Amyotrophic Lateral Sclerosis (ALS) What, When and Where?

Tania Beltran Papsdorf, MD

Midwest Mechanical Ventilation and Critical Care Conference

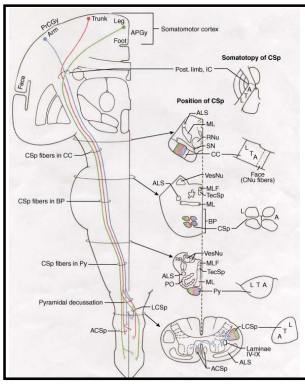
September 13, 2019

ALS

- A neurodegenerative disease that affects the motor neurons in the motor cortex (***upper motor neurons***), brainstem and spinal cord (***lower motor neurons***).
- Clinically, patients have muscular weakness, atrophy, dysarthria, dysphagia, twitching (fasciculations), cramping and emotional lability.

Clinical Symptoms

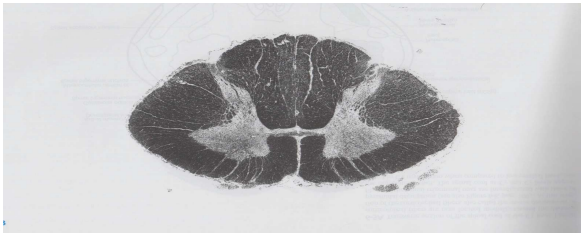
- ***Upper motor neurons*** direct the ***lower motor neurons*** to produce voluntary movements such as walking or chewing.
- Lower motor neurons control movement in the arms, legs, chest, face, throat, and tongue.
- Upper motor neurons: corticospinal neurons.
- Spinal motor neurons: anterior horn cells.



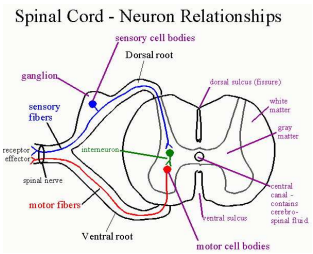
Corticospinal Tracts

From Neuroanatomy: An atlas of structures, sections and systems, 2008

Anterior Horn Cells



From Neuroanatomy: An atlas of structures, sections and systems, 2008



ALS

- Disruptions between the upper motor neurons (UMN) and the lower motor neurons (LMN) cause limb muscles to become stiff and deep tendon reflexes become overactive.
- Spasticity: increased tone in the muscle that renders it resistant to stretch and causes stiff and slow movement with little weakness.

Clinical Symptoms

- ALS may start in any body segment either in an upper motor neuron, lower motor neuron pattern or both with the spread from one body segment to others.
- Asymmetric limb weakness is often the presenting symptom in 80% of patients
  - Often a dropped hand or foot

Clinical Symptoms

- Bulbar onset: dysarthria, dysphagia

Clinical Symptoms

- Pseudobulbar affect: UMN dysfunction
  - sudden outbursts of involuntary laughter or crying
  - loss of voluntary cortical inhibition to brainstem centers that produce the facial and respiratory functions associated with those behaviors
  - bilateral corticobulbar lesions or loss of corticocerebellar control of affective displays.

Other Clinical Symptoms

- Extraocular motor neurons are spared until very late in the disease.
- Autonomic symptoms are not typical
- Multifactorial constipation and urinary urgency from a spastic bladder

Other Clinical Symptoms

- Sensory symptoms may occur in 20% of patients, but usually with a normal clinical sensory examination.
- Cognitive symptoms in the form of frontotemporal dementia or dysfunction may be present in anywhere from 15% to 50% of patients.

ALS Epidemiology

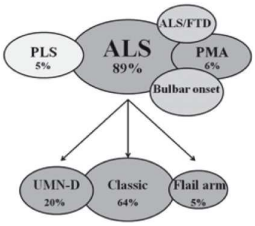
- Annual Incidence rate of 0.4 to 1.76 per 100,000 in the population.
- Most adults develop between ages 40-60
- Men: Women ratio is 1.5:1

ALS

- Life expectancy on average is from 2-5 years
- No effective treatment
- Death usually results from respiratory muscle insufficiency or complications from dysphagia
- Approximately 10% of patients with ALS will live >10 years

Motor Neuron Disease

- Most frequent type is ALS
  - amyotrophy indicates denervation atrophy and weakness of muscles
  - comprises approximately 90% of motor neuron diseases.
- Subgroups of ALS include:
  - Classic ALS
  - Upper motor neuron-dominant (UMN-D)
  - Flail-arm (onset of muscle weakness in the proximal upper extremities while the legs may be spared for a long time)



Etiology

- Most cases (90-95%) are Sporadic with no known cause
  - sporadic ALS has been linked to tobacco use, military service, agricultural/factory work, and periods of heavy muscle use, but none have ever demonstrated a causal relationship

Familial ALS

- Approximately 5-10% are Familial
  - autosomal dominant but can be autosomal recessive or X-linked

Cirulli ET, Lasseigne BN, Petrovski S, et al.

