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Tecnología de avanzada al servicio del humanismo médico

INSTITUTO DE NEUROCIENCIAS

Unidad de Enfermedades Neuromusculares

ALS - CLINICAL UPDATE

XXII World Congress of Neurology
Santiago - Chile 2015
Changing Neurology Worldwide

CINRG
Cooperative International Neuromuscular Research Group

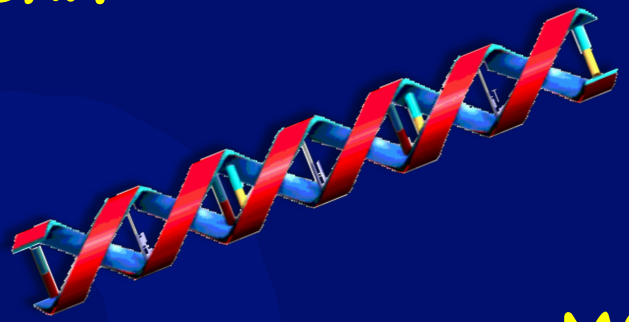
Dr. Alberto L Dubrovsky
Prof. Adjunto de Neurología UBA
Prof. Titular de Neurociencias Univ. Favaloro
Director del Departamento de Neurología
y Unidad de Enfermedades Neuromusculares
Instituto de Neurociencias , Fundacion Favaloro

MOTOR NEURON DISEASES

ALS

"the 3rd most common neurodegenerative disease overall"

PRE MOLECULAR ERA → ONE DISEASE



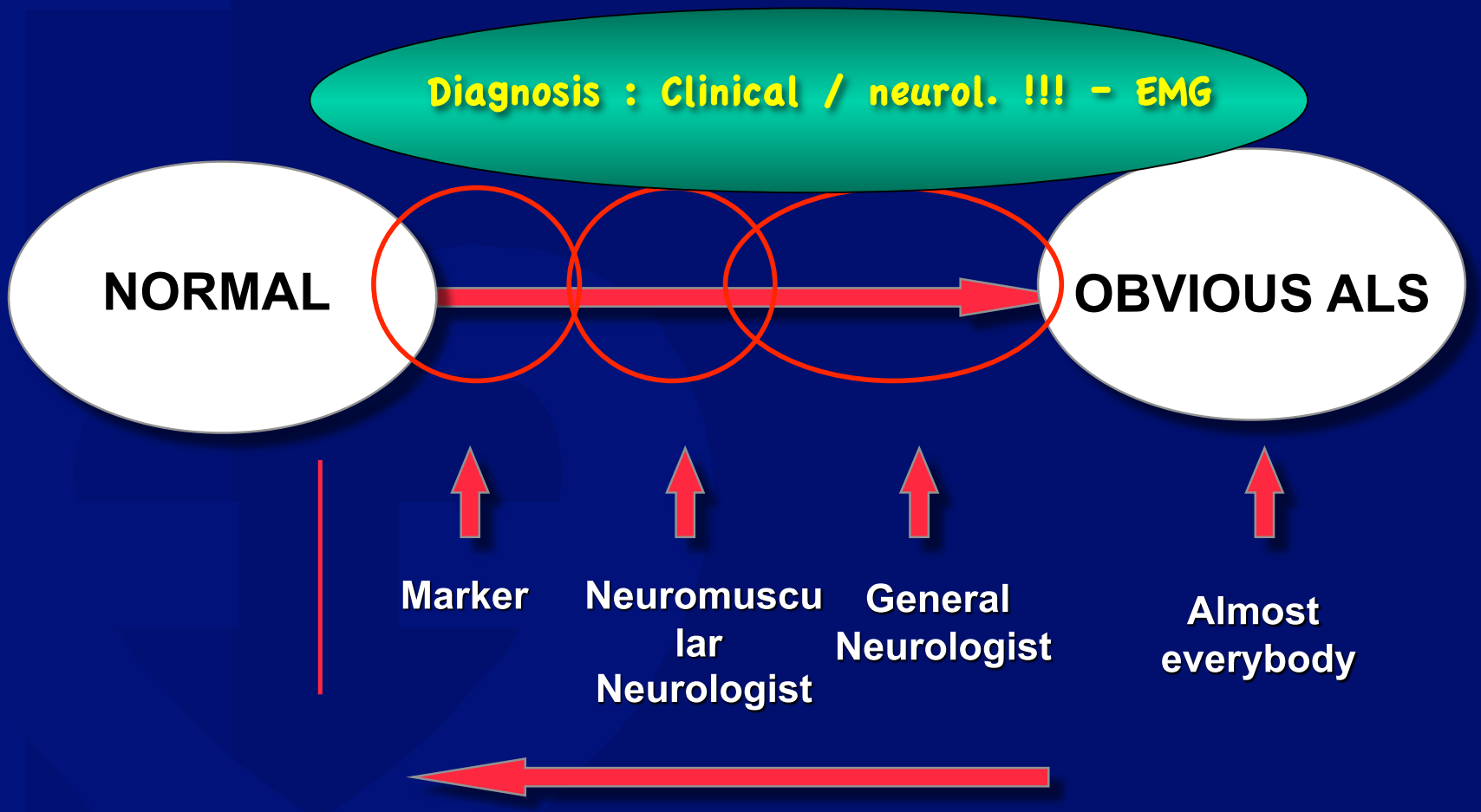
POST MOLECULAR ERA → MORE THAN ONE DISEASE … SYNDROME ?

- ALS : multisystem disorder in which there is a progressive motor system involvement (early)
- Multisystem involvement: concurrent cognitive, behavioural, or dysexecutive symptoms.
- In a subgroup of patients a more florid dementia consistent with a frontotemporal dementia are evident

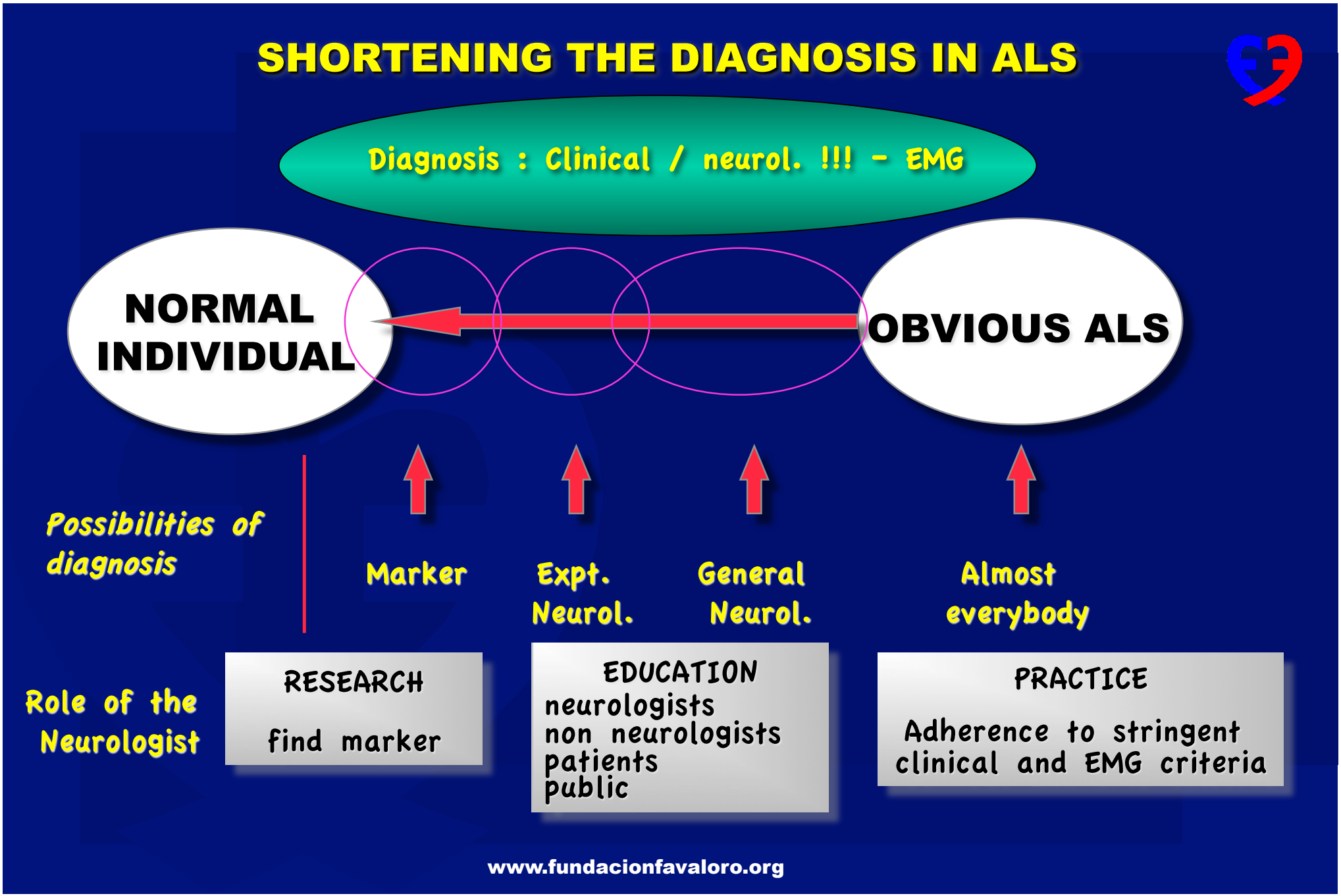
ALS (classic...)

