

Clinical Aspects of ALS

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Objectives

- Discuss the epidemiology of ALS
- Compare and contrast the clinical features and prognosis of ALS and ALS variants
- Describe how the diagnosis of ALS is made in a patient and list the diagnostic criteria
- Discuss the relationship between motor neuron disease and frontotemporal dysfunction
- Describe how the clinical assessment of a patient with possible ALS is performed and how the diagnosis is made
- Describe the standard of care treatment options available for patients with ALS



Case 1

- A 63 year old right handed man presents to neurology clinic complaining of inability to lift things with his right arm for the past 3 months (wife states 6 months)
 - Muscle jerks all over his body
 - Right hand seems smaller
- Physical exam
 - Muscle atrophy in the right arm
 - Fasciculations in multiple muscles of the arms and chest
 - Weakness on muscle strength testing in the right > left arms
 - Increased deep tendon reflexes in both upper and lower extremities
 - Prominent jaw jerk reflex



Case 2

- 58 year old woman is referred to the neurology department for trouble swallowing. She notes that over the past 6 months she has more difficulty with chewing and swallowing tough or dry foods. Her speech has become more nasal, slow and effortful. Her husband also comments on her loss of interest in gardening (formerly an important hobby) and how she seems to cry about “everything” now.
- Physical exam
 - Slow, dysarthric, strained, hypernasal speech
 - Increased reflexes in the arms and legs, + several pathologic reflexes
 - Normal strength on manual muscle testing
 - No muscle atrophy noted anywhere



Case 3

- 67 year old man with 6 months of difficulty walking. He has noted that his right foot slaps as it hits the ground
- Physical exam
 - Weakness in right dorsiflexion and hip flexion. Unable to stand on tiptoe with right foot
 - Subtle muscle atrophy in the right calf muscles with fasciculations
 - Normal arm strength
 - Increased reflexes in the arms and legs, positive Babinski sign bilaterally



Case 4

- 75 year old farmer presents as a transfer to the ICU from an outside hospital. He presented with altered mentation and respiratory failure requiring mechanical ventilation. No clear pulmonary pathology was noted on chest x-ray.
- Extubated at OSU, but 4 hours later became obtunded, found to have elevated PCO₂ and was placed back on mechanical ventilation
- His wife reports that he has had some trouble lifting heavier objects and opening jars at home “for a while.”
- Physical Exam
 - Frequent muscle fasciculations and muscle atrophy noted in the upper extremities



Historical Aspects

- Progressive muscular atrophy described by Aran and Duchenne in 1849-50
- Degeneration of anterior horn cells in the spinal cord in this disorder recognized by Luys in 1860
- 1859 Charcot and Cruveilhie described the clinical features of typical ALS and noted the involvement of corticospinal tracts and anterior horn cells pathologically
 - Coined the term Amyotrophic Lateral Sclerosis



Epidemiology

- Incidence averages about 1.8/100,000 across multiple studies
 - Some regional variations with higher incidence
 - Guam/Western Pacific
 - Kii peninsula in Japan
 - Southern New Guinea
 - Age range varies from teenagers to extreme elderly
 - Average onset in the late 50's
 - Men and women relatively equally affected- slight male predominance
 - No clear ethnic or racial risks in general
 - Average life expectancy is 3-4 years with high variability
 - About 10% of patients live > 10 years
 - Some die within a year
- Majority of cases are sporadic
- Familial ALS recognized since near the time of original descriptions of the disease
 - Historically about 10% of cases
 - Familial cases have similar differences in phenotypic variability and rate of progression to sporadic



Clinical Features

- Clinical features and range of presentations is highly diverse
- Symptoms/signs can start anywhere in the body
 - Limb onset is most common
 - Bulbar symptoms – impaired speech and swallowing
 - Neck and/or weakness
 - Respiratory difficulties
- Muscle cramps are common
- Possible cognitive impairment
- Initial deficits are often focal and limited
 - ALS frequently mistaken for other problems
 - Diagnostic uncertainly even among experienced physicians
- Progression over time is inevitable and is a hallmark of the disease



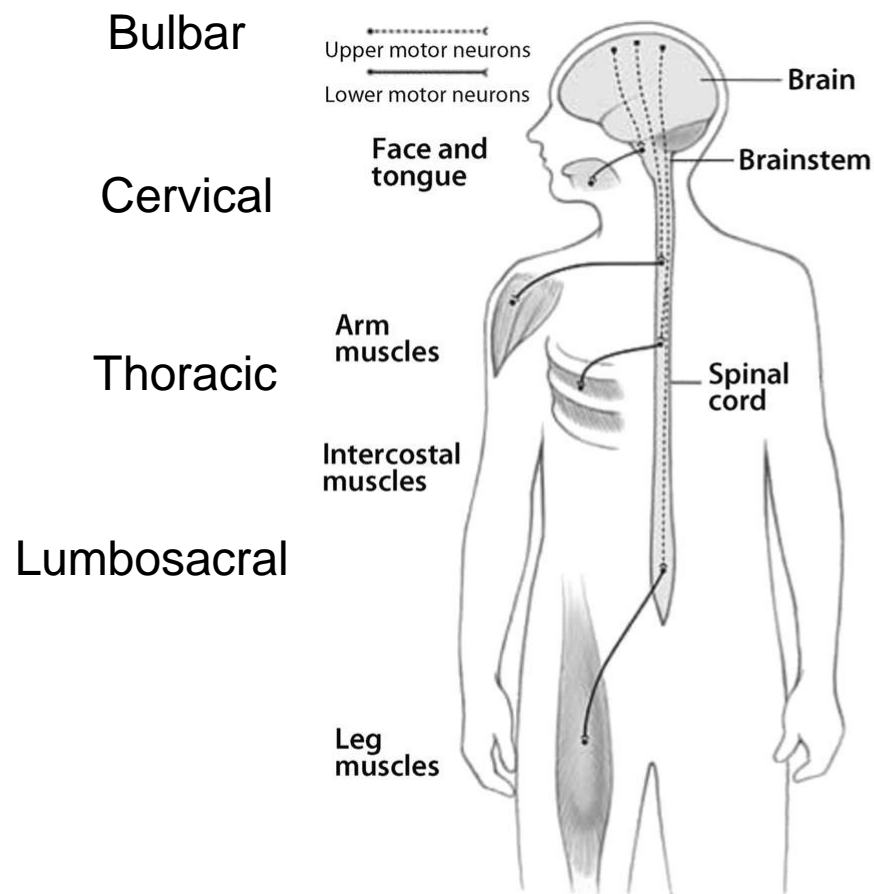
Signs and Symptoms not Consistent with ALS

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- **Sensory abnormalities**
 - **Bowel and bladder dysfunction**
 - **Eye movement abnormalities**
 - **Autonomic dysfunction**
 - **Visual and hearing abnormalities**
 - **Abnormal movements**



Clinical Signs/Physical Exam

- Presence of upper motor neuron and lower motor neuron signs in same region(s)
- Progression within and between regions