Familial ALS

- Protein misaggregation has been noted pathologicaly but also oxidative stress and RNA processing
- Because these genes which have been found to be mutated have a major role in RNA trafficking, impairment of this function has been suggested as a potential cause of ALS

Cirulli ET, Lasseigne BN, Petrovski S, et al.

C9ORF72

- Large hexanucleotide (GGGGCC) repeat expansion in the first intron of C9ORF72 located on chromosome 9p21 is the most common mutation detected in patients with familial ALS (30-40%). 7% sporadic.
- Multiple nuclear RNA foci of an abnormal mRNA have been detected in brain tissues from patients
- Toxic gain-of-function mechanism

C9ORF72

- Higher frequency of cognitive impairment seen, affecting up to 40–50% of cases
- Bulbar onset more frequent and a lower median survival rate
- C9ORF72 expansion is more frequent among patients with onset **>61 years**

SOD1

- Superoxide dismutase
- 12% of familial ALS and 1.5% of sporadic ALS
- Autosomal dominant and recessive
- Lower motor neuron syndrome predominates
- Onset in lower limbs
- Another toxic gain of function mutation (oxidative stress)

Cirulli ET, Lasseigne BN, Petrovski S, et al.

TAR DNA binding protein-43 (TDP-43)

- Transactive response (TAR)-DNA binding protein (4% genetic ALS, 1% sporadic)
- TDP-43:
  - an RNA and DNA binding protein involved in regulation of gene expression and splicing
  - Plays a role in transcriptional repression and an activation of exon skipping
  - Ubiquitously expressed nuclear protein

Cirulli ET, Lasseigne BN, Petrovski S, et al.

TAR DNA binding protein-43 (TDP-43)

- Limb onset 80% (upper limb)
- Bulbar or respiratory 20%
- Short or long survival
- Both upper and lower motor neurons
- Predominant lower motor neuron is common
- No pure upper motor syndrome
- FTD

FUS/TLS

- 4-5% of SOD1-negative ALS, 1% sporadic
- Autosomal dominant and recessive
- RNA-binding protein FUS (*FUsed in Sarcoma, translated in liposarcoma)*
- Resemble ALS in onset (arms >legs>bulbar)
- Younger age of onset and rapid progression, shorter life span
- Lower motor neuron predominates

Ubiquilin 2

- Proteins that deliver ubiquitinated proteins to the proteasome for degradation
- Dominant X-linked transmission mode
- <1% familial and <1% sporadic
- 90% penetrant in women.
- Early onset, average 35 years, range 30–43
- FTD

Other genes implicated

- SQSTM1: Autosomal dominant, 1% familial, <1% sporadic. Paget disease, FTD, Inclusion body myositis.
- Optineurin (*OPTN):* Autosomal dominant and recessive, <1% familial and sporadic. Open-angle glaucoma, Paget disease.
- VCP: Autosomal dominant
- PFN1: Autosomal dominant
- ANG (angiogenin)

Cirulli ET, Lasseigne BN, Petrovski S, et al.

Electrodiagnostic testing in ALS

- Normal sensory responses except in a few rare instances
- Motor responses are normal or reduced in amplitude
- Needle EMG examination demonstrates fasciculations, fibrillation potentials and positive sharp waves with *neurogenic motor unit potentials*

El Escorial Criteria

- The El Escorial World Federation of Neurology criteria
  - mainly *clinical* and form the gold standard of ALS diagnosis.
  - first proposed in 1994 and revised in 2000 with modifications proposed in December 2006 during a consensus conference in Awaji-shima, Japan

Table 3
Diagnostic categories in the revised El Escorial criteria

Category of ALS	UMN Findings Body Segments[a] on Physical Examination		LMN Findings Body Segments on Physical Examination		Additional Tests
Clinically definite	3	+	3		
Clinically probable	2 Some UMN signs rostral to the LMN signs	+	2		
Clinically probable Laboratory supported	1 At least 1	+ OR +	1 0	+ +	Acute and chronic denervation in at least two limbs by EMG
Clinically possible	1 At least 2	+ OR	1 0		
Definite familial Laboratory supported	1	+	1	+	Documented genetic mutation

[a] Body segments are craniobulbar, cervical, thoracic, and lumbosacral.