- Neurodegenerative disease
- 10% FALS
- More frequent after 5^{th} / 6^{th} decade
- 20%(?) associated FTD
- Incidence: 0.6 - 2.6 / new cases /100000
- Prevalence 0.8 y el 8.5 / 100000
- Male / female 1.2:1 /2.6:1
- Mean survival after diagnosis : 3 years

DIAGNOSIS IN ALS



SHORTENING THE DIAGNOSIS IN ALS



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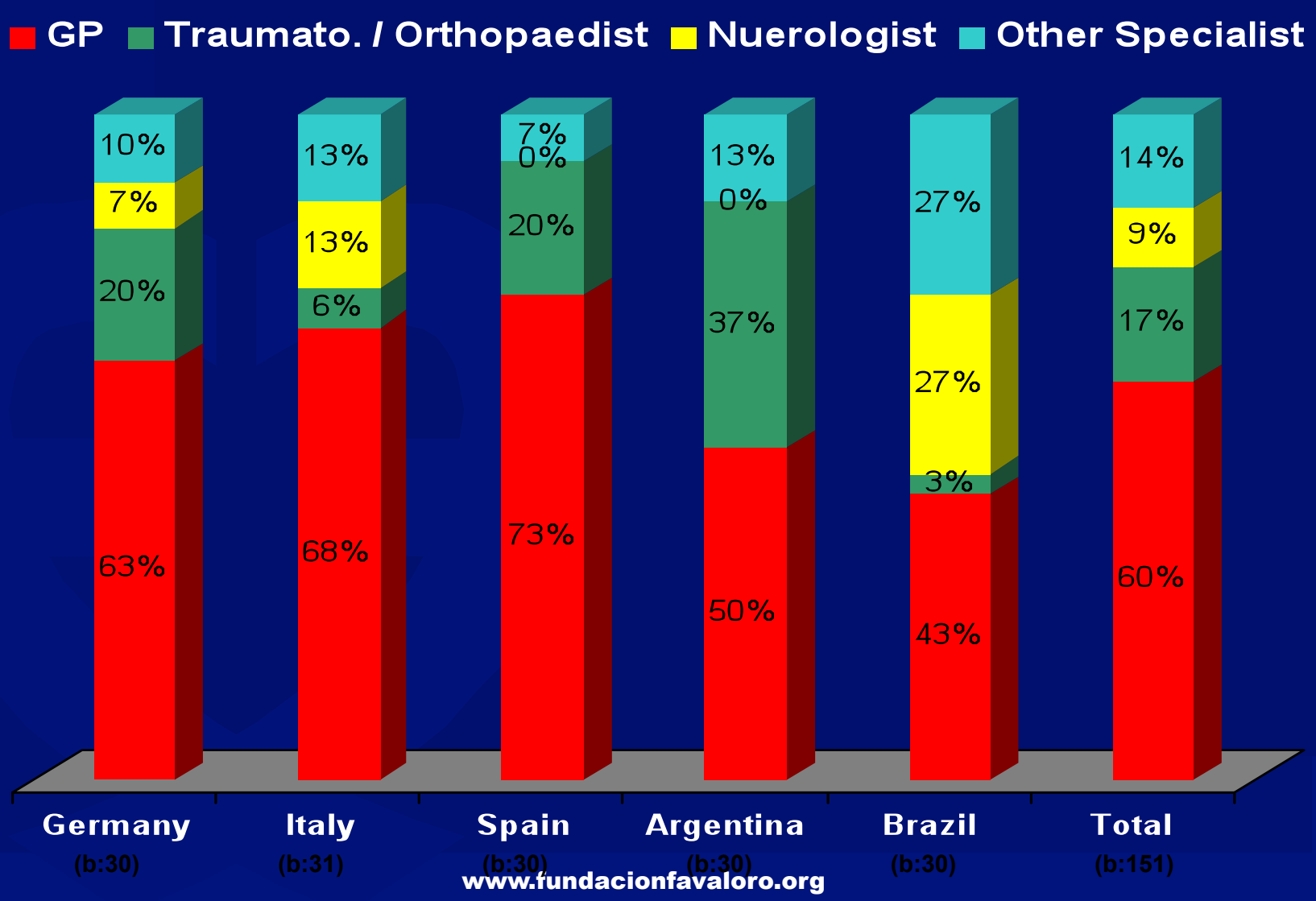
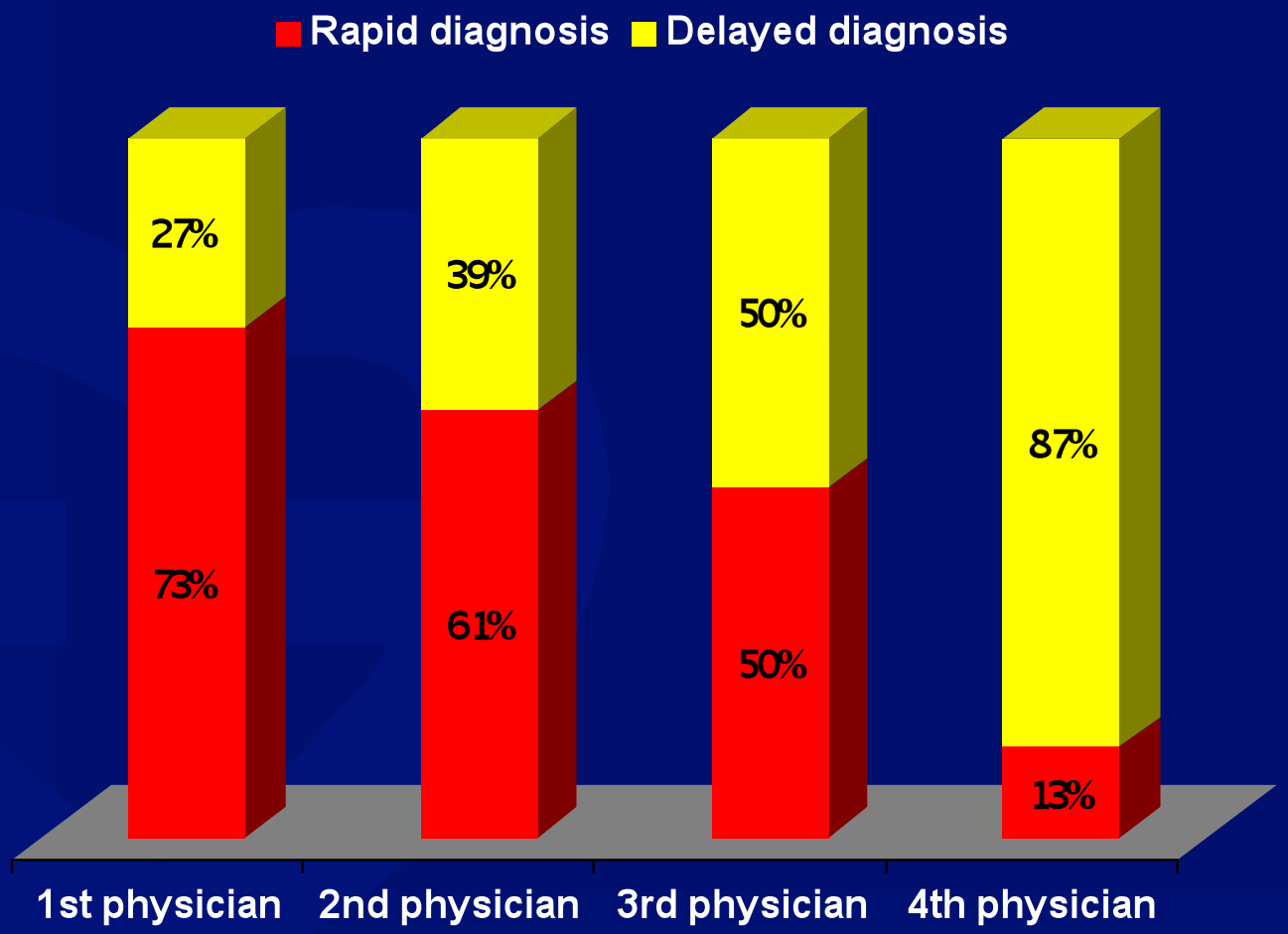
FIRST PHYSICIAN SEEN