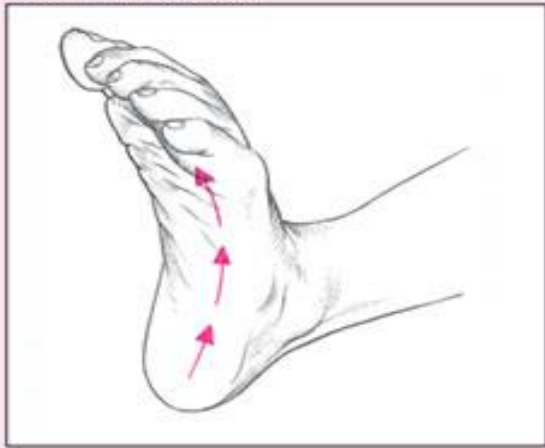


Muscle Atrophy

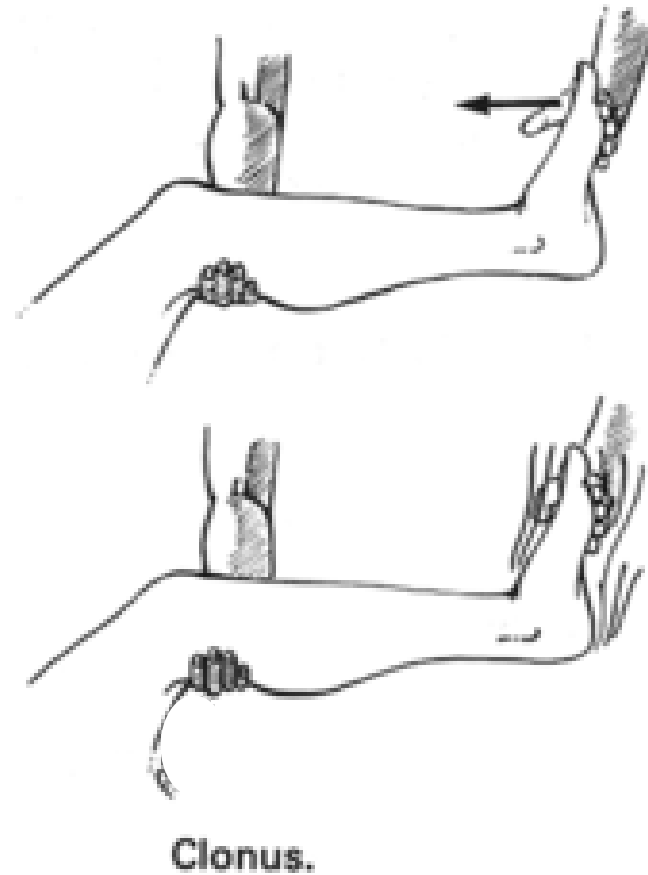


Upper Motor Neuron Signs

NORMAL TOE FLEXION



POSITIVE BABINSKI'S REFLEX



ALS “variants”

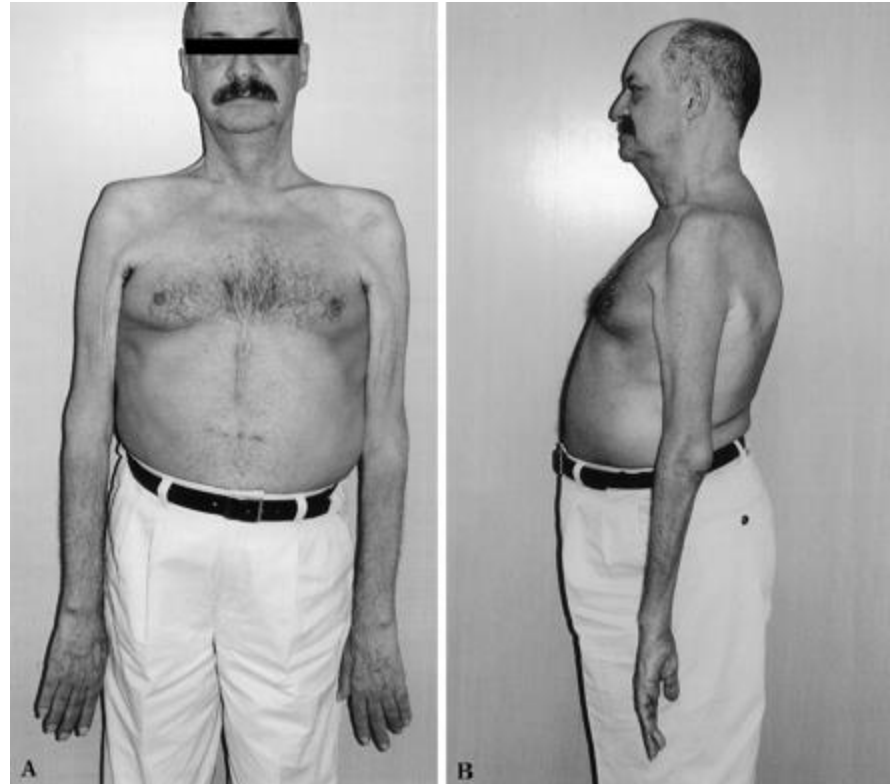
Pattern	Upper Motor Neuron Involvement Only	Lower Motor Neuron Involvement Only	Upper and Lower Motor Neuron Involvement
Limb onset	Primary lateral sclerosis	Progressive muscular atrophy	Classic ALS
Bulbar onset	Pseudobulbar palsy	Progressive bulbar palsy	Classic ALS

- Most common presentation is limb onset with presence of upper and lower motor neuron findings
 - 2/3 of patients
 - Frequently distal signs and symptoms predominate
 - LMN findings may initially be more notable



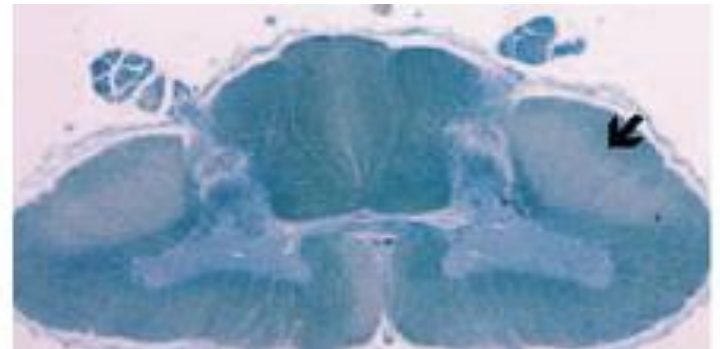
Primary Muscular Atrophy

- May account for 10 to 25% of patients eventually diagnosed with ALS
 - 70% develop UMN signs and evolve into ALS within 6 years
 - Patients with exclusively LMN signs/symptoms during life nearly always have pathological evidence of corticospinal tract degeneration
- Slowly progressive forms may be confined to upper or lower extremities
 - BAD (brachial amyotrophic diplegia)
 - LAD (leg amyotrophic diplegia)



Primary Lateral Sclerosis

- Rare- Accounts for only about 2-5% of “ALS patients”
- Syndrome of progressive upper motor neuron dysfunction without alternative cause
- Spasticity (not weakness) produces functional impairment
- Age of onset may be closer to 50 years (distinguishes from hereditary spastic paraparesis)
- Most commonly involves the lower extremities initially unilaterally and spreads in ascending pattern
- Life expectancy much better than ALS
- LMN findings may not develop for 20 years (or ever)
 - > 3-5 years without LMN signs to define PLS
 - Periods of clinical stability
- Unique features
 - Eye movement abnormalities
 - Urinary urgency and incontinence
 - ?Higher rate of cognitive abnormalities
- List of alternative diagnoses is much larger



PLS

Table 4. Pathology findings on autopsy of PLS patients, published 1977–1997.

Onset (years)	Gender	Duration (years)	Symptom onset	Description
67	M	5	LE	Betz cells in the precentral gyrus “probably” decreased; degeneration of corticospinal tract from medullary pyramids throughout the spinal cord.
66	F	3	B	Bilateral atrophy of precentral gyrus, with loss of Betz cells and marked gliosis; degeneration of corticospinal tract from internal capsule through the spinal cord. Intracytoplasmic eosinophilic inclusion bodies in the hypoglossal nucleus and anterior-horn neurons in the cervical and lumbar regions.
71	M	6	LE	Degeneration of corticospinal tract from the cerebral peduncles through all levels of the spinal cord, with no loss of Betz cells or LMNs. Adenocarcinoma of the lungs with metastases.
66	M	11	LE	Degeneration of corticospinal tract from medulla through all levels of the spinal cord; no loss of Betz cells or LMNs. Arthritic ridge at C6–7; cystic areas of encephalomalacia in right caudate, thalamus, and frontal gyrus.
60	M	1	LE	Degeneration of corticospinal tract from internal capsule through all levels of the spinal cord; no loss of Betz cells or LMNs. EMG showed 1–2+ fasciculations.
71	M	15	LE	Loss of Betz cells in the precentral gyrus; degeneration of corticospinal tract from internal capsule through all levels of the spinal cord, with gliosis of the anterior horn but no loss of LMNs. EMG showed occasional fibrillation potentials.