From Duleep A and Shefner J., 2013

Table 4
Awaji modifications to the diagnostic categories of the revised El Escorial criteria

Category of ALS	UMN Findings Body Segments[a] on Physical Examination		LMN Findings Body Segments[a] on Physical Examination Or Electrophysiologic Testing[b]	Additional Tests
Clinically definite	3	+	3	
Clinically probable	2 Some UMN signs rostral to the LMN	+	2	
Clinically possible	1	+	1	
	At least 2	+	0	
Definite familial Laboratory supported	1	+	1	+ Documented genetic mutation

[a] Body segments are craniobulbar, cervical, thoracic, and lumbosacral.
[b] Electrophysiologic examination:
- Evidence of acute denervation in the form of fibrillation potentials and positive sharp waves

AND
- Evidence of chronic reinnervation in the form of voluntary motor unit potentials of increased amplitude, increased duration, or polyphasia, that may exhibit decreased recruitment (if there is concomitant UMN dysfunction, a decreased recruitment pattern may not be clear)

OR
- Evidence of chronic reinnervation as above, with evidence of acute denervation in the form of fasciculation potentials preferably of complex morphology, or instability when studied with a high band pass filter and trigger delay line, which suggests their origin from reinnervated motor units.

From Duleep A and Shefner J., 2013

Recommended Electrodiagnostic studies

- At a minimum, NCS of a patient with suspected ALS should include testing of at least:
  - one motor nerve with F wave study and one sensory nerve in an upper and lower extremity on the most symptomatic side.

Recommended Electrodiagnostic studies

- Needle EMG study of a patient with suspected ALS should include:
  - testing of at least three limbs, sampling muscles innervated by at least two different nerve roots, and peripheral nerves and proximal and distal muscles.
  - at least one bulbar muscle, such as a facial muscle, masseter muscle, or tongue.
  - Finally, needle EMG should be done on at least two thoracic paraspinal muscles.

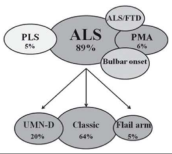
Table 1
Mimics of motor neuron disease

Disease	Presentation	Distinguishing Features	Role of Electrodiagnostic Testing
Cervical radiculomyelopathy	LMN dysfunction at the level of stenosis with UMN findings below	Neck pain and radicular sensory symptoms in arms	No EMG findings in bulbar or thoracic paraspinal muscles
Concomitant cervical and lumbar stenosis	Like cervical radiculomyelopathy, but with LMN findings also in lumbosacral myotomes	Neck and back pain, radicular sensory symptoms in the arms and legs	No EMG findings in bulbar or thoracic paraspinal muscles
Benign fasciculation syndrome	Frequent fasciculations, diffuse or focal; cramps	Normal neurologic examination	No EMG findings other than fasciculation potentials
Multifocal motor neuropathy with conduction block	LMN limb weakness, often upper extremities	Not myotomal, often in patients younger than 45 yr old	Conduction block in motor nerve NCS nonentrapment sites
Inflammatory myopathies	LMN limb weakness, dysphagia	IBM: finger flexor, quadriceps weakness Polymyositis or dermatomyositis: proximal muscle weakness	Fibrillation potentials/ positive sharp waves; small amplitude and short duration motor unit potentials and occasionally neuropathic MUPs (IBM only) with normal or early recruitment

From Duleep A and Shefner J., 2013

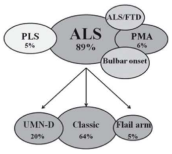
Other Types of Motor Neuron Disease

- Primary Lateral Sclerosis (PLS):
  - Slowly progressive ***upper motor neuron*** dysfunction
  - Spasticity and difficult walking
  - Can develop bulbar symptoms



Other Types of Motor Neuron Disease

- Progressive Muscular Atrophy (PMA):
  - ***Lower motor neuron***
  - Usually evolves into ALS