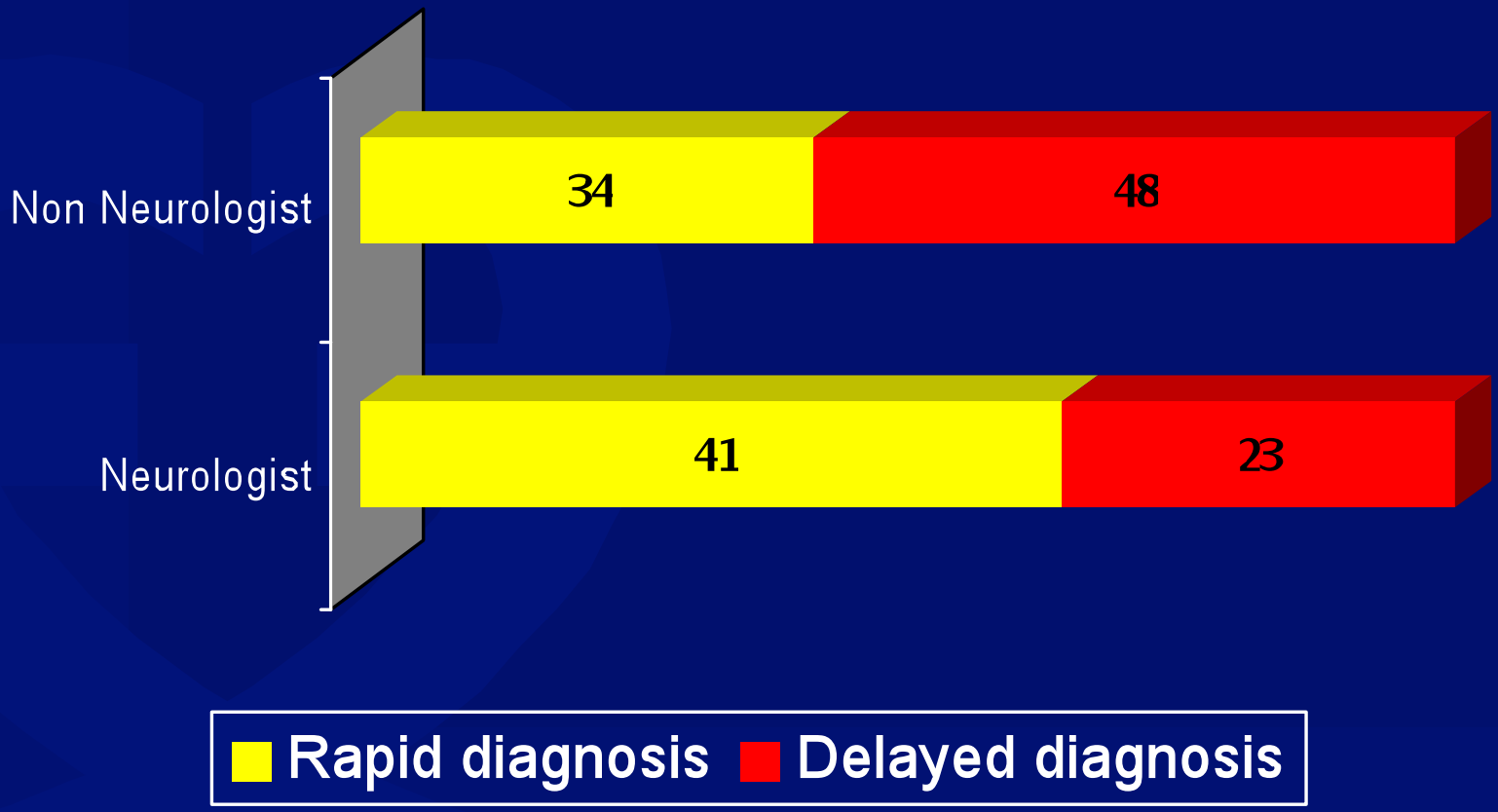


NEUROLOGIST CONSULTATION



IMPACT OF THE FIRST SPECIALIST SEEN BY THE PATIENT

b:146



TIME-TAKEN ACCORDING TO INITIAL SYMPTOMS (TOTAL)

Time-Elapsed Between: (means) *	Total (146)	Bulbar onset (27)	Limb onset (119)	Upper Limb (50)	Lower Limb (51)	Both (9)	Fascicul. (27)	No Fascicul. (119)
First symptoms and first consultation	(4.5 m)	3.1 m	4.8 m	4.3 m	4.7 m	3.1 m	5.7 m	4.2 m
First symptoms and first consultation with a Neurologist	(10.2 m)	8.2 m	10.6 m	9.3 m	11.4 m	12.0 m	10.9 m	10.1 m
First consultation with a Neurologist and diagnosis confirmation	(7.1 m)	7.3 m	7.0 m	6.3 m	9.6 m	1.5 m	4.9 m	7.6 m
First symptoms and diagnosis confirmation	(17.3 m)	15.5 m	17.6 m	15.6 m	21.0 m	13.5 m	15.8 m	17.7 m

*Note: * Means are calculated excluding 5 patients for whom time-taken to diagnose esceeds 10 years*

GENES KNOWN TO CARRY ALS-CAUSING MUTATIONS

Alan E Renton1, Adriano Chiò2 & Bryan J Traynor1,3
Nature Neuroscience
VOLUME 17 | NUMBER 1 | JANUARY 2014

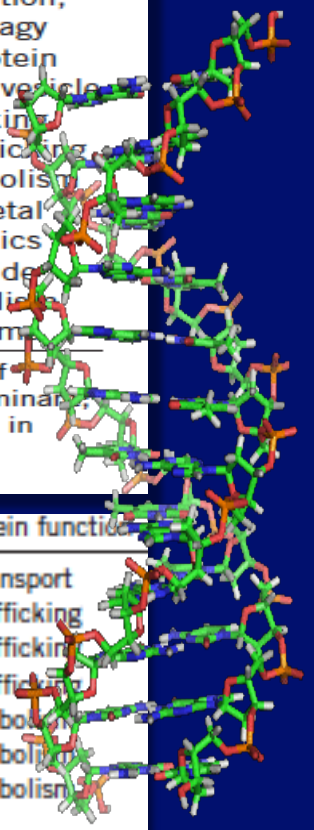
Gene	Location	Inheritance	Percentage explained		Putative protein function
			Familial ALS	Sporadic ALS	
TARDBP	1p36	AD	4	1	RNA metabolism
SQSTM1	5q35	AD	1	<1	Ubiquitination; autophagy
C9ORF72	9p21	AD	40	7	DENN protein
VCP	9p13	AD	1	1	Proteasome; vesicle trafficking
OPTN	10p13	AR and AD	<1	<1	Vesicle trafficking
FUS	16p11	AD and AR	4	1	RNA metabolism
PFN1	17p13	AD	<1	<1	Cytoskeletal dynamics
SOD1	21q22	AD and AR	12	1–2	Superoxide metabolism
UBQLN2	Xp11	XD	<1	<1	Proteasome

Values represent the percentage of ALS explained by each gene in populations of European ancestry. References are provided in the main text. AD, autosomal dominant; AR, autosomal recessive; XD, X-linked dominant; DENN, differentially expressed in normal and neoplasia.