Few available pathological studies have common findings of degeneration and loss of myelinated fibers of the corticospinal tracts +/- loss of Betz cells.
No loss of lower motor neurons



Table 3. Proposed PLS diagnostic criteria by Pringle et al.⁵³

Clinical

Insidious onset of spastic paresis, usually beginning in the lower extremities, but occasionally bulbar or in an upper extremity.

Adult onset; usually fifth decade or later.

Absence of family history.

Gradually progressive course.

Duration ≥ 3 years.

Clinical findings limited to those usually associated with corticospinal dysfunction.

Symmetric distribution, ultimately developing severe spastic spinobulbar paresis.

Laboratory studies to help exclude other diseases

Normal serum chemistries, including normal vitamin B₁₂ levels.

Negative serologic tests for syphilis; in endemic areas, negative Lyme and HTLV-1 serologies.

Normal cerebrospinal fluid parameters, including absence of oligoclonal bands.

Absent denervation potentials on EMG or at most, *occasional* fibrillation and increased insertional activity in a few muscles (late and minor).

Absence of high-signal lesions on MRI similar to those seen in multiple sclerosis.

Additionally suggestive of PLS

Preserved bladder function.

Absent or very prolonged latency on cortical motor evoked responses in the presence of normal peripheral stimulus-evoked maximal compound muscle action potentials.

Focal atrophy of precentral gyrus on MRI.

Decreased glucose consumption in pericentral region on PET scan.

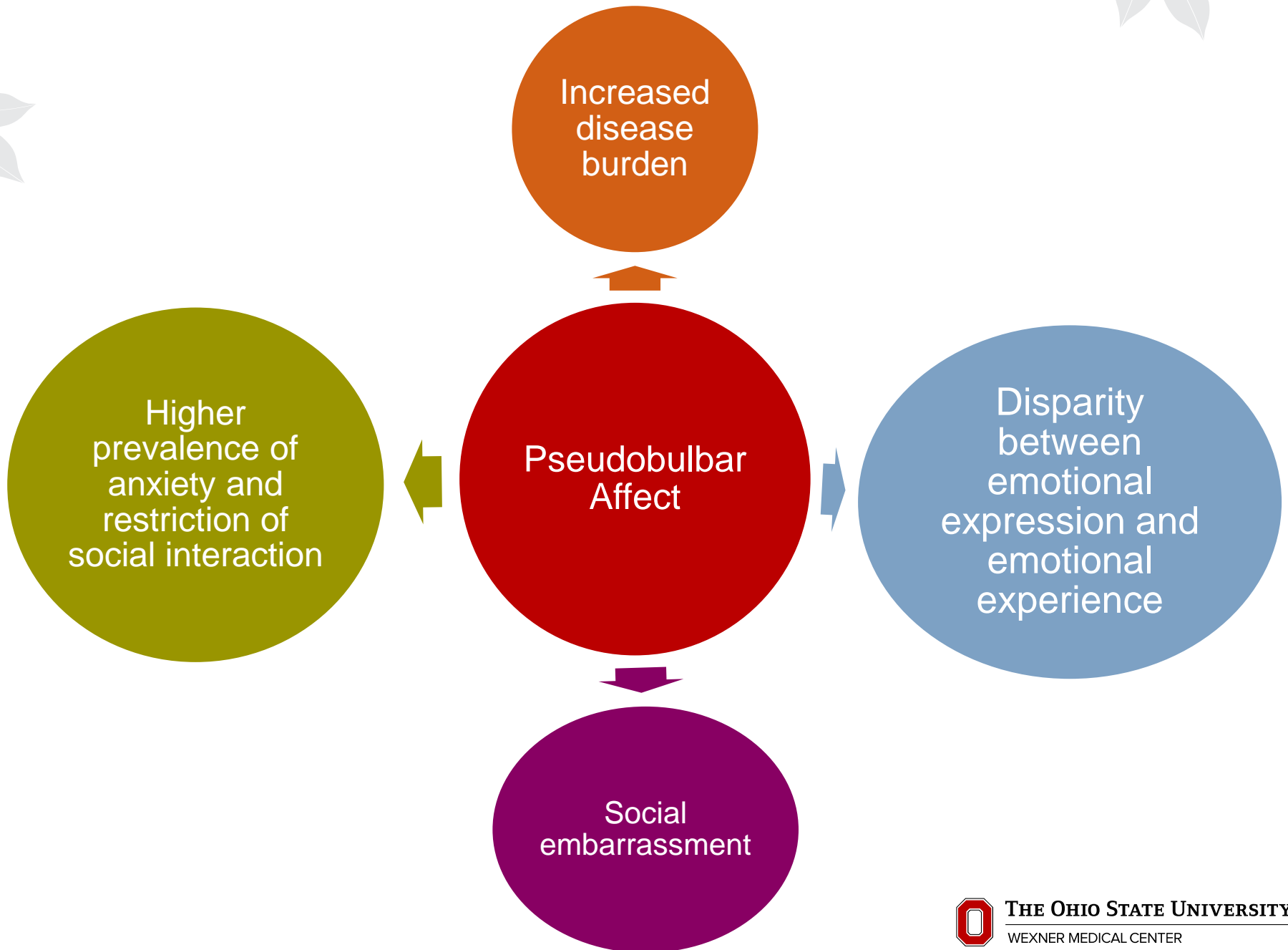
PLS, primary lateral sclerosis; HTLV-1, human T-cell lymphocytotropic virus-1; MRI, magnetic resonance imaging; PET, positron emission tomography.



Pseudobulbar and Progressive Bulbar Palsy

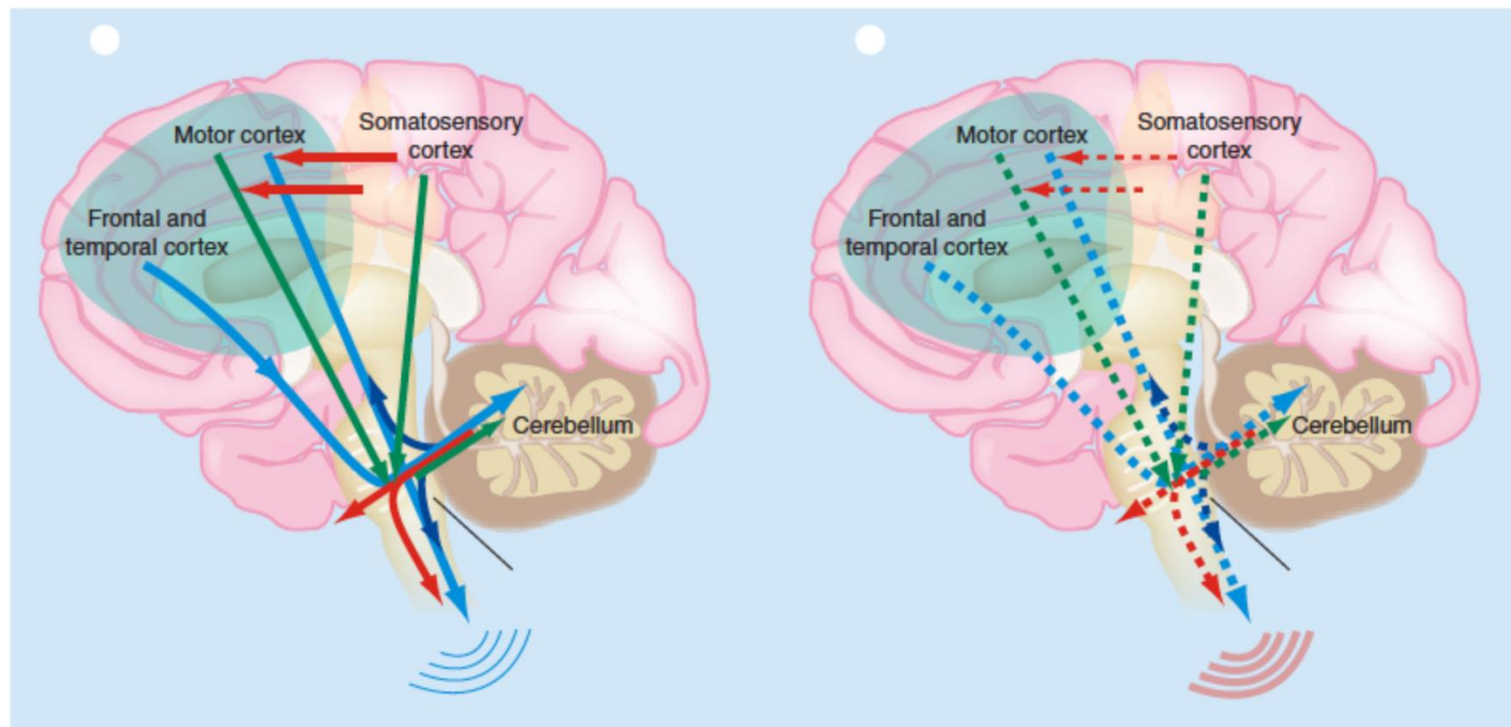
- Accounts for initial symptoms in about 1/3
- More common in women
- Increased prevalence of cognitive impairment
- Presence of tongue atrophy is highly specific
- Pathological reflexes
- Slowing of tongue, blinking and facial movements
- Pseudobulbar affect often present (some consider this evidence of UMN dysfunction)