Other Types of Motor Neuron Disease

- Progressive Bulbar Palsy (PBP):
  - Weakness and wasting predominate in the motor nuclei of the lower brainstem (muscles of the jaw, face, tongue, pharynx, larynx)
  - Survival is shorter than in limb onset ALS

Other Types of Motor Neuron Disease

- Spinomuscular atrophy (SMA) :
  - Types I-III are genetic types of lower motor neuron diseases
  - Kennedy's disease: an X-linked type of SMA passed on from mother of carriers to their sons
  - Post-polio syndrome

Treatment

- Riluzole prolongs life on average 3 months
  - reduces glutamate-induced excitotoxicity

Radivaca (Edaravone)

- The mechanism of action is unknown. It is also used to treat patients after stroke in Japan. The drug is known to be an antioxidant, and oxidative stress has been hypothesized as the mechanism by which it may help those in ALS.
- Adverse reactions include mostly those related to sulfite sensivities as the drug contains this an an inactive ingredient: anaphylaxis, asthma, bruising, gait disturbances, headache, skin reactions, eczema, glucosuria and fungal skin infections
- The cost: approximately $145,000/year.

The Trial

-Patient with ALS: 69 Radicava and 68 in placebo
-6 months of treatment with Edaravone (Radicava)
-Japanese patients, median age range 60 years (range 29-75), 59% male
-93% were living independently at the time of screening
-Randomized, placebo –controlled, double blind
-**The following screening criteria**:
-Functionality retained most activities of daily living (score of 2 or better on each individual item of the ALSFRS-R)
-**NORMAL respiratory function, FVC 80%**
-Definite or Probable ALS based on El Escorial revised criteria
-**Disease duration of 2 years or less**

Radivaca (Edaravone)

- -90% were also on Riluzole
- -Dosing: 60mg over 60 minutes daily for 14 days, then 14 days drug-free period, then daily dosing cycles for 10 days out of 14 day periods, followed by 14 day drug-free periods
- 24 week period: decline in ALSFRS-R scores was **-5.01** (+/- 0.64) in those with Radicava and **-7.50** (+/- 0.66) in placebo with confidence intervals of 95%.
- **The p value was 0.0013** (less than one in a thousand chance of being wrong)
- 33% **relative difference** in ALSFRS decline over 6 months ie only decline 2 points instead of 3

Radivaca (Edaravone)

- In 2 earlier and broader ALS study populations, they saw a favorable result in the same subset but **not** in the overall population.
- While the p value is low, the power of the study is also low which affects the p value.
- A small p value has little value in establishing the veracity of a claim when the power is low. Power is important because the proportion of false positive results **increases** in underpowered studies.

Table Amyotrophic lateral sclerosis (ALS) quality measures approved by the American Academy of Neurology

Measure title and description
1. ALS multidisciplinary care plan developed or updated
Percentage of patients diagnosed with ALS for whom a multidisciplinary care plan was developed, if not done previously, and the plan was updated at least once annually.
2. Disease-modifying pharmacotherapy for ALS discussed
Percentage of patients with a diagnosis of amyotrophic lateral sclerosis with whom the clinician discussed disease-modifying pharmacotherapy (riluzole) to slow ALS disease progression at least once annually.
3. ALS cognitive and behavioral impairment screening
Percentage of patients diagnosed with ALS who are screened at least once annually for cognitive impairment (e.g., frontotemporal dementia screening or ALS Cognitive Behavioral Screen [CBS]) and behavioral impairment (e.g., ALS CBS).
4. ALS symptomatic therapy treatment offered
Percentage of visits for patients with a diagnosis of ALS with patient offered treatment for pseudobulbar affect, sialorrhea, and ALS-related symptoms.
5. ALS respiratory insufficiency querying and referral for pulmonary function testing
Percentage of patients with a diagnosis of amyotrophic lateral sclerosis who were queried about symptoms of respiratory insufficiency (awake or associated with sleep) and referred for pulmonary function testing (e.g., vital capacity, maximum inspiratory pressure, sniff nasal pressure, or peak cough expiratory flow), at least every 3 months.
6. ALS noninvasive ventilation treatment for respiratory insufficiency discussed
Percentage of patients diagnosed with ALS and respiratory insufficiency with whom the clinician discussed at least once annually treatment options for noninvasive respiratory support (e.g., noninvasive ventilation, assisted cough).
7. ALS screening for dysphagia, weight loss, and impaired nutrition
Percentage of patients diagnosed with ALS who were screened at least every 3 months for dysphagia, weight loss, or impaired nutrition and the result(s) of the screening(s) was documented in the medical record.
8. ALS nutritional support offered
Percentage of patients diagnosed with ALS and dysphagia, weight loss, or impaired nutrition who were offered at least once annually dietary or enteral nutrition support via percutaneous endoscopic gastrostomy or radiographic inserted gastrostomy.
9. ALS communication support referral
Percentage of patients diagnosed with amyotrophic lateral sclerosis who are dysarthric who were offered a referral at least once annually to a speech-language pathologist for an augmentative/alternative communication evaluation.
10. ALS end of life planning assistance
Percentage of patients diagnosed with ALS who were offered at least once annually assistance in planning for end of life issues (e.g., advance directives, invasive ventilation, hospice).
11. ALS falls querying
Percentage of visits for patients with a diagnosis of amyotrophic lateral sclerosis with patient queried about falls within the past 12 months.