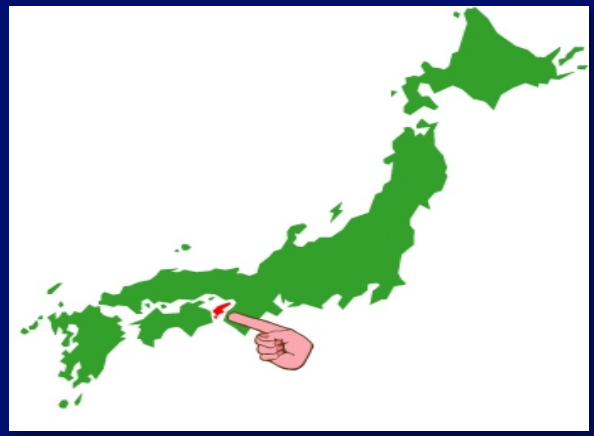
OTHER GENES IMPLICATED IN THE PATHOGENESIS OF ALS

Gene	Location	Inheritance	Predominant clinical syndromes	Putative protein function
DCTN1	2p13	AD	PMA; Perry syndrome	Axonal transport
ALS2	2q33	AR	Juvenile PLS; infantile HSP	Vesicle trafficking
CHMP2B	3p11	AD	Familial ALS; sporadic ALS; FTD	Vesicle trafficking
FIG4	6q21	AD and AR	CMT; familial ALS	Vesicle trafficking
HNRNPA2B1	7p15	AD	Multisystem proteinopathy; ALS	RNA metabolism
ELP3	8p21	Undefined	Sporadic ALS	RNA metabolism
SETX	9q34	AD	Juvenile ALS; ataxia with oculomotor apraxia	RNA metabolism
HNRNPA1	12q13	AD	Multisystem proteinopathy; ALS	RNA metabolism
ATXN2	12q24	Undefined	Sporadic ALS; ataxia	Endocytosis; RNA translation
ANG	14q11	AD	Familial ALS; sporadic ALS	Angiogenesis
SPG11	15q14	AR	Juvenile ALS; HSP	DNA damage repair
VAPB	20q13	AD	PMA; FALS	Vesicle trafficking
NEFH	22q12	AD	Familial ALS; sporadic ALS	Axonal transport

AD, autosomal dominant; AR, autosomal recessive; CMT, Charcot-Marie-Tooth disease; HSP, hereditary spastic paraplegia; PLS, primary lateral sclerosis; PMA, progressive muscular atrophy.

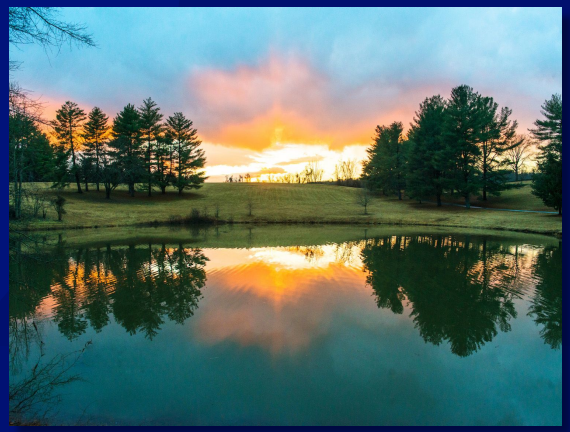


ALS DIAGNOSTIC CONSENSUS



El Escorial, Spain
1990

Airlie VA, USA
1998



Awaji-shima, Japan
2006

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CRITERIA FOR THE DIAGNOSIS OF AMYOTROPHIC LATERAL SCLEROSIS

1) Signs of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathologic examination

2) Signs of upper motor neuron (UMN) degeneration by clinical examination,

3) Progressive spread of signs within a region or to other regions,

ABSENCE OF

A) Electrophysiological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration

B) Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.

Upper motor neuron predominance

ALS

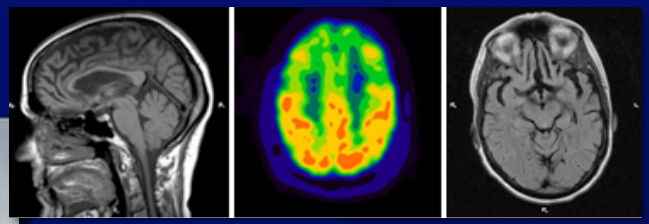
Lower motor neuron predominance

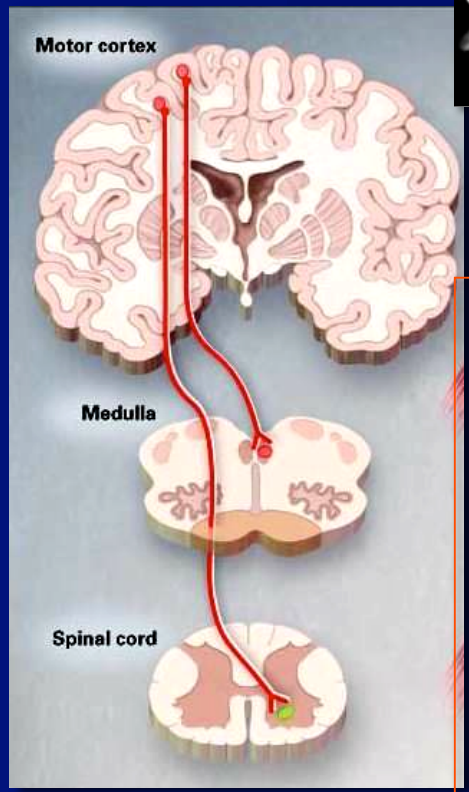
PLS
(Primary Lateral Sclerosis)

ALS
Amyotrophic Lateral Sclerosis

SMA
(Spinal Muscular Atrophy)

UMN



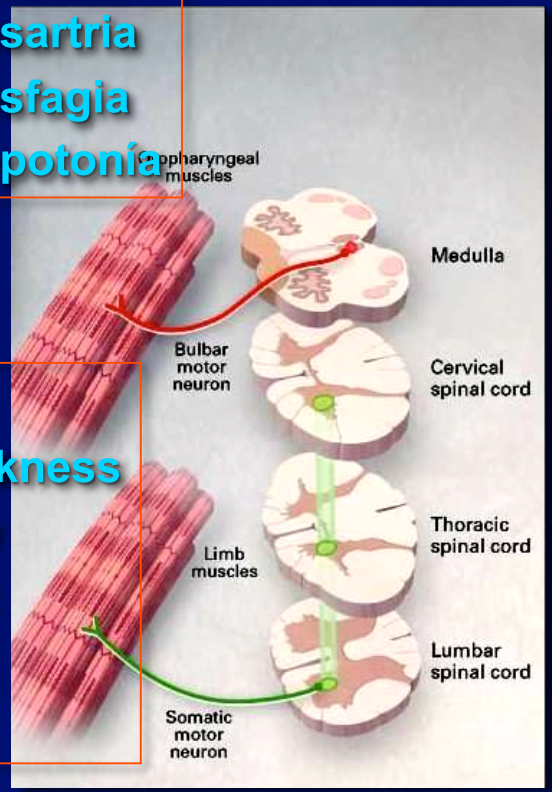


SIGNS
- Hyper active TR
- Hyper active jaw reflex
- Spasticity
- Babinski sign
- Hoffmann sign
- Clonus
- Weakness
- Pseudobulbar affect
- Disap. Cut. Abdom. R

LMN

SIGNS
- Dysartria
- Dysfagia
- Hypotonía

SIGNS
- Segmental weakness
- Muscle atrophy
- Hypo active TR
- Fasciculations
- Cramps



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REGIONS

BULBAR	CERVICAL	TORACIC	LUMBAR
Jaw *Facial* *Larinx* *Palat* *Tongue*	*Neck* *UL* *Diaphragm*	*Trunk* *Abdomen* *(above D6)*	*Trunk* *Abdomen* *(below D6)* *LL*

ALS DIAGNOSIS

Criteria - diagnostic accuracy levels - El Escorial - Airlie II

History & Neurologic Examination

EMG

Lab test / imaging (rule out other...)

DEFINITE ALS

Upper and lower motor signs found in the bulbar region and at least two regions along the neuraxis (cervical, thoracic, lumbosacral)
Alternatively, UMN and LMN signs can be present in three regions, sparing bulbar areas at the time of diagnosis.

PROBABLE LABORATORY SUPPORTED

UMN and LMN signs in only one region; however, electrophysiological evidence of denervation in at least two regions where other aetiologies have been excluded.)

