Malattie del Motoneurone e SLA

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Motor neuron diseases

Spinal muscular atrophie

Idiopathic motor neuron disease
Amyotrophic lateral sclerosis
Progressive bulbar palsy
Progressive muscular atrophy
Primary lateral sclerosis
Juvenile motor neuron disease
Monomelic motor neuron disease
Familial motor neuron disease

Excitotoxin-induced motor neuron disease
Guam-type MND (Western Pacific ALS), with or without Parkinson-Dementia Complex
Lathyrism

Metabolic and immunological
Hexosaminidase deficiency
Monoclonal gammopathy

Viral and transmissible
Poliomyelitis
Creutzfeldt–Jakob disease
AIDS
Post-encephalitic myelopathy
Herpes zoster myelitis (segmental)
? Other viruses, e.g. Coxsackie virus infection

System degenerations
Spino-cerebellar degenerations
Shy–Drager syndrome
Olivo-ponto-cerebellar degeneration
Joseph-Machado disease
Huntington's disease

Heavy metal poisoning
Lead and other heavy metals
Mercury
Manganese

Others
Stiff man syndrome
Post-traumatic
Syringomyelia
Post-irradiation syndromes
Electric shock and lightening injuries

The majority of patients with adult-onset motor neuron disease will be found to have

IDIOPATHIC ALS

SCLEROSI LATERALE AMIOTROFICA: Cenni storici

- *1869: Charcot e Joffroy descrissero 2 casi di Atrofia muscolare progressiva (PMA) caratterizzati da atrofia dei cordoni anteriori e posterolaterali del midollo spinale*

- *1874: Charcot diede la prima definizione sistematica della Sclerosi laterale amiotrofica (SLA) conosciuta anche con il termine di "Maladie de Charcot", caratterizzata dalla degenerazione del 1° e 2° motoneurone*

- *1875: Erb descrive la sclerosi latarale primaria (PLS)*

Jean Martin Charcot

- *la SLA, conosciuta anche come "**Lou Gerigh disease**" (1939) e' un disturbo inevitabilmente fatale e solo minimamente rallentato dalle terapie disponibili*

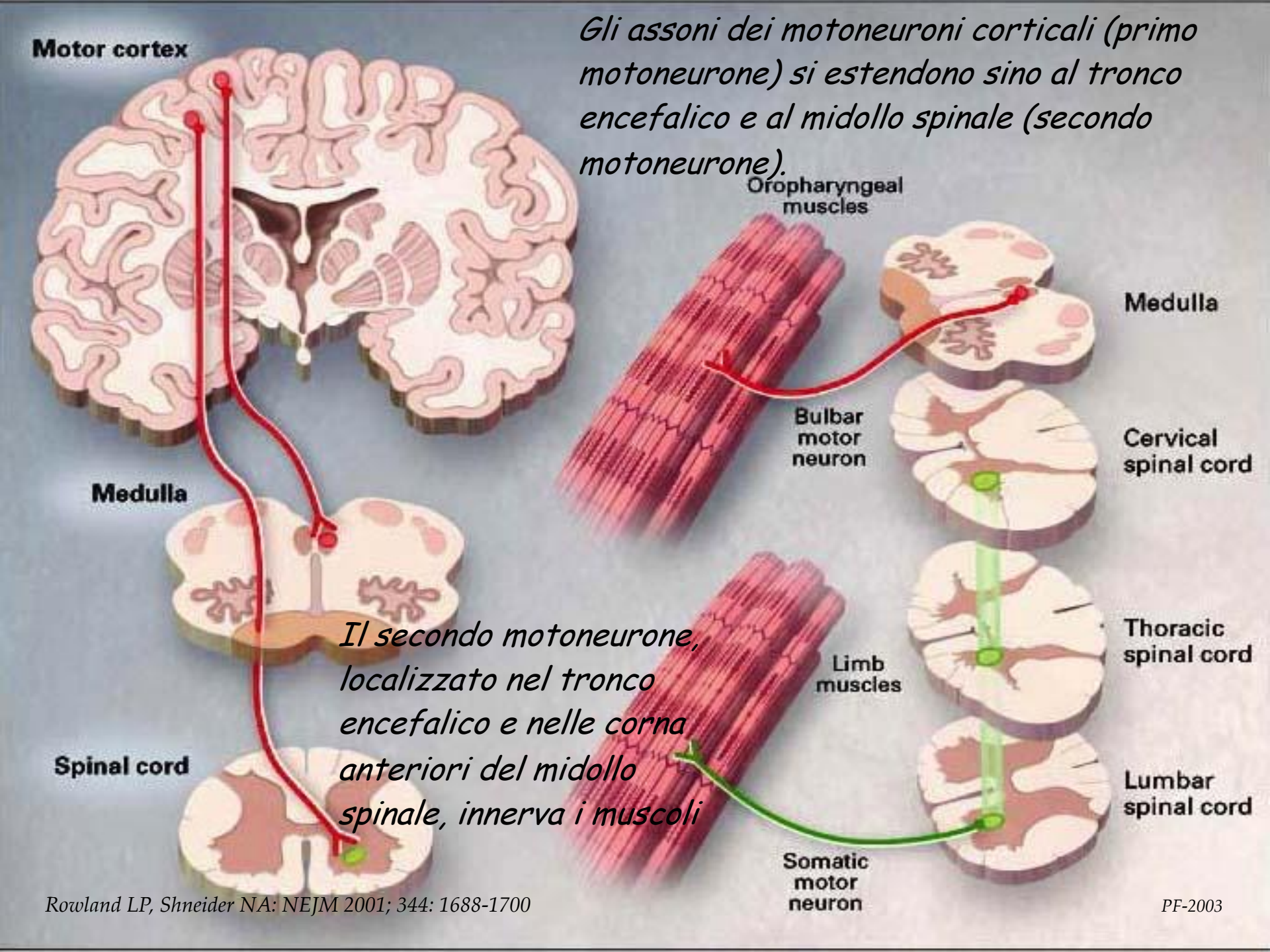
Definizione di malattia:

La Sclerosi laterale amiotrofica (SLA), è una malattia degenerativa dell'età adulta, a decorso progressivo, caratterizzata da interessamento di:

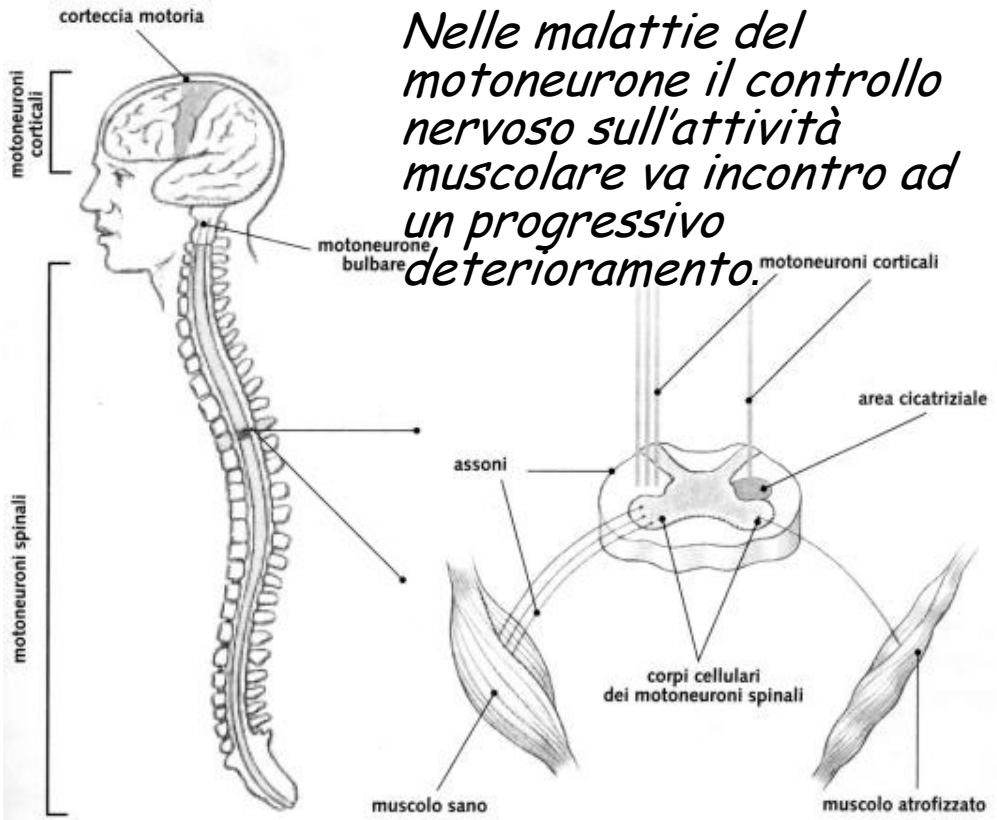
- *Motoneurone corticale (1°motoneurone)*
  → spasticità agli arti, soprattutto inferiori