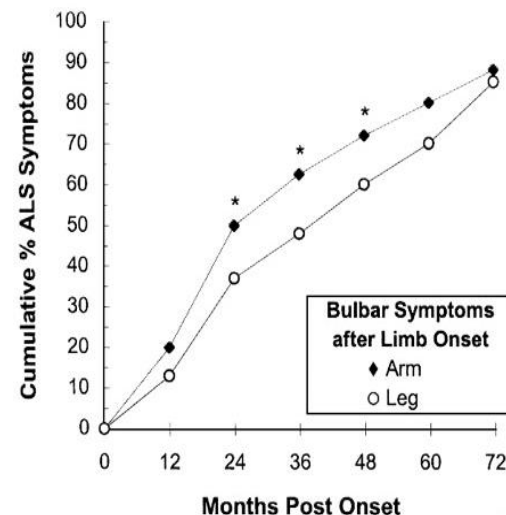
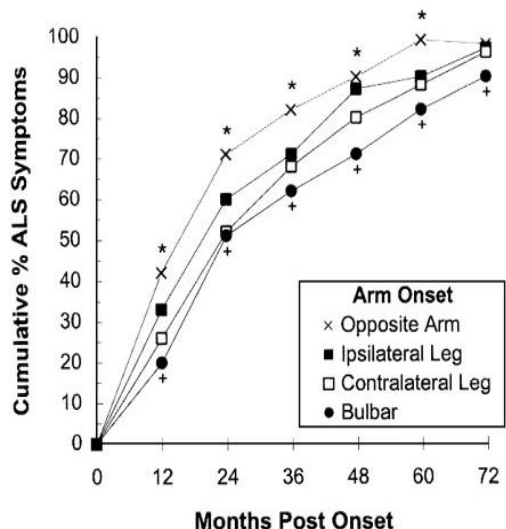
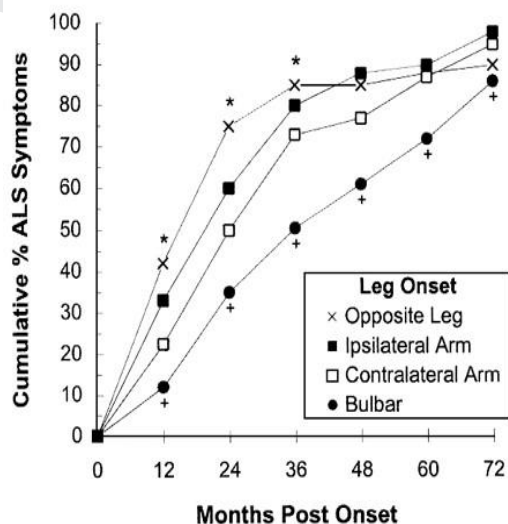


Pseudobulbar Affect

- Pathophysiology not well understood
 - Cerebellum has role in modulating emotional responses based on input from the frontal and temporal cortex
 - Somatosensory cortex has inhibitory effects on the frontal and temporal cortices
 - Disruption of corticopontine-cerebellar circuits results in impairment of this modulation



Progression of ALS



- Segmental Spread
- Progression tends to be fairly linear in individual patients with variability between patients

... From the part [of the limb] first affected the disease spreads to other parts of the same limb. Before it has attained a considerable degree in one limb, it usually shows itself in the corresponding limb on the other side; often in the muscles corresponding to those in which it commenced – from Gowers'