Possible

Probable

Probable (laboratory supported)

Definite

PROBABLE ALS

UMN and LMN signs in at least two spinal regions. At least one UMN sign should be present rostral to at least one LMN sign

POSSIBLE ALS

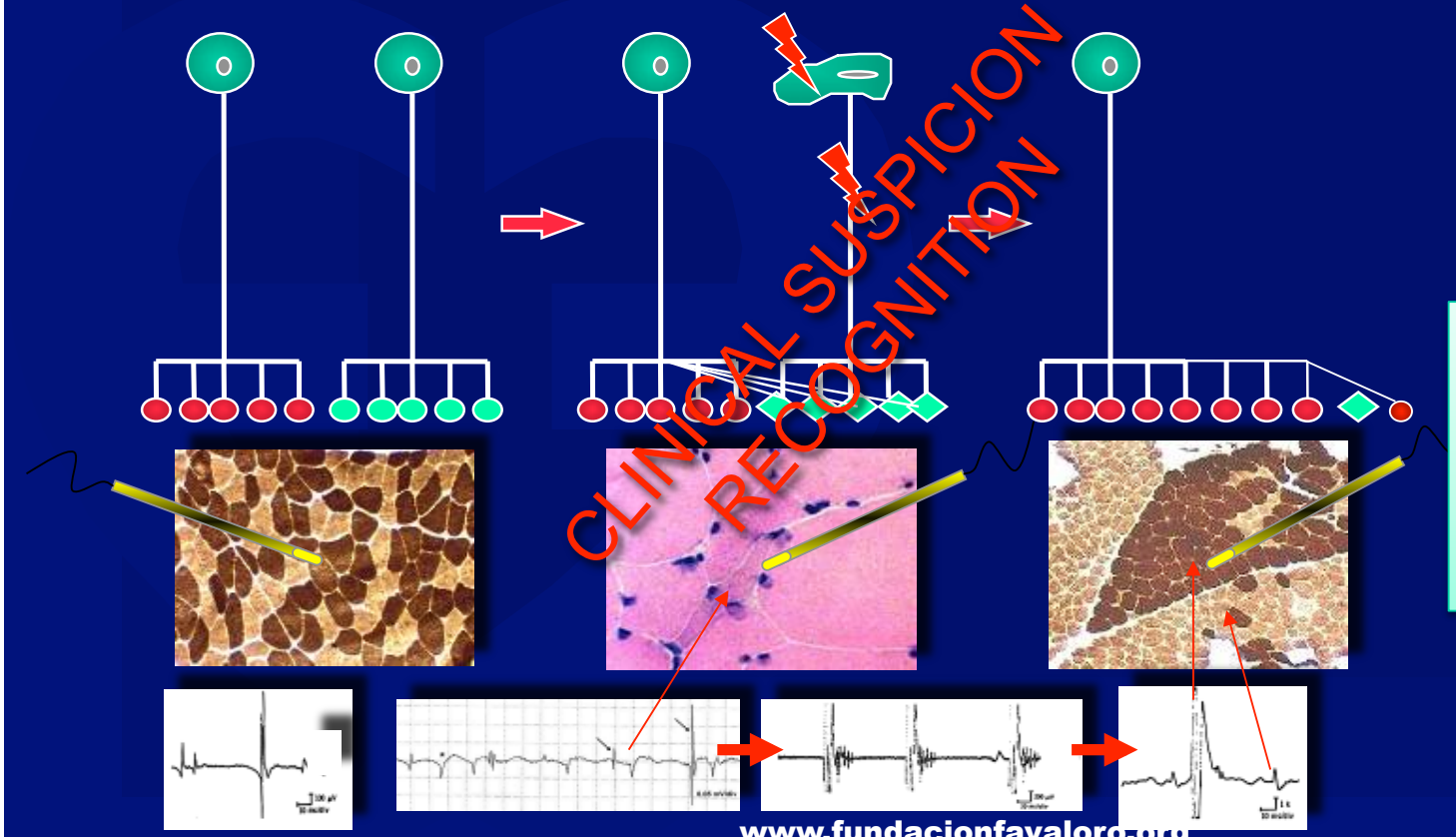
UMN and LMN findings in only one region or UMN findings in at least two regions or LMN signs rostral to UMN signs.

EMG in ALS

Detect LMN involvement in at least two (three) regions, especially in areas that are not clinically affected, or in regions where the UMN signs makes it difficult to identify superimposed LMN involvement.

MUSCLE DENERVATION
- Fibrillations
- Positive sharp waves
- Loss of MUAP's

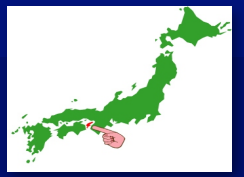
- FASCICULATIONS



MUAP :
- Reduced in number
- High frequency MUAP discharge (> de 10 Hz)

MUSCLE REINERVATION
- Increased MUAP duration and amplitude.
- Increased Polyphasia
- Satellite MUAP's.
- MUAP's instability

Awaji – Shima 2006



Consensus aimed at recruiting an increased number of ALS patients in an earlier stage of the disease (for studies / clinical trials).

Adds great value to electrophysiology IN THE CLINICAL CONTEXT

Confirms the importance of excluding other pathologies using EMG or CS

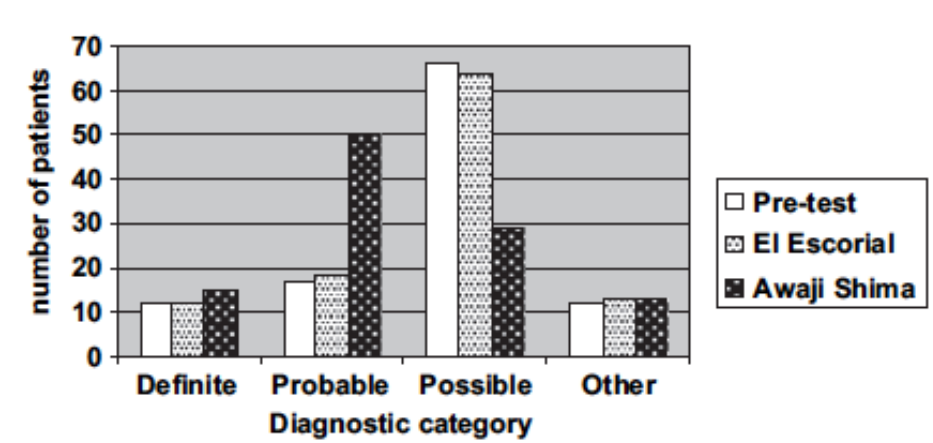
Reaffirms the equivalence between EMG and clinical examination , rendering the category of “Laboratory Supported” unnecessary

Fasciculations in a muscle with neurogenic elements are equivalent to the signs of active denervation (fibs and psw)

An evaluation of neurophysiological criteria used in the diagnosis of motor neuron disease

C P Douglass,[1] R H Kandler,[2] P J Shaw,[3] C J McDermott[3]

J Neurol Neurosurg Psychiatry 2010 81: 646-649



Awaji Criteria for the Diagnosis of Amyotrophic Lateral Sclerosis

A Systematic Review

João Costa, MD, PhD; Michael Swash, MD; Mamede de Carvalho, MD, PhD

ARCH NEUROL/VOL 69 (NO. 11), NOV 2012

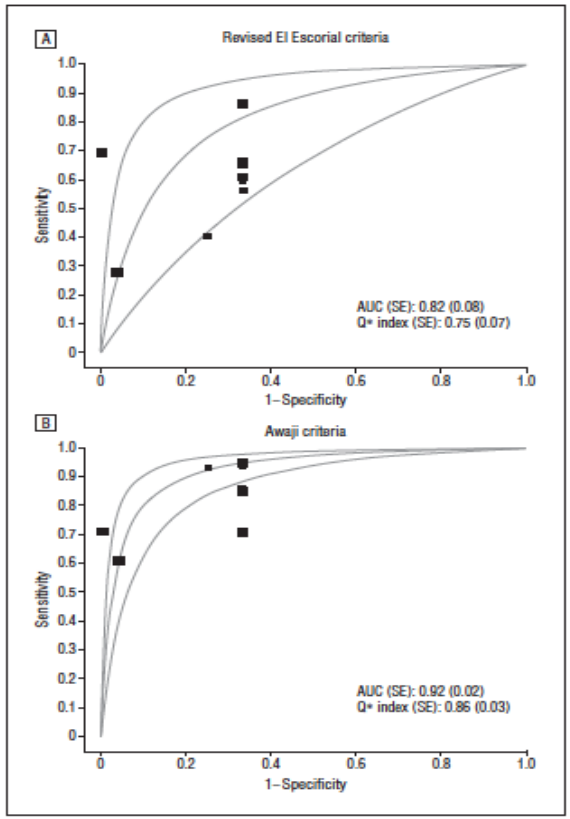


Figure 3. Summary receiver operating characteristic plots (and 95% CI) of sensitivity and specificity. AUC indicates area under the curver.