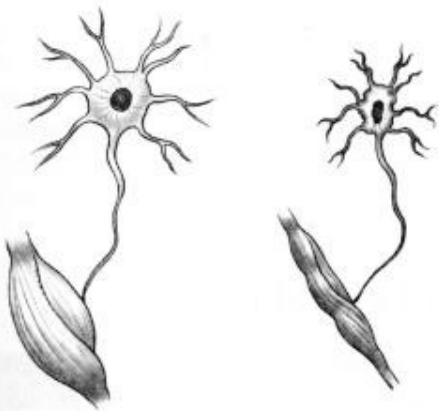
- *Motoneurone bulbare (2° motoneurone, tronco encefalico)*
  → disfagia, disfonia, disartria

- *Motoneurone spinale (2° motoneurone, midollo spinale)*
  → ipostenia e ipotrofia muscolare a livello degli arti e del tronco


Motor cortex
Gli assoni dei motoneuroni corticali (primo motoneurone) si estendono sino al tronco encefalico e al midollo spinale (secondo motoneurone).
Oropharyngeal muscles
Medulla
Bulbar motor neuron
Cervical spinal cord
Medulla
Il secondo motoneurone, localizzato nel tronco encefalico e nelle corna anteriori del midollo spinale, innerva i muscoli
Limb muscles
Thoracic spinal cord
Lumbar spinal cord
Spinal cord
Somatic motor neuron
Rowland LP, Shneider NA: NEJM 2001; 344: 1688-1700
PF-2003

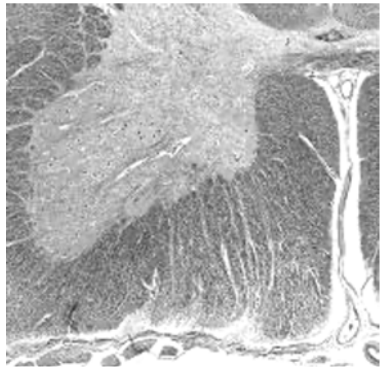
Nelle malattie del motoneurone il controllo nervoso sull'attività muscolare va incontro ad un progressivo deterioramento.





la perdita del primo motoneurone determina spasticità muscolare, mentre la perdita del secondo motoneurone determina ipostenia e atrofia muscolare.

Definizione di malattia:

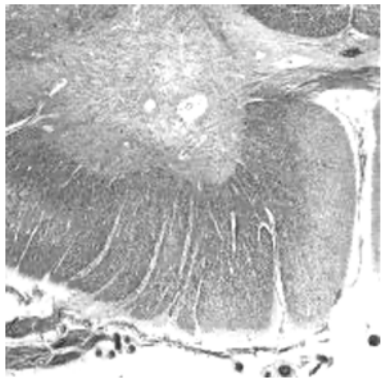


Malattia del motoneurone

"SCLEROSI LATERALE"
consistenza delle colonne laterali del midollo spinale nelle autopsie dove la gliosi segue la degenerazione del tratto corticospinale

"AMIOTROFICA"
atrofia muscolare che insieme ad ipostenia e alle fascicolazioni significano coinvolgimento del secondo motoneurone

Soggetto normale



Definizione di malattia:

MALATTIA DEL MOTONEURONE (MOTOR NEURON DISEASE, MND in UK)

Atrofia Muscolare Progressiva (PMA)
Sclerosi Laterale Primaria (SLP)
Paralisi Bulbare Progressiva (PBP)
Sclerosi Laterale Amiotrofica (SLA)

*La **SLA "classica"**, la più comune tra le malattie primitive del motoneurone dell'età adulta, si riferisce a una forma specifica in cui vi sia un uniforme interessamento sia del primo che del secondo motoneurone.*

Epidemiologia

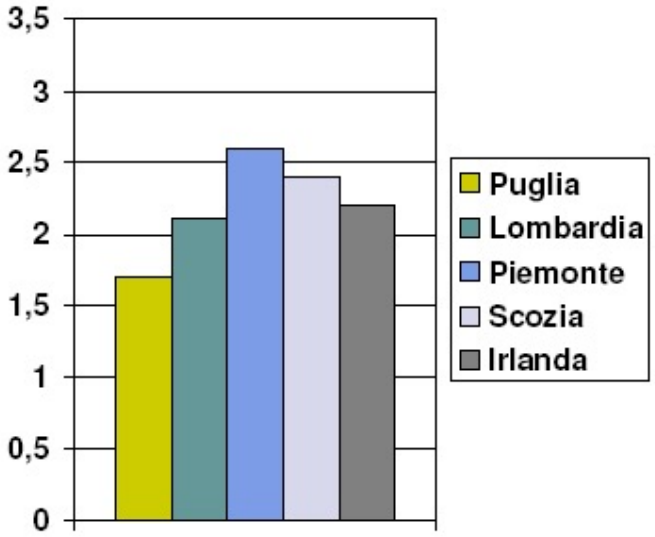
Studi epidemiologici prospettici di popolazione (ottenuti dai registi europei nazionali e regionali utilizzando i critieri diagnostici di El Escorial) hanno evidenizato **TASSI DI INCIDENZA STANDARDIZZATI OMOGENEI** nei paesi occidentali

