosphorylation [5,11,50].	Mutation may impair mitochondrial import and oxidative phosphorylation [5,11,50].
OPTN	Gene encodes optineurin protein involving in the membrane trafficking, exocytosis and golgi function [5,11,50].	Mutations cause autophagy in the neuron cells [5,11,50].
VCP	Valosin-containing protein encodes a protein involving in the apoptosis, cell division and repairing DNA damages [5,11,50].	Mechanism is unknown.
UBQLN2	Ubiquilin2 is responsible for the degradation of misfolded proteins [66].	Mutations cause neuro-inflammation and formation of protein aggregates like TDP-43 [66].
PFNF1	Protein is involving in the neuronal growth and differentiation, membrane trafficking and actin cytoskeleton formation [3,4,5,11,50].	Mechanism is unknown [3,4,5,11,50].
TBK1	Gene encodes a protein kinase involving in the autophagy and immune response [67].	Mutation may cause autophagy in the neuron cells [67].

Environmental exposure

The gene–time–environment hypothesis of amyotrophic lateral sclerosis suggests that genetic susceptibility, age-related cellular damage, and a burden of environmental exposures combine to trigger amyotrophic lateral sclerosis.

Treatment

Disease-modifying treatments

- Only two drugs with regulatory approval are available
- Riluzole and edaravone
    - They are of marginal efficacy and only in select populations, and merely lengthen survival by a few months.

Lancet 2022; 400: 1363–80

Symptomatic treatments

Symptom	Nonpharmacologic Management	Pharmacologic Management
Bulbar segment		
Dysarthria	Early voice banking, augmentative communication devices	None
Dysphagia/weight loss	Alteration of food consistencies, behavioral strategies for eating (small bites, chin tuck), offer feeding tube placement	None
Weak cough	Insufflator-exsufflator, aggressive secretion management	None
Sialorrhea	Suction device, radiation therapy	Tricyclic antidepressants, anticholinergics, botulinum toxin injection to the salivary glands
Thickened secretions	Ensure adequate hydration	Guaifenesin, nebulized medications (saline bullets, albuterol with acetylcysteine)
Laryngospasm	Botulinum toxin to laryngeal adductor muscles, tracheostomy	Clonazepam
Jaw clenching/ biting	Bite guard	Clonazepam, baclofen, botulinum toxin injection to specific muscles
Pseudobulbar affect	None	Dextromethorphan HBr/quinidine sulfate, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants
Limb-related		
Weakness	Energy conservation, bracing and adaptive equipment	None

CONTINUUM (MINNEAP MINN) 2020;26(5, PERIPHERAL NERVE AND MOTOR NEURON DISORDERS): 1323–1347.

Symptom	Nonpharmacologic Management	Pharmacologic Management
Spasticity	Stretching regimen	Oral centrally acting muscle relaxants (baclofen, tizanidine), benzodiazepines, gabapentin, intrathecal baclofen via pump, botulinum toxin injection to specific muscles
Cramps	Stretching/position change	Mexiletine, phenytoin, levetiracetam
Contractures	Splints in neutral for wrists/fingers and ankles	None
Respiratory		
Respiratory insufficiency	Noninvasive positive pressure ventilation, invasive ventilation	Morphine for air hunger
Other		
Cognitive-behavioral impairment	Caregiver education regarding presence of cognitive-behavioral issues	Low-dose SSRIs, low-dose trazodone, low-dose atypical antipsychotics (olanzapine, quetiapine, aripiprazole)[a]
Depression	Counseling	Antidepressant medications
Anxiety	Meditation, biofeedback	Buspirone, antidepressants with anxiolytic indication (SSRIs, serotonin norepinephrine reuptake inhibitors [SNRIs]), benzodiazepines
Insomnia	Sleep hygiene	Melatonin, sedative hypnotics, trazodone, mirtazapine
Anorexia	Offer feeding tube placement	Megestrol, dronabinol, mirtazapine, steroids

CONTINUUM (MINNEAP MINN) 2020;26(5, PERIPHERAL NERVE AND MOTOR NEURON DISORDERS): 1323–1347.