Upper motor neuron predominance

ALS

Lower motor neuron predominance

PLS
(Primary Lateral Sclerosis)

ALS
Amyotrophic Lateral Sclerosis

SMA
(Spinal Muscular Atrophy)

UMN

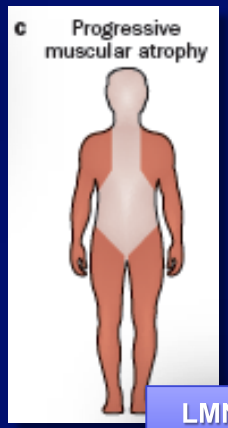
LMN

UMNs of arms and legs are primarily involved / later discrete LMN involvement can be detected

UMN and LMN in the bulbar muscles

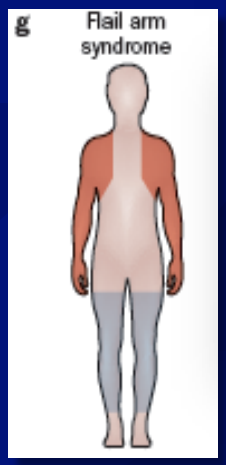
Respiratory muscles

Patchy UMN and LMN involvement in all limbs.

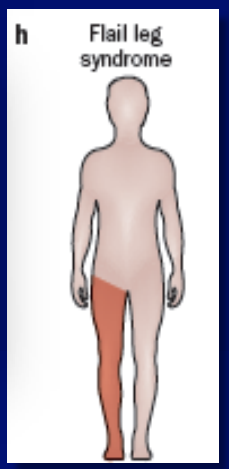


LMNs in arms and legs are involved, often proximally

Uunilateral UMN involvement with sparing of the face, and sometimes discrete LMN involvement, can be observed.



Flail arm syndrome, LMN involvement is restricted to the upper limbs, but mild UMN signs can be detected in the legs.
Flail leg syndrome, LMN involvement is restricted to the lower limbs, and is often asymmetric



Only LMNs restricted to the distal limbs are involved

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Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study

Adriano Chiò,[1,2] Andrea Calvo,[1] Cristina Moglia,[1] Letizia Mazzini,[3] Gabriele Mora,[4] PARALS study group*

Table 1 Mean age at onset, mean time delay from onset to diagnosis and frequency of frontotemporal dementia

Phenotype	No of cases (%)	Age at onset (years) (mean (SD))	Age at onset (years) (median (IQR))‡	Diagnostic delay (months) (mean (SD))	Diagnostic delay (months) (median (IQR))‡	Cases with FTD (%)
Classic	404 (30.3)	62.8 (11.3)	64.6 (56.1–70.6)	10.9 (9.6)	8 (5–13)	16 (4.0)
Bulbar	456 (34.2)	68.8 (9.7)	69.9 (62.9–75.0)	9.8 (7.0)	8 (5–12)	41 (9.0)
Flail arm	74 (5.5)	62.6 (11.8)	63.3 (54.8–72.2)	12.8 (11.0)	9 (5–15)	1 (1.4)
Flail leg	173 (13.0)	65.0 (9.6)	65.6 (58.5–71.2)	13.1 (10.1)	11 (7–17)	7 (4.1)
Pyramidal	120 (9.1)	58.3 (13.5)	60.1 (49.2–68.3)	15.9 (13.4)	12 (6–22)	3 (2.5)
Respiratory	14 (1.1)	62.2 (8.6)	62.0 (58.3–65.3)	6.4 (4.3)	5 (3–9)	–
PLMN	38 (2.9)	56.2 (11.3)	55.2 (45.7–61.3)	15.5 (12.4)	14 (10–19)	–
PUMN	53 (4.0)	58.9 (10.9)	56.5 (48.3–62.6)	15.9 (14.3)	15 (10–19)	2 (3.8%)
Overall ALS	**1332**	**64.3 (11.3)**	**65.3 (59.7–71.8)**	**10.8 (10.4)**	**9 (5–14)**	**70 (5.4%)**
		p=0.0001*		p=0.0001*		p=0.0001†

*ANOVA.
†χ^2 test.
‡Q1–Q3.
ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; PLMN, pure lower motor neuron phenotype; PUMN, pure upper motor neuron phenotype.

J Neurol Neurosurg Psychiatry 2011;**82**:740–746.

ALS - AGE AT ONSET

- (CLASSIC….) Usually in the fifth or sixth decade of life.

- Juvenile ALS : before 25 years, (course of progression is generally slower) than in other forms

- The probability of carrying a genetic mutation is inversely related with the age at onset of patients: the younger the age at onset, the higher the likelihood of having a genetic mutaion.

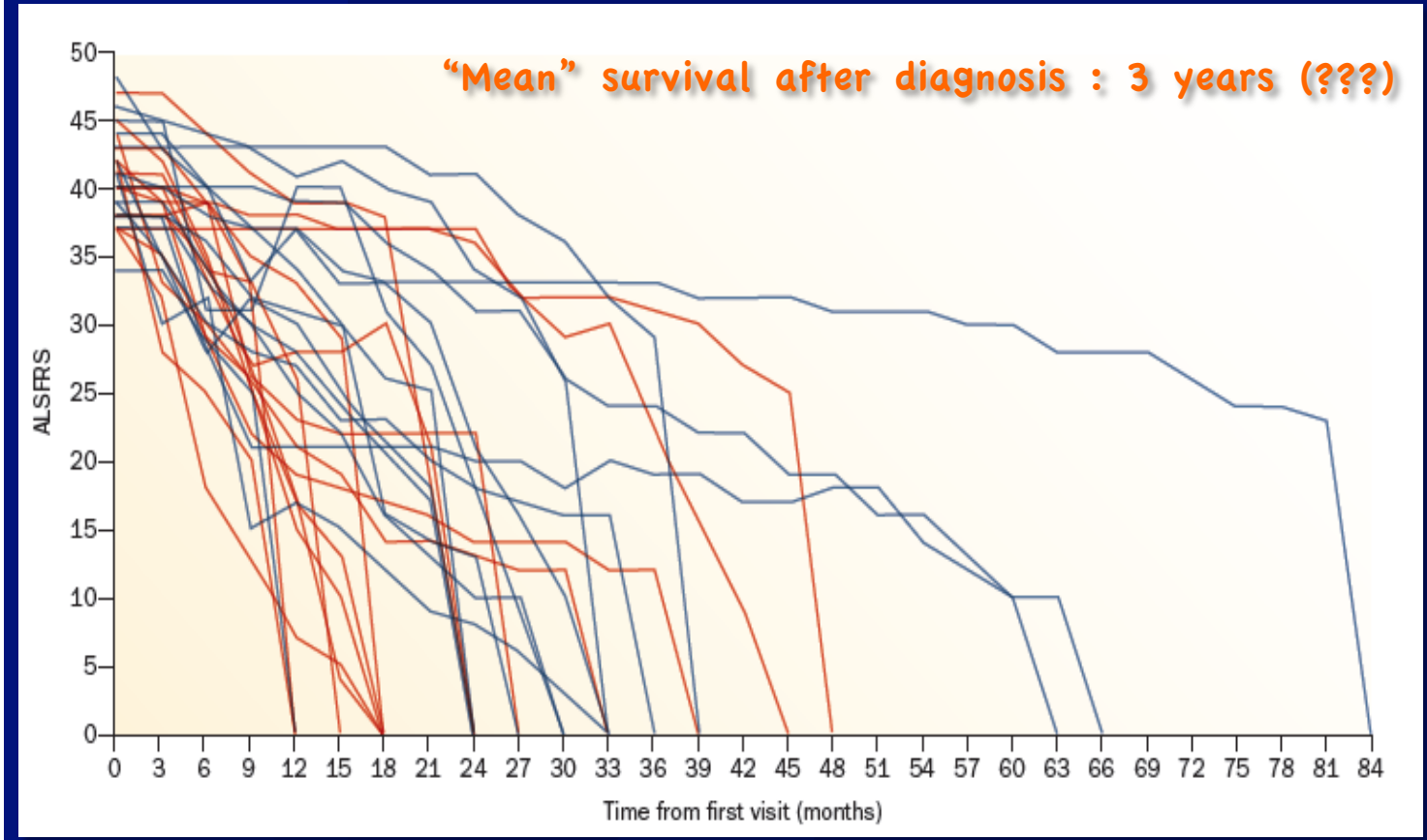
- Mutations in *ALS2, SETX and FUS causes juvenile ALS.*

- 60% of patients with disease onset between 20 and 40 years of age have predominantly upper motor neuron involvement, and relatively few of these patients (15%) have bulbar-onset disease.

- Older age at onset associated with decreased likelihood of upper motor neuron involvement (20%), increased probability of bulbar onset (up to 50% with onset after 80 years of age), and poor prognosis.

- Onset after 80 years is associated with a particularly short survival.