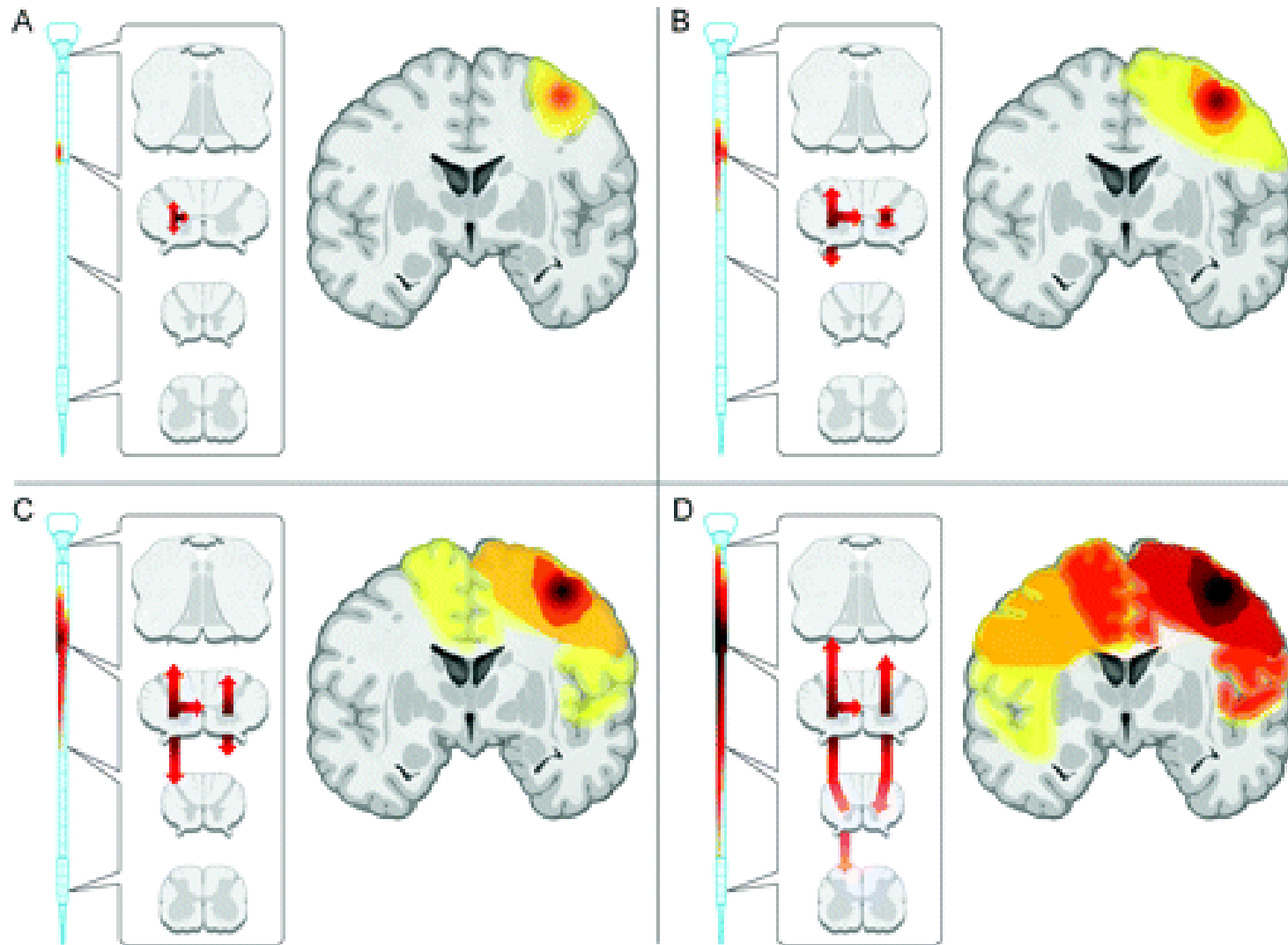


Progression of ALS

- Numerous studies suggest the following principles in most patients
 - Initially focal symptoms are common
 - Onset site is randomly localized in the neuroaxis
 - Both UMN and LMN deficits are often maximal in the same region
 - UMN and LMN deficits are variable in the severity of involvement
 - UMN and LMN deficits spread regionally from the onset site
 - There is also a preference for caudal spread

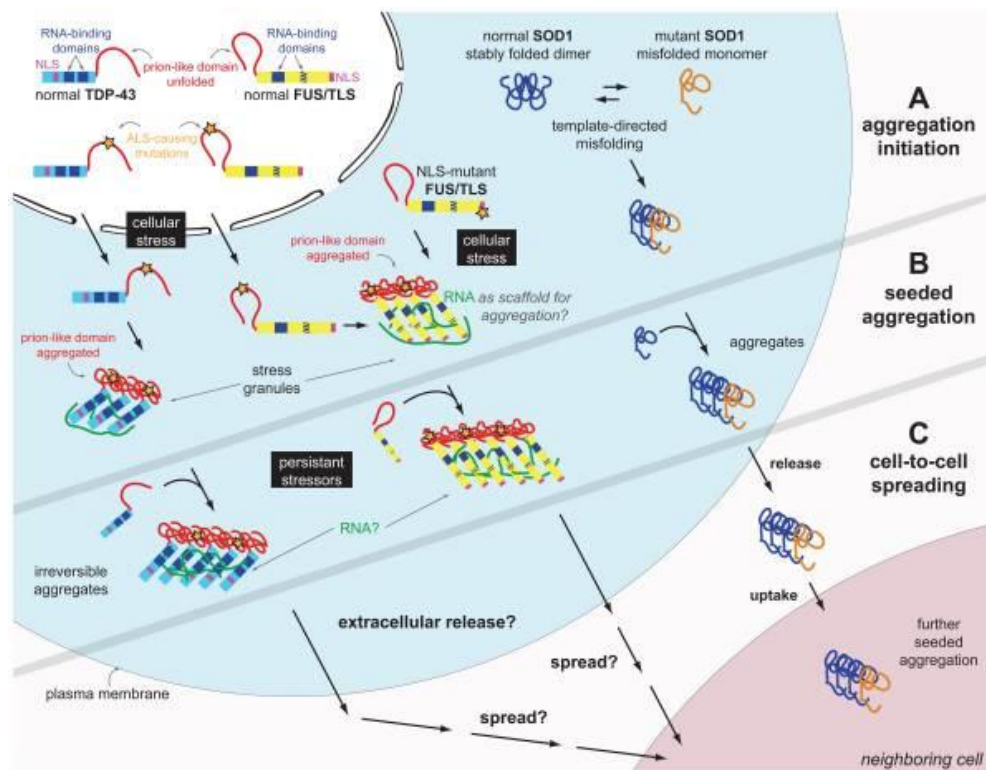


Progression of ALS



ALS Progression

- Possibly related to prion-like spread of misfolded and aggregated proteins
 - Amyloid precursor protein-Beta-amyloid in Alzheimer's Disease
 - α -synuclein in Parkinson's Disease
 - Tau in Alzheimer's and Frontotemporal lobar dementia
- Both inherited and sporadic ALS, affected neurons and glial cells contain abnormal protein accumulations
 - a main component of proteinaceous cytoplasmic inclusions in essentially all sporadic ALS cases is the RNA/DNA-binding protein TDP-43
 - Other abnormally accumulated proteins are found in genetic/familial causes of ALS – SOD1, FUS/TLS



ALS: More than Just a Disease of Motor Neurons

- Behavioral and cognitive abnormalities have been recognized in ALS since the late 1800's
 - Overlooked in past due to prominence of motor manifestations
 - Increasing number of reports began to emerge in the 1980's of overlap syndromes with dementia and motor neuron disease



ALS and Cognitive Impairment

- Typical pattern is similar to frontotemporal dementia
 - Impairment in executive and language function
- Symptoms may precede, co-occur or follow the onset of motor symptoms
- In one of the largest studies to date, 51% of 279 patients demonstrated evidence of cognitive impairment on detailed testing
- 15% of these patients met research criteria for frontotemporal dementia
- Most series indicate increased risk in bulbar onset ALS patients
- There appears to be a continuum of cognitive impairment from none to severe dementia
 - Often goes unnoticed due to subtle nature
 - Dysarthria and communication issues make testing difficult



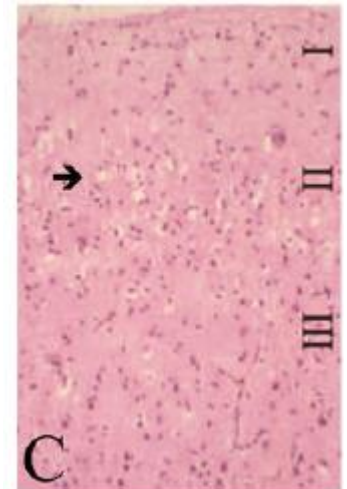
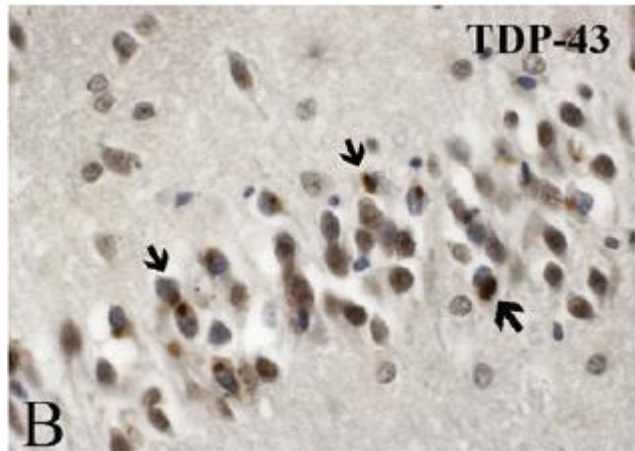
Patterns of Abnormality

- Frontotemporal Lobar Degeneration Divided into 3 Pattern
 - Behavioral variant
 - Non-fluent Progressive Aphasia
 - Semantic Dementia
- Behavioral variant FTD variant is most common in ALS, but the other types have been described
- Clinical features include
 - Disinhibition
 - Impulsiveness
 - Changes in sleep and eating patterns
 - Decreased attention
 - Purposelessly overactive
 - Socially inappropriate behavior
 - Mental inflexibility
 - Poor insight
 - Distractibility and apathy
 - Impaired verbal fluency