RG Miller, BR Brooks, RJ Swain-Eng 2013

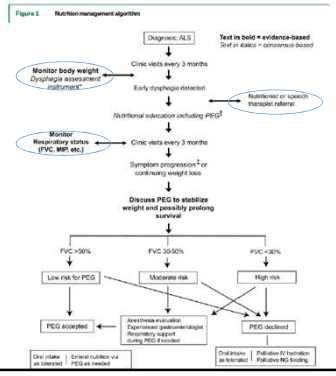
ALS Quality Measures

- **ALS Quality Measures**

1. ALS multidisciplinary care plan developed or updated
-once annually.
2. Disease-modifying pharmacotherapy for ALS discussed
-once annually.
3. ALS cognitive and behavioral impairment screening
-once annually.
4. ALS symptomatic therapy treatment offered
- pseudobulbar affect, sialorrhea, and ALS-related symptoms.
5. ALS respiratory insufficiency querying and referral for pulmonary function testing
-Every 3 months. Symptoms respiratory insufficiency (awake or associated with sleep), referred for pulmonary function testing

ALS Quality Measures

- 6. ALS noninvasive ventilation treatment for respiratory insufficiency discussed
  -Once annually treatment options for noninvasive respiratory support (e.g., noninvasive ventilation, assisted cough).
  7. ALS screening for dysphagia, weight loss, and impaired nutrition
  -Every 3 months for dysphagia, weight loss, or impaired
  8. ALS nutritional support offered
  -Once annually dietary or enteral nutrition support via percutaneous endoscopic gastrostomy or radiographic inserted gastrostomy.
  9. ALS communication support referral
  -Once annually to a speech-language pathologist for an augmentative/alternative communication evaluation.
  10. ALS end of life planning assistance
  -Once annually assistance in planning for end of life issues (e.g.,advance directives, invasive ventilation, hospice).
  11. ALS falls querying
  - Once annually queried about falls



RG Miller, CE Jackson, E.J. Kasarskis et al, 2009

References

- Duleep A and Shefner J. Electrodiagnosis of Motor Neuron Disease. Phys Med Rehabil Clin N Am 24 (2013) 139–151.
- National Institute of Neurological disorders and Stroke. Motor Neuron Disease Fact Sheet. http://www.ninds.nih.gov/disorders/motor_neuron_diseases/detail_motor_neuron_diseases.htm. Accessed December 4, 2014.
- Ropper AH, Samuels MA. 2009. Adam and Victor's Principles of Neurology. 9th edition. New York: McGraw-Hill Companies Inc.
- Miller RG, Brooks BR, Swain-Eng RJ, et al. Quality improvement in neurology: Amyotrophic lateral sclerosis Quality improvement in neurology: Amyotrophic lateral sclerosis Quality improvement in neurology: Amyotrophic lateral sclerosis. Neurology (2013).
- RG Miller, CE Jackson, E.J. Kasarskis et al. Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Drug, nutritional, and respiratory therapies (an evidence-based review). Neurology (2009):1218-1226.
- Haines, D. Neuroanatomy: An atlas of structures, sections and systems. 7th edition. Philadelphia: Lippincott Williams and Wilkins.
- Cirulli ET, Lasseigne BN, Petrovski S, et al. Exome sequencing in amyotrophic lateral sclerosis identifies risk genes and pathways. Science 2015;347(6229):1436-1441.
- Goutman SA. Diagnosis and Clinical Management of Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. Continuum (Minneap Minn)2017;23(5):1332-1359.