Spinal muscular atrophy

Spinal muscular atrophy (SMA)

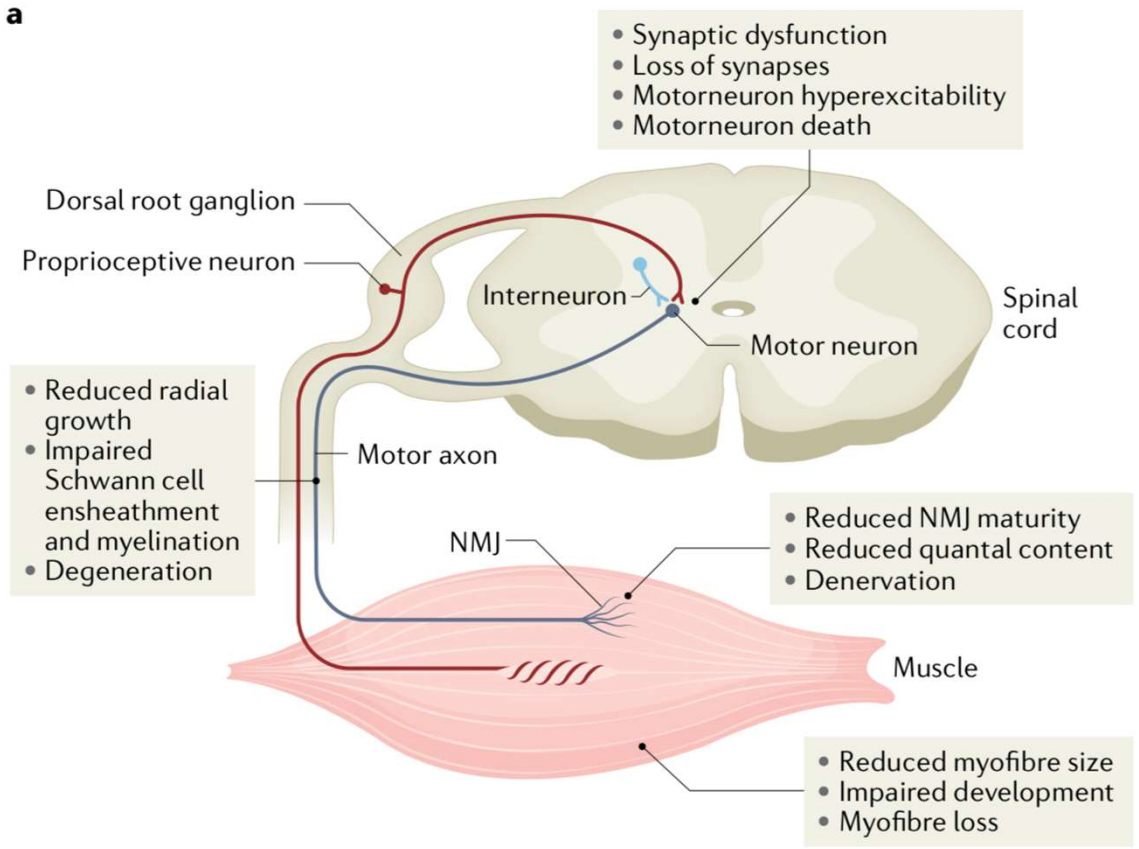
- Classic spinal muscular atrophy (SMA) is an autosomal recessive disease caused by mutations in SMN1 on chromosome 5 leading to reduced expression of survival motor neuron protein (SMN).
- This causes dysfunction and degeneration of α-motor neurons in the spinal cord and brainstem, in addition to progressive muscle atrophy and weakness of limb, trunk, bulbar and respiratory muscles.

Mercuri, E., Sumner, C.J., Muntoni, F. et al. Spinal muscular atrophy. Nat Rev Dis Primers 8, 52 (2022).

Epidemiology

- The worldwide incidence of SMA is 1 in 10,000 live births or 7.8–10 in 100,000 live births

Pathophysiology



Mercuri, E., Sumner, C.J., Muntoni, F. et al. Spinal muscular atrophy. Nat Rev Dis Primers 8, 52 (2022).