PATTERNS OF DISEASE PROGRESSION



SPINAL ONSET

BULBAR ONSET

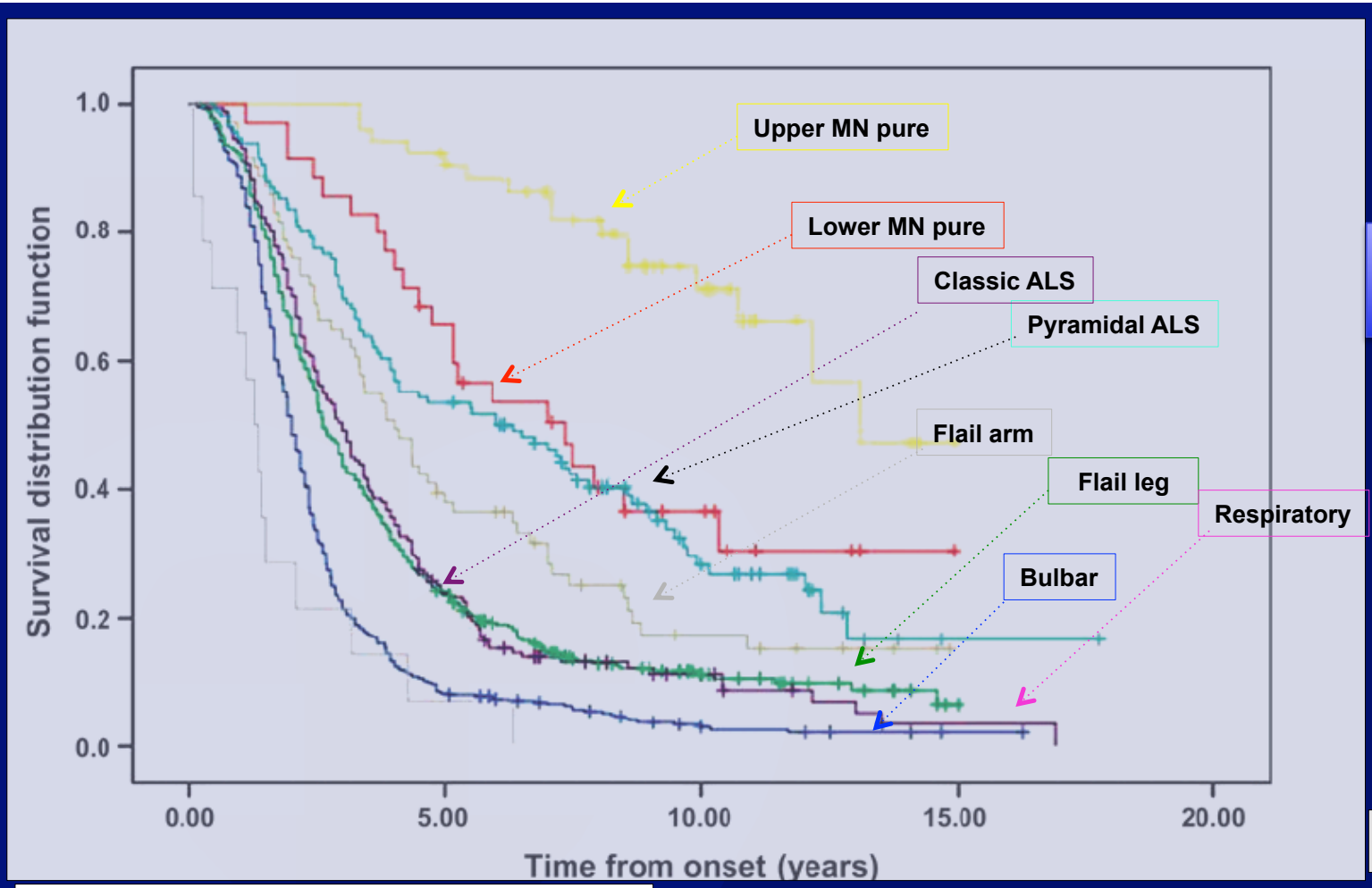
SURVIVAL

- 10 % survive > 10 years
- SOD1 Ala4Val : rapid
- SOD1 Asp90Ala : slow
- Hexanucleotide (GGGGCC) expansion mutation in the *C9orf72: shorter survival*

No strict correlation between survival and mutation

EPIGENETIC ENVIRONMENTAL FACTORS ?

Bart Swinnen and Wim Robberecht Nature Reviews / Neurology
VOLUME 10 | NOVEMBER 2014 |



SURVIVAL AND ALS PHENOTYPE

(TRACHEOSTOMY FREE)

J Neurol Neurosurg Psychiatry 2011;**82**:740–746.

Figure 3 Tracheostomy free survival, according to amyotrophic lateral sclerosis (ALS) phenotype. Yellow, PUMN; red, PLMN; light blue, pyramidal ALS; grey, flail arm; violet, classic ALS; green, flail leg; blue, bulbar; cyan, respiratory. Crosses are censored patients. PLMN, pure lower motor neuron phenotype; PUMN, pure upper motor neuron phenotype.

Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study

Adriano Chiò,[1,2] Andrea Calvo,[1] Cristina Moglia,[1] Letizia Mazzini,[3] Gabriele Mora,[4] PARALS study group*

OVERALL SURVIVAL IN ALS

MULTIDISCIPLINARY PATIENT'S CARE

- PHYSICAL THEREPAY
- NUTRITIONAL CARE
- SPASTICITY
- CRAMPS
- PAIN
- CONSTIPATION
- PEG
- PSYCHOLOGICAL SUPPORT
- RESPIRATORY CARE
- NIV, COUGH ASSISTANCE,
- EARLY INFECTION TREATMENTS,
- ETC, ETC, ETC

Special Article

AMERICAN ACADEMY OF NEUROLOGY.

Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

R.G. Miller, MD, FAAN
C.E. Jackson, MD, FAAN
E.J. Kasarskis, MD, PhD, FAAN
J.D. England, MD, FAAN
D. Forshew, RN
W. Johnston, MD
S. Kalra, MD
J.S. Katz, MD
H. Mitsumoto, MD, FAAN
J. Rosenfeld, MD, PhD, FAAN
C. Shoesmith, MD, BSc
M.J. Strong, MD
S.C. Woolley, PhD

Address correspondence and reprint requests to American Academy of Neurology, 1080

ABSTRACT

Objective: To systematically review evidence bearing on the management of patients with amyotrophic lateral sclerosis (ALS).

Methods: The authors analyzed studies from 1998 to 2007 to update the 1999 practice parameter. Topics covered in this section include breaking the news, multidisciplinary clinics, symptom management, cognitive and behavioral impairment, communication, and palliative care for patients with ALS.

Results: The authors identified 2 Class I studies, 8 Class II studies, and 30 Class III studies in ALS, but many important areas have been little studied. More high-quality, controlled studies of symptomatic therapies and palliative care are needed to guide management and assess outcomes in patients with ALS.

Recommendations: Multidisciplinary clinic referral should be considered for managing patients with ALS to optimize health care delivery and prolong survival (Level B) and may be considered to enhance quality of life (Level C). For the treatment of refractory sialorrhea, botulinum toxin B should be considered (Level B) and low-dose radiation therapy to the salivary glands may be considered (Level C). For treatment of pseudobulbar affect, dextromethorphan and quinidine should be considered if approved by the US Food and Drug Administration (Level B). For patients who develop fatigue while taking riluzole, withholding the drug may be considered (Level C). Because many patients with ALS demonstrate cognitive impairment, which in some cases meets criteria for dementia, screening for cognitive and behavioral impairment should be considered in patients with ALS (Level B). Other management strategies all lack strong evidence.

Neurology® 2009;73:1227–1233

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY.

Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Drug, nutritional, and respiratory therapies (an evidence-based review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

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Objective: To systematically review evidence bearing on the management of patients with amyotrophic lateral sclerosis (ALS).

Methods: The authors analyzed studies from 1998 to 2007 to update the 1999 practice parameter. Topics covered in this section include slowing disease progression, nutrition, and respiratory management for patients with ALS.

Results: The authors identified 8 Class I studies, 5 Class II studies, and 43 Class III studies in ALS. Important treatments are available for patients with ALS that are underutilized. Noninvasive ventilation (NIV), percutaneous endoscopic gastrostomy (PEG), and riluzole are particularly important and have the best evidence. More studies are needed to examine the best tests of respiratory function in ALS, as well as the optimal time for starting PEG, the impact of PEG on quality of life and survival, and the effect of vitamins and supplements on ALS.

Recommendations: Riluzole should be offered to slow disease progression (Level A). PEG should be considered to stabilize weight and to prolong survival in patients with ALS (Level B). NIV should be considered to treat respiratory insufficiency in order to lengthen survival (Level B), and may be considered to slow the decline of forced vital capacity (Level C) and improve quality of life (Level C). Early initiation of NIV may increase compliance (Level C), and insufflation/exsufflation may be considered to help clear secretions (Level C).