Incidenza: 1.7-2.5/100.000 per anno
Prevalenza: 4-6/100.000
M>F: 1.3:1 (nelle forme familiari M=F)
Picco di età all'esordio: 58-63 (SALS), 47-52 (FALS)
Rapida riduzione incidenza >80 anni

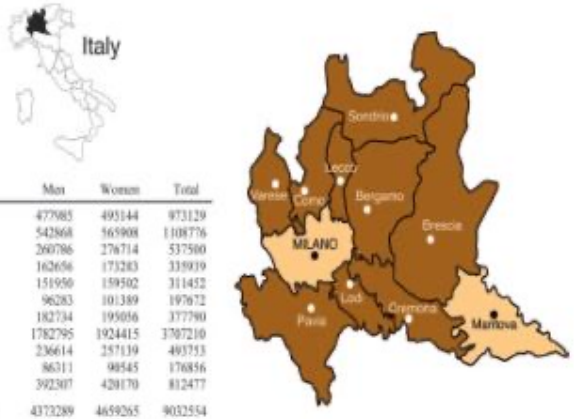
Table 4 Comparison of age-specific and age-adjusted incidence rates to the 1990 U.S. population from selected prospective register studies

Region (ref.)	Years	45–54 y: M/F	55–64 y: M/F	65–74 y: M/F	45–74 y: M/F	45–74 y: M+F	95% CI	M:F: ratio
Scotland[3]	1989	2.8/0.7	7.1/4.6	12.3/6.9	6.7/3.8	5.2	4.1–6.4	1.8
Ireland[4]	1995–1997	NA	NA	NA	6.7/5.3	6.0	5.1–6.9	1.3
Piemonte[5]	1995–1996	2.1/1.6	7.5-4.7	10.4/8.6	6.1/4.7	5.4	4.6–6.3	1.3
Puglia[6]	1998–1999	2.2/1.5	5.4/2.3	10.6/5.2	5.5/2.9	4.1	2.6–5.7	1.7
Lombardy	1998–2002	2.7/1.1	6.2/3.5	7.2/6.4	5.1/3.5	4.2	3.4–5.1	1.3

NA = not available.



Epidemiologia: SLA in Lombardia



Province	Men	Women	Total
Bergamo	477985	495144	973129
Brescia	542868	565908	1108776
Como	260786	276714	537500
Cremona	162656	173283	335939
Lecco	151950	159502	311452
Lodi	96283	101389	197672
Mantova	182734	195056	377790
Milano	1782795	1924415	3707210
Pavia	236614	257139	493753
Sondrio	86311	90545	176856
Varese	392307	420170	812477
Lombardy	4373289	4659265	9032554
Study area	2407760	2539794	4947554

HIGH LIGHT

Incidence of ALS in Lombardy, Italy

E. Beghi, MD; A. Millul, MD; A. Micheli, MD; E. Vitelli, MD; and G. Logroscino, MD, PhD; for the SLALOM Group*

Abstract—*Objective:* To assess the incidence and trends of ALS in a large population at risk. *Methods:* This study was performed in nine provinces of Lombardy in Northern Italy (population 4,947,554). Patients with newly diagnosed ALS were enrolled during the period 1998 to 2002 through a prospective regional register. For each patient, the main demographic and clinical information was collected by the caring physicians and reviewed by a panel of experts according to the original and revised El Escorial diagnostic criteria. Overall, age- and sex-specific and standardized annual incidence rates were calculated for the entire population and for each year and province separately. *Results:* We studied 517 patients (M:F ratio 1.3) aged 18 to 92 years (mean 63.6). Onset of symptoms was bulbar in 29% of cases. ALS was definite in 45%, probable in 27%, probable laboratory supported in 3.5%, possible in 15%, and suspected in 10%. Mean disease duration at diagnosis was 10.6 months. The standardized incidence rate was 2.09 per 100,000/year (95% CI: 1.17 to 3.18). The rate, which was 2.43 in men and 1.76 in women, tended to increase up to ages 65 to 74 and to decrease thereafter. The rate was unchanged over time and presented moderate variations across provinces. The incidence rate of definite ALS was 0.93 (spinal-onset ALS 1.35; bulbar-onset ALS 0.74) and was consistently higher in men with spinal-onset ALS vs men with bulbar-onset ALS and women. *Conclusions:* The incidence of ALS varied according to age, sex, and site of onset. No temporal and geographic clusters were detected over a 5-year period.