Table 1 | **Historical classification of SMA**

SMA type	Typical age at presentation (range)	Maximal motor function achieved with supportive care	Feeding and communication	Pulmonary function	Survival[a] with supportive care
0	Fetal	Nil	Nil	Very poor	Days–weeks
1	3 months (0–6 months)	No sitting or rolling	Poor, requires support	Poor, requires support	Months (median ~10 months)
2	12 months (7–18 months)	Sits, no walking	Variably affected	Reduced, often needs support	Years (median >20 years)
3	3 years (1.5–10 years)	Walks (limited)	Normal	No symptoms, mild reduction possible	Normal
4	>18 years	Walks (normal)	Normal	Normal	Normal

SMA, spinal muscular atrophy. [a]Survival includes 'event-free survival' (ventilation support for <16 h/day for ≥14 days).

Mercuri, E., Sumner, C.J., Muntoni, F. et al. Spinal muscular atrophy. Nat Rev Dis Primers 8, 52 (2022).

Diagnosis

- Genetic diagnosis
- 95% of patients with SMA harbour homozygous deletions of exons 7 and 8 or only of exon 7 in SMN1.
- Biallelic mutations in SMN1 provide genetic confirmation of 5q-SMA.
- New recommendations highlight the need to also determine SMN2 copy number as it provides information on disease severity in symptomatic patients and identifies which presymptomatic patients should undergo treatment.

Mercuri, E., Sumner, C.J., Muntoni, F. et al. Spinal muscular atrophy. Nat Rev Dis Primers 8, 52 (2022).

Treatment

- Nusinersen, onasemnogene abeparvovec and risdiplam have received regulatory approval by the FDA and EMA for the treatment of SMA, and are available in many countries worldwide.

Mercuri, E., Sumner, C.J., Muntoni, F. et al. Spinal muscular atrophy. Nat Rev Dis Primers 8, 52 (2022).

Kennedy’s disease or spinal bulbar muscular atrophy

Spinal bulbar muscular atrophy

- Slowly progressive multisystem disorder predominately affecting the peripheral nervous system
- An inherited X-linked mutation of the androgen receptor gene with males usually affected but rarely females may exhibit some mild symptoms (such as cramps).
- The slowly progressive disease course of lower motor neuron dysfunction in this rare disorder leads to the frequent misdiagnosis as amyotrophic lateral sclerosis (ALS).
- The disease spectrum encompasses in addition to the hallmark of progressive motor deficit, other manifestations such as sensory neuronopathy and hormonal dysregulation (infertility, gynecomastia) which is often times unnoticed or unlinked to the primary symptoms

Acta Neurologica Belgica (2020) 120:1289–1295

Epidemiology

- Difficult to estimate the exact prevalence of Kennedy’s disease since it is rare with variable incidence across different populations.

Pathophysiology

- The only X-linked polyglutamine disease caused by an expansion in CAG triplet repeats (> 38 repeats) leading to the formation of an abnormal protein.
- This disorder has a remarkable phenomenon of genetic anticipation where longer triplet repeats lead to a longer polyglutamine expansion causing earlier disease onset with worse clinical manifestation.

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Spinal bulbar muscular atrophy

Table 1 Manifestations and diagnostic findings in Kennedy's disease

Neurological manifestations (according to system involvement)	Non-neurological manifestations
Lower motor neuron disorder	Gynecomastia
Weakness, muscle atrophy (including tongue), cramps, fasciculations, dysarthria, dysphagia, dysphonia, muscle atrophy, quivering chin, tremor	Decreased facial hair growth
Myopathy	Decreased libido
Weakness, cramps, muscle atrophy, postural tremor, fatigue, myalgias	Erectile dysfunction
Sensory neuronopathy	Sterility
Numbness, tingling, parasthesias	Testicular atrophy
Central nervous system	
Postural and kinetic tremor, jaw tremor, memory dysfunction, poor sleep quality, sleep apnea	