Neurology® 2009;73:1218–1226

GENES / MUTATIONS AND ALS PHENOTYPES

NO genes have been shown to have a definite effect on phenotype. (but

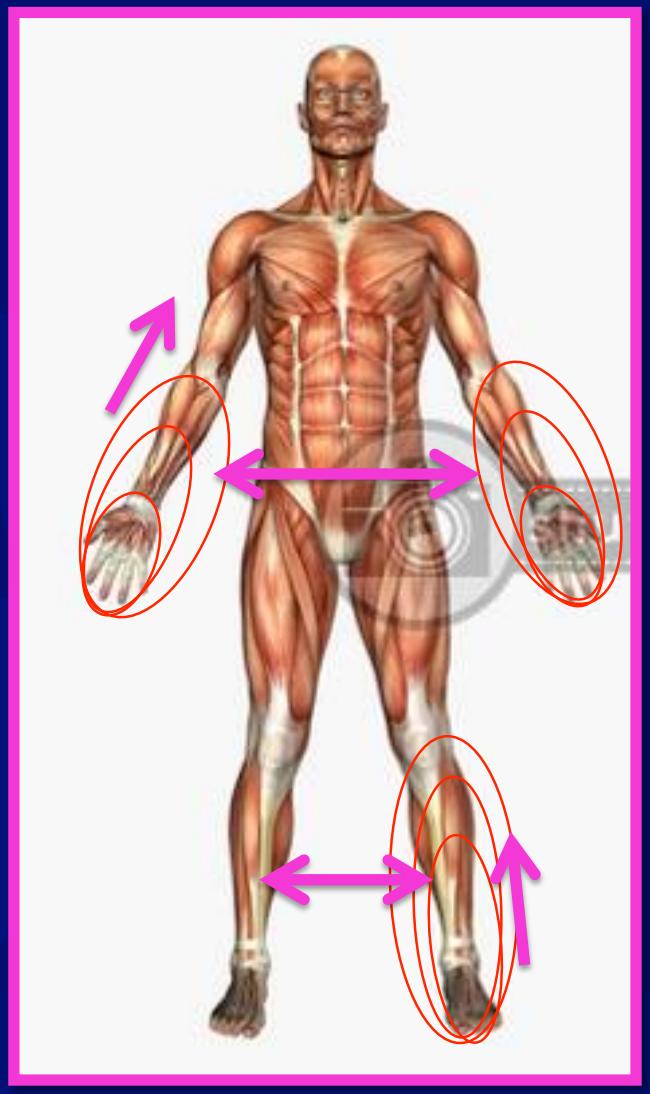
SOD1

- Phenotypic heterogeneity even within the same mutation
- Some specific missense mutations carry a consistently worse (ie, A4V, G41S) or better (ie, H46R) phenotype

FUS

- Also phenotypic heterogeneity
- some mutations / more defined phenotypes (ie: R514S and R521C missense mutations ----predominantly proximal and axial phenotype) (P525L missense mutation ----- a very young age at onset (<30 years), with a bulbar presentation and a short duration.

ALS SPREAD



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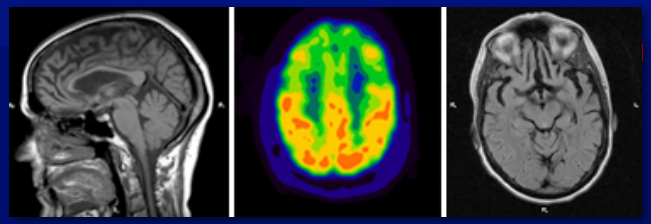
FRONTO TEMPORAL DEMENTIA / ALS



- Disinhibited type
  - Increased interest in sexual activity
  - Lack of judgment
  - Swearing
  - Violation of personal space
  - Impulsive buying
  - Paranoia
  - Criminal activity
  - Grandiose thinking
  - Ignoring social etiquette
- Apathetic type
  - Blunted emotions
  - Disinterested and withdrawn
  - Lack of attention to personal hygiene
  - Lack of empathy
- Stereotypical type
  - Hoarding
  - Food fads, overeating
  - Ritualistic/repetitive behavior

ALS → ALS-FTD → FTD-MND → FTD

normal cognition	mild cognitive impairment	Behaviour abnormalities	frankly demented.

% : depends on the test / authors

Involvement of the frontotemporal lobes
dysexecutive syndrome, behavioral changes, and language dysfunction.

ALS-FTD

-Onset: 50's slightly more common in men than women. ALS symptoms precede, simultaneous, or after the signs and symptoms of FTD. Most common :cognitive change first followed by weakness.

-Interval between the cognitive symptoms and weakness may be a few months to up to 7 years, with a mean of 2 years

Behavior Matters—Cognitive Predictors of Survival in Amyotrophic Lateral Sclerosis

William T. Hu[1,2,3]*, Matthew Shelnutt[1,3], Ashley Wilson[1], Nicole Yarab[1], Crystal Kelly[1], Murray Grossman[4], David J. Libon[5], Jaffar Khan[1], James J. Lah[1,2,3], Allan I. Levey[1,2,3], Jonathan Glass[1,2,3]

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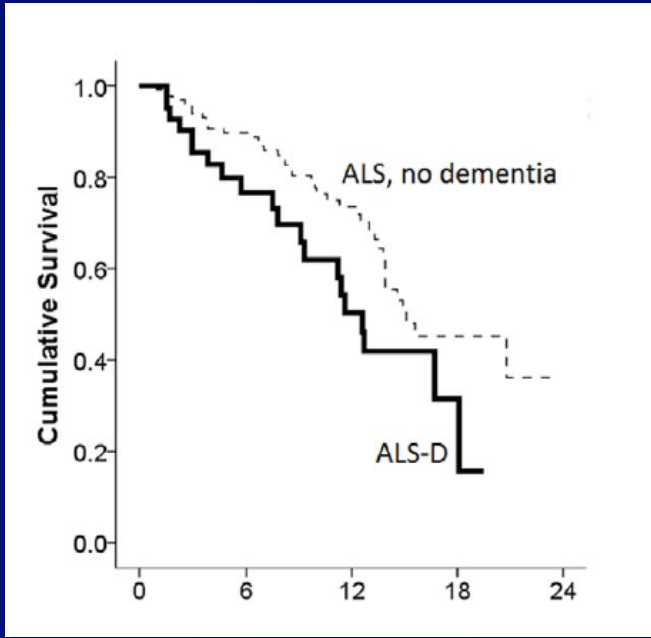

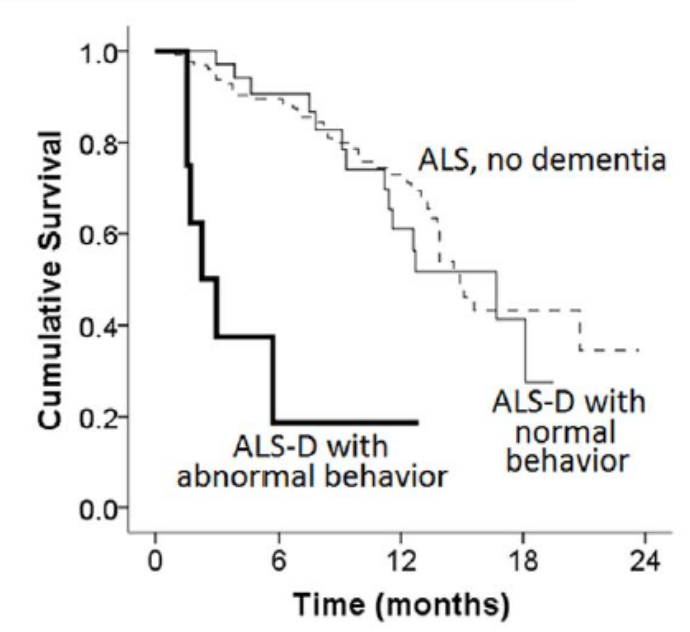

Figure 3. Kaplan-Meier analysis of the effects of dementia and abnormal behavior on ALS survival. Top: ALS-dementia (ALS-D) patients have poorer survival than non-demented ALS patients ($p = 0.03$). Bottom: ALS-D patients with abnormal behavior had significantly worse survival than ALS-D patients with normal behavior and non-demented ALS patients ($p < 0.001$).
doi:10.1371/journal.pone.0057584.g003

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ALS patients are still waiting for us to know how to diagnose, understand and find how to stop this disease.

For all of us (patients, physicians and scientists) this is a matter of time…..

But the meaning of time is different…

ADM
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