NEUROLOGY 2007;68:141–145

Incidenza annua: 2.09/100.000

M (2.43)/F (1.76): 1.3/1

Aumento sino a 65-74 aa

Rapido decremento >75 aa

Esordio: spinale 1.35, bulbare 0.74

Table 2 Age-specific incidence rates of ALS by sex

	Men			Women			Total		
Age group, y	No. of cases	Rate per 100,000/y	95% CI	No. of cases	Rate per 100,000/y	95% CI	No. of cases	Rate per 100,000/y	95% CI
<45	32	0.5	−0.2 to 1.9	13	0.2	−0.3 to 1.9	45	0.3	−0.4 to 1.5
45–54	46	2.7	2.0–4.0	20	1.1	0.5–2.7	66	1.9	1.1–3.2
55–64	94	6.2	5.4–7.4	53	3.5	2.7–4.8	147	4.8	4.0–6.0
65–74	78	7.2	6.4–8.5	91	6.4	5.6–7.6	169	6.8	5.9–7.9
75+	43	6.7	6.0–8.1	47	3.8	3.0–5.1	90	4.7	3.9–5.9
Total	293	2.43	1.54–3.55	224	1.76	0.89–2.91	517	2.09	1.17–3.18

Table 3 Crude incidence rates of ALS by main demographic and clinical variables

Variable	No. of cases	Rate per 100,000/y	95% CI
Year of diagnosis			
1998	98	1.98	1.16–3.20
1999	96	1.94	1.12–3.16
2000	96	1.94	1.12–3.16
2001	118	2.39	1.55–3.58
2002	109	2.20	1.39–3.42
Province of residence			
Bergamo	83	1.71	0.91–2.95
Brescia	105	1.89	1.08–3.11
Como	77	2.87	2.07–4.11
Cremona	35	2.08	1.39–3.47
Lecco	21	1.35	0.73–2.88
Lodi	31	3.14	2.46–4.38
Pavia	49	1.98	1.24–3.30
Sondrio	20	2.26	1.65–3.80
Varese	96	2.36	1.55–3.58
Site of onset			
Bulbar*	182	0.74	−0.12 to 1.90
Spinal	335	1.35	0.45–2.46
El Escorial category			
Definite	231	0.93	0.05–2.07
Probable laboratory supported	18	0.07	−0.52 to 1.65
Probable	138	0.56	−0.29 to 1.74
Possible	79	0.32	−0.48 to 1.57
Suspected	51	0.21	−0.54 to 1.53

* Includes 33 cases with generalized (bulbar and spinal) onset.

Valutando separatamente
sesso e sito di esordio

↓

Incidenza > M con esordio spinale
rispetto alle altre categorie

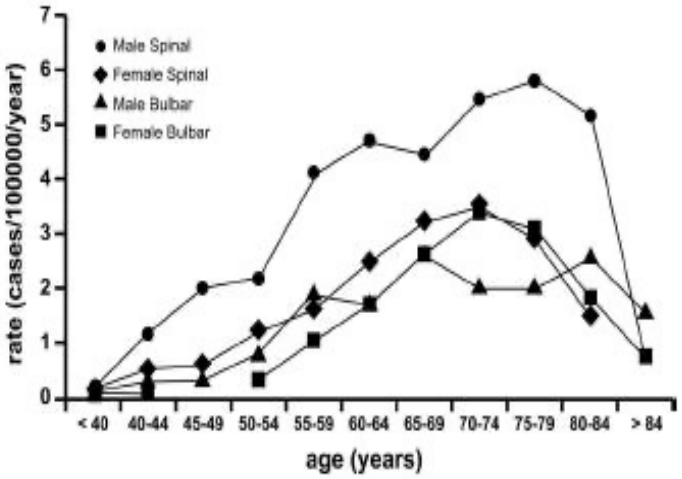


Figure 2. Crude incidence rate by