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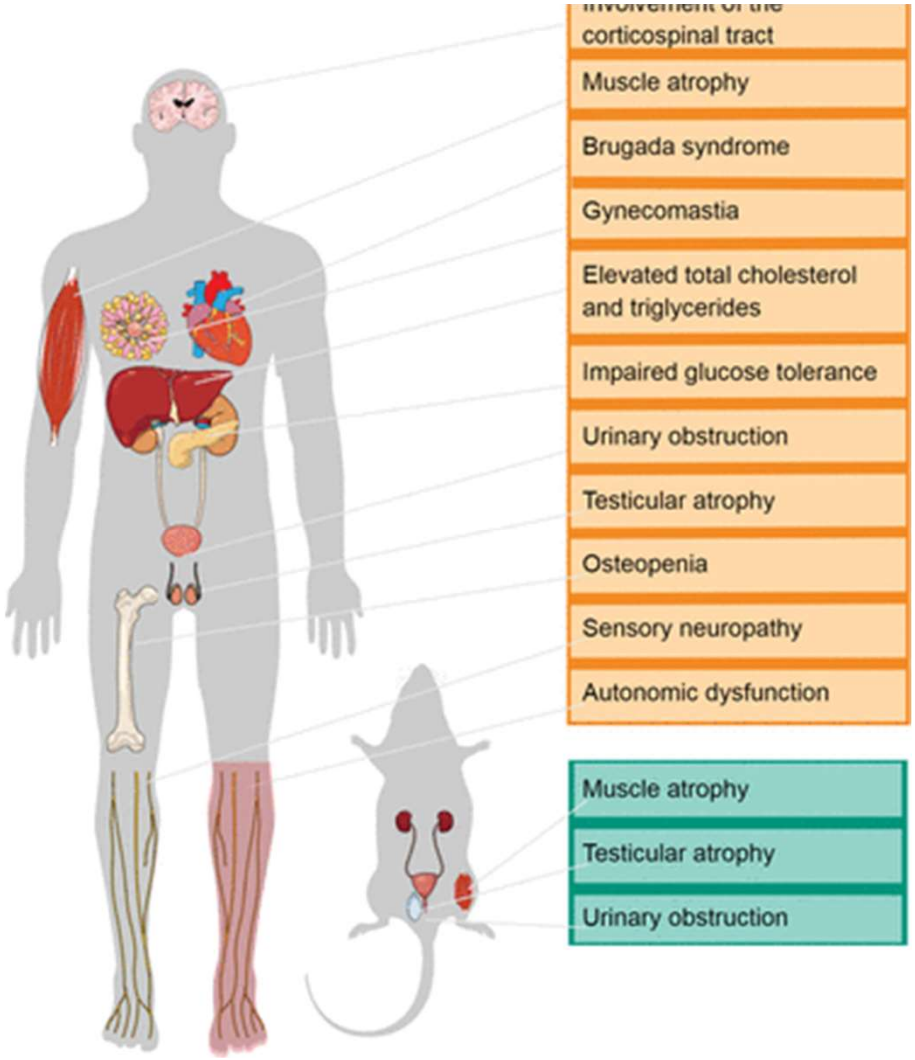

Manzano R,Sorarú G, Grunseich C, et al. J Neurol Neurosurg Psychiatry 2018;89:808–812.

Diagnostic studies

- **Electrophysiological study** includes a relatively inactive and chronic slowly progressive motor axonal polyneuropathy with evidence of sensory polyneuronopathy.
- **Needle electromyographic examination** reveals chronic neurogenic changes along with a relatively less pronounced spontaneous activity in the form of fibrillation potentials and positive sharp waves.
- **Nerve conduction studies** in almost all patients reveal evidence of sensory neuronopathy of the axonal type.

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Treatment

- No specific treatment for disease progression
- Symptomatic treatment

Hereditary spastic paraplegia (HSP)

Hereditary spastic paraplegia (HSP)

- A rare neurodegenerative disorder with the predominant clinical manifestation of spasticity in the lower extremities.
- Categorised based on inheritance, the phenotypic characters, and the mode of molecular pathophysiology, with frequent degeneration in the axon of cervical and thoracic spinal cord's lateral region, comprising the corticospinal routes

Meyyazhagan A, Orlacchio A. Hereditary Spastic Paraplegia: An Update. Int J Mol Sci. 2022 Feb 1;23(3):1697.

Epidemiology

- The prevalence ranges from 0.1 to 9.6 subjects per 100,000 reported around the globe.

Meyyazhagan A, Orlacchio A. Hereditary Spastic Paraplegia: An Update. Int J Mol Sci. 2022 Feb 1;23(3):1697.