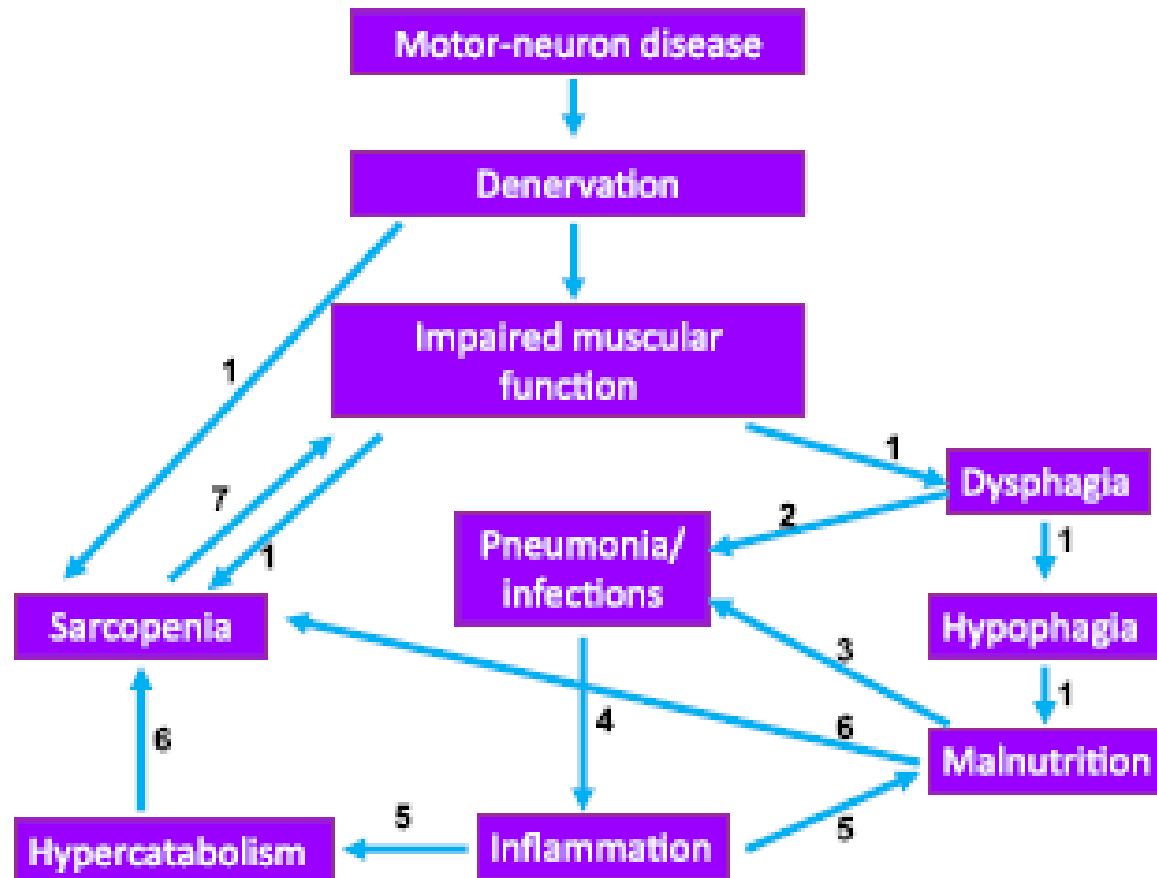
Neuropathology in ALS/FTD

- Atrophy of frontal lobes
- Superficial spongiosis, neuronal cell loss and astrogliosis in layer II of frontal and temporal cortex
- Accumulation of TDP-43 (also found in ALS without cognitive impairment)
 - Accumulation in the parahippocampal gyrus and amigdala seems mildly associated with FTD



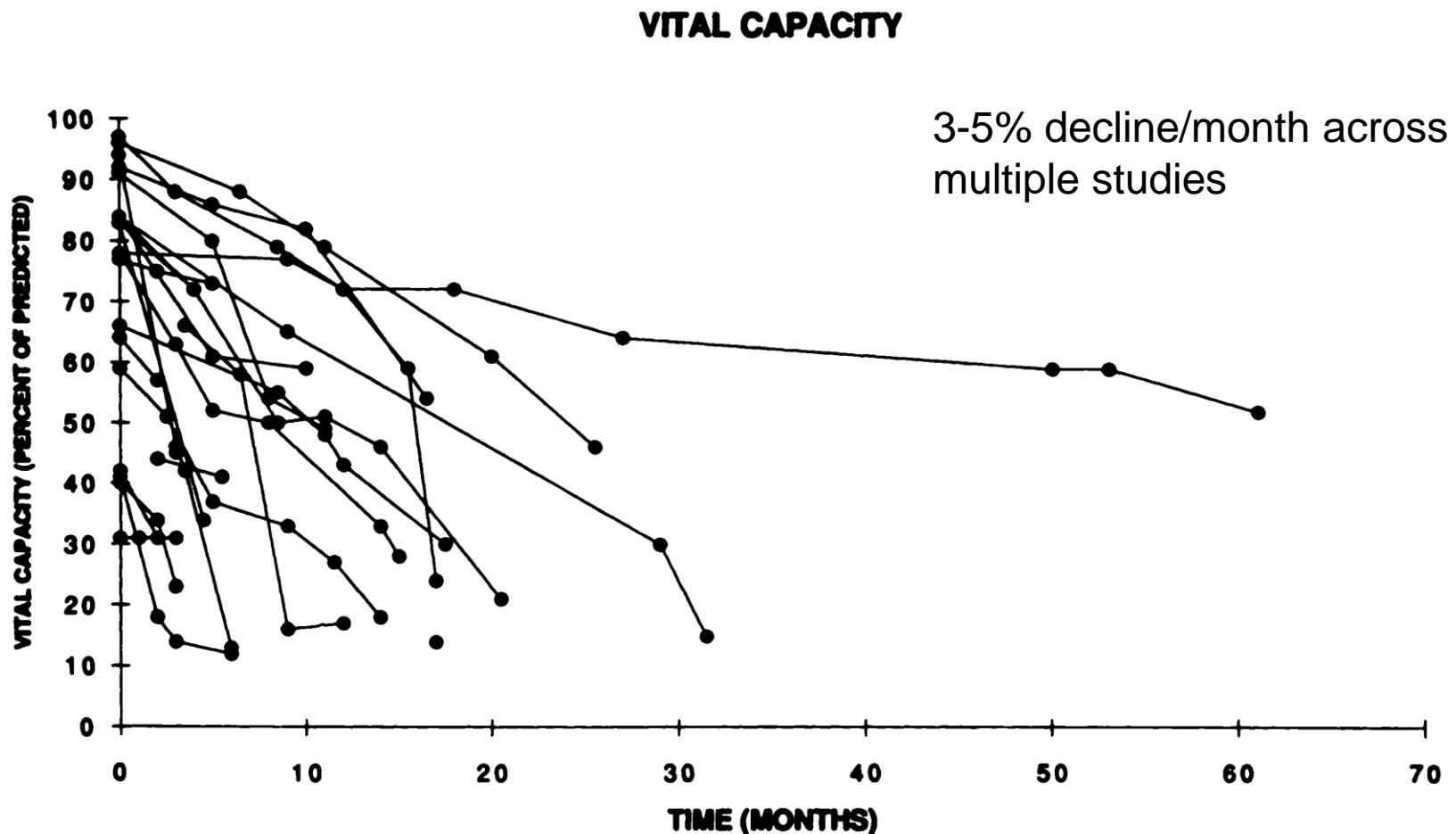
Nutrition and ALS

- Prevalence of malnutrition varies from 16-53% depending on definition used
- Low BMI and malnutrition have a negative impact on survival and quality of life in ALS



Respiratory Function in ALS

- Most deaths occur due to respiratory failure
- Rate of decline in respiratory muscle strength measures tends to be linear but with significant inter-patient variability



Respiratory Function in ALS

- FVC at initial evaluation <75% has been shown to predict shorter survival
 - <75%: Median survival of 2.9 years
 - >75% Median survival of 4.08 years ($p < 0.001$)
- Sniff Nasal Pressure < 40 cm H₂O associated with median survival of 6 months and <30 cm had median survival of 3 months
- Hypercapnia (hypoventilation) only becomes apparent when respiratory muscle weakness is profound
 - First develops during sleep
 - REM sleep accompanied by reduced skeletal muscle activity
 - Central sleep apneas – related to hypoventilation
 - Obstructive sleep apnea may also develop
 - Increased nocturnal arousals
 - Hypoventilation with associated sleep disruption affects daytime levels of alertness and energy
 - Predictor of impending mortality



ALS Diagnosis

- No laboratory tests are available to confirm the diagnosis of sporadic ALS
- Electromyography and nerve conduction studies
 - Very helpful to define existence, distribution and approximate duration of LMN involvement
 - Performed in work up of majority of patients
 - Can help to exclude alternative diagnoses
 - Myasthenia gravis
 - Inclusion body myopathy
 - Kennedy syndrome
 - Multifocal motor neuropathy
 - Demonstrates active **and** chronic denervation in multiple muscles supplied by multiple root levels and in multiple regions – possibly even before clinical symptoms

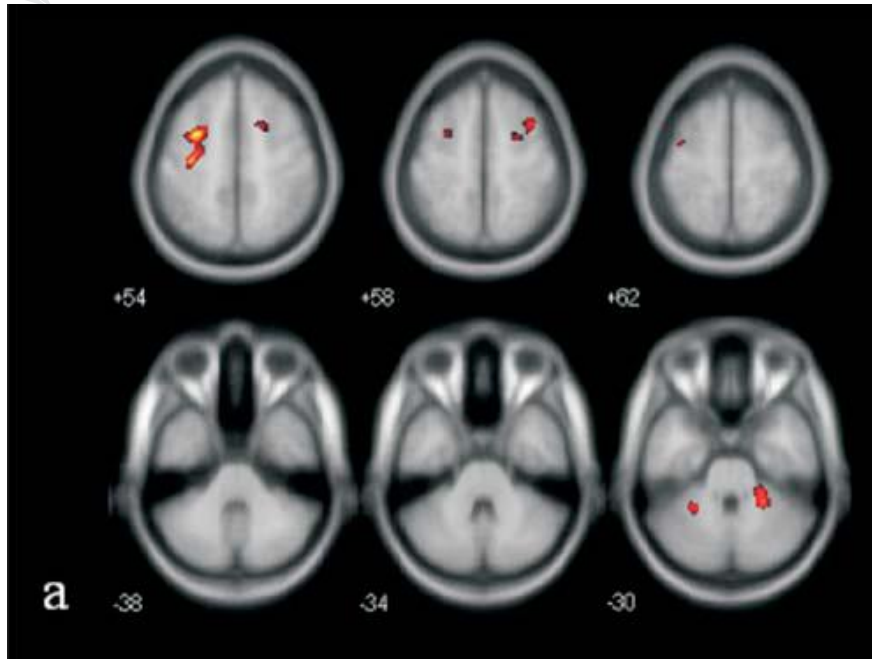


ALS Diagnosis

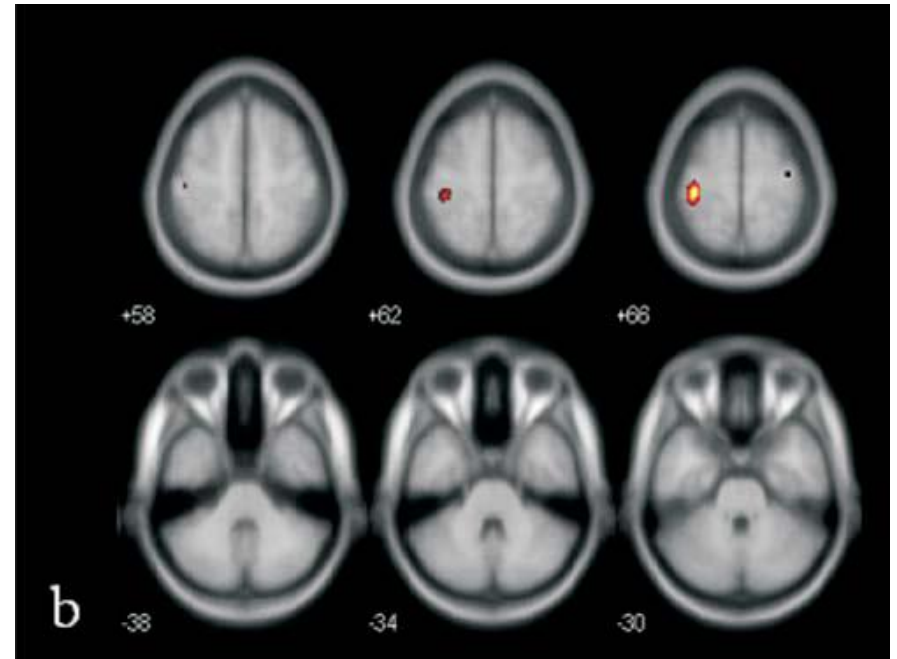
- Defining UMN involvement is primarily clinical
 - Increased reflexes
 - Increased muscle tone/spasticity
 - Pathological reflexes
 - Pseudobulbar affect
- Experimental methods include
 - Transcranial magnetic stimulation m
 - Prolonged central motor conduction time
 - Decrease in TMS amplitude
 - Advanced neuroimaging techniques
 - Diffusion tensor MRI and diffusion tensor tractography
 - Positron Emission Tomography
 - Functional MRI



fMRI in ALS



ALS



Control



ALS Diagnostic Criteria

Diagnostic Classification: Awaji-Shima Consensus Recommendations and the Revised El Escorial Criteria

- ➔ Clinically definite ALS is defined by clinical or electrophysiological evidence by the presence of LMN as well as UMN signs in the bulbar region and at least 2 spinal regions or the presence of LMN and UMN signs in 3 spinal regions.
- ➔ Clinically probable ALS is defined on clinical or electrophysiological evidence by LMN and UMN signs in at least 2 regions with some UMN signs necessarily rostral to (above) the LMN signs. The revised El Escorial Criteria have an additional category “Probable ALS–Laboratory Supported,” which is defined when clinical signs of UMN and LMN dysfunction are found in only 1 region but electrophysiological signs of LMN loss are observed in ≥ 2 regions.
- ➔ Clinically possible ALS is defined when clinical or electrophysiological signs of UMN and LMN dysfunction are found in only 1 region or UMN signs are found alone in ≥ 2 regions or LMN signs are found rostral to UMN signs.