Hereditary spastic paraplegia (HSP)

Table 1. The clinical manifestations of pure and complex HSP and a list of the prevalent clinical manifestations observed in HSP.

Pure HSP	Complex HSP
• Progressive lower-extremity spastic weakness • Difficulty walking—need for canes, walkers, or wheelchairs • Mild diminution of lower-extremity vibration sensation • Hypertonic urinary bladder disturbance • Possible urinary urgency • Lower-extremity paraesthesias • Normal strength and dexterity of the upper extremities • No involvement of speech, chewing, or swallowing • Disabling symptoms without shortened life span	Impairments present in uncomplicated HSP plus other neurologic findings such as: Ataxia Seizures Intellectual disability Dementia Muscle atrophy Extrapyramidal disturbance Peripheral neuropathy

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Hereditary spastic paraplegia (HSP)

Table 2. Classification of HSP.

Criteria for Classification	Types
Symptoms and signs (Harding's classification)	Pure HSP Complex HSP
Age and onset of spasticity (Harding's classification)	Type I HSP (Early onset < 35 years) Type II HSP (Classical/late onset > 35 years)
Inheritance pattern	Autosomal dominant HSP Autosomal recessive HSP X-linked HSP Mitochondrial HSP *De Novo*
Intracellular involvement	Membrane/organelle trafficking Axonal transport Dysfunction of mitochondria Defective lipid metabolism Abnormalities in the myelination process

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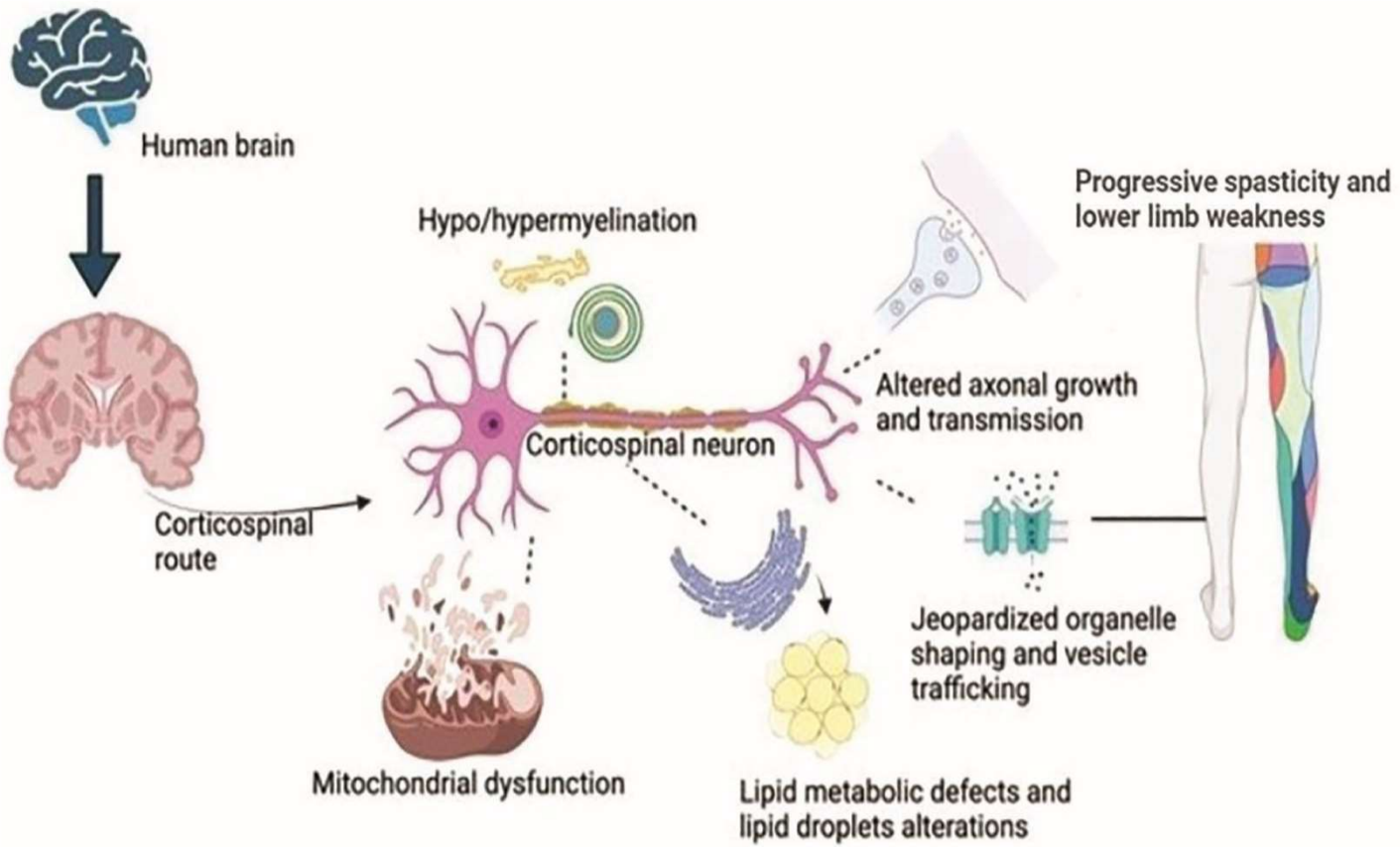