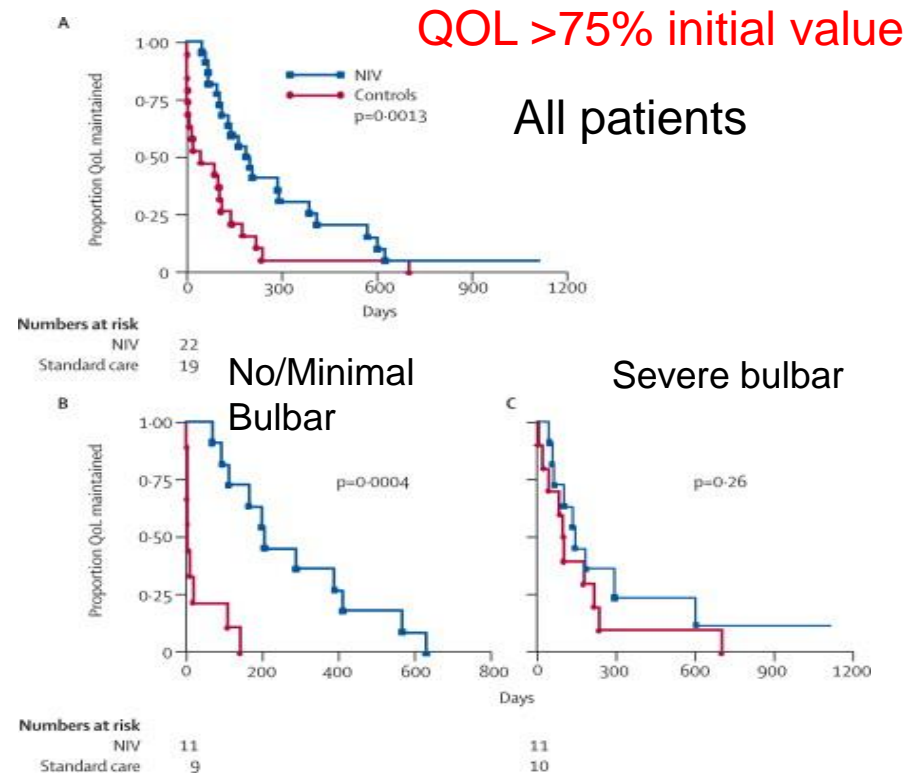
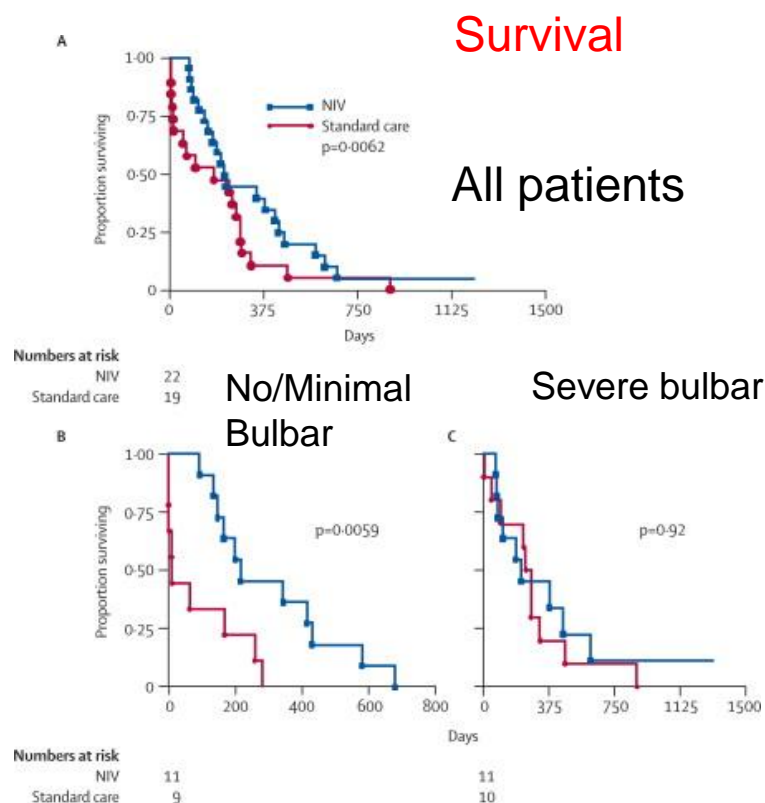
ALS Treatment

- Multidisciplinary care is important for prolonged survival and improved quality of life
- Progression of symptoms necessitates anticipation of future needs
- Respiratory and nutritional support
 - Non-invasive ventilation
 - Increases survival by 15-20 months
 - Better tolerate in patients without severe bulbar symptoms
 - Percutaneous endoscopic gastrostomy tube
- Disease modifying treatment : Riluzole
 - Probably has multiple effects in ALS
 - Reduces extracellular glutamate concentrations
 - Survival advantage of 2-3 months

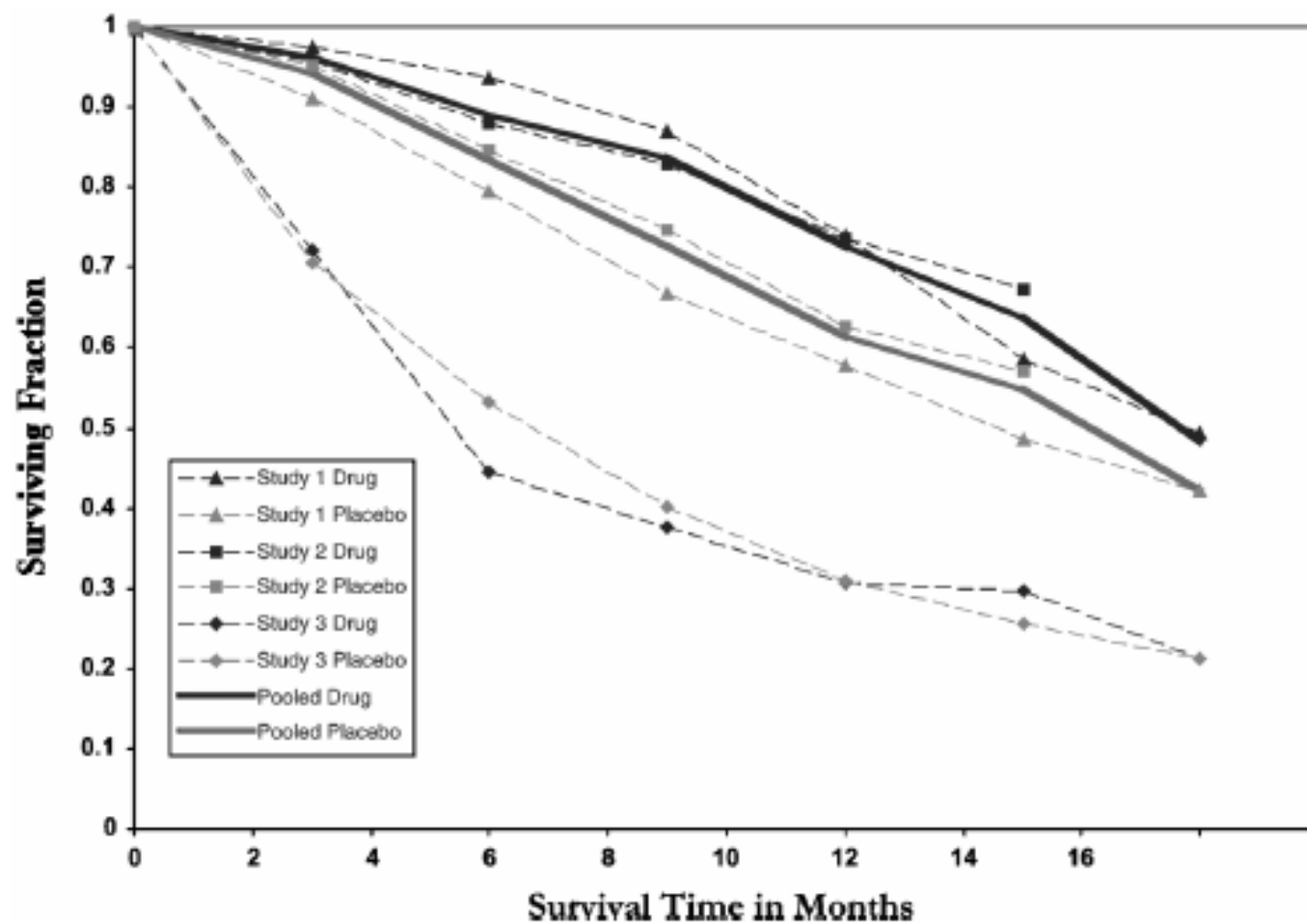


Randomized controlled study of BiPap in 41 ALS patients

- 22 to BiPAP and 19 to standard care once maximum inspiratory pressure was <60% predicted or symptomatic daytime hypercapnea was present



Riluzole in ALS



From a combined analysis of all three trials, there was a survival advantage ($p=0.004$) with riluzole at 12 months



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