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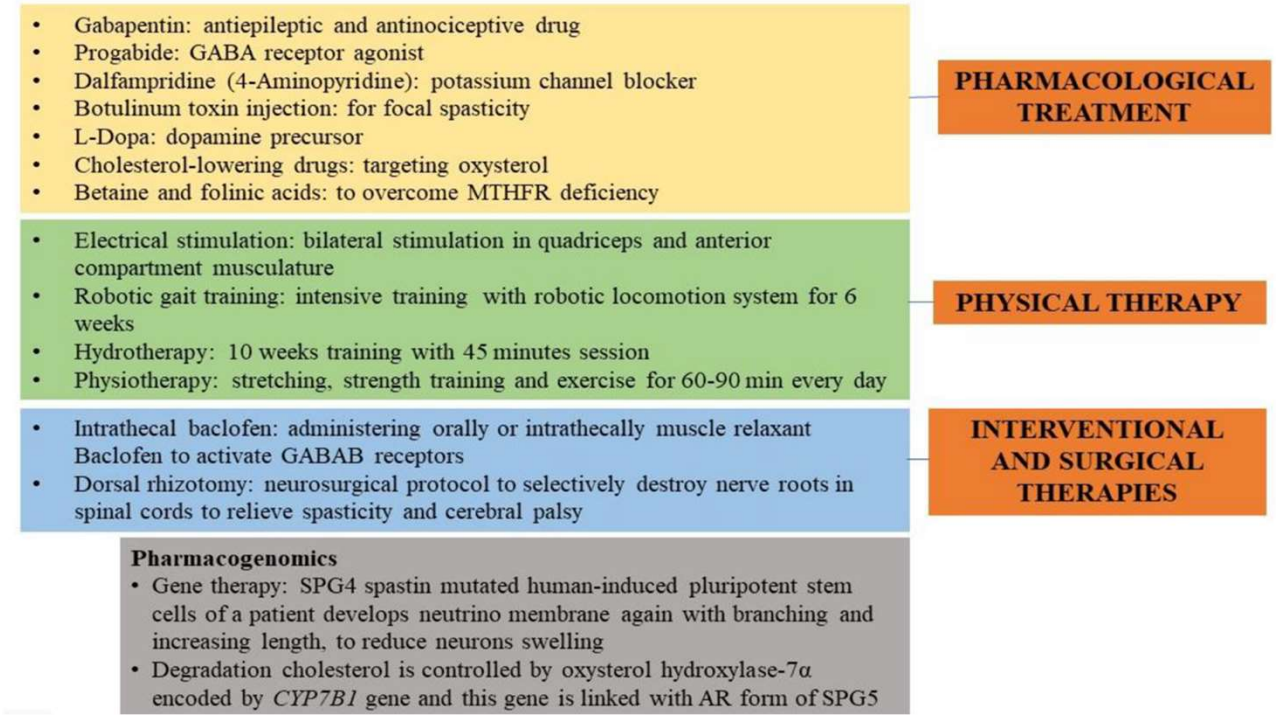

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Thank you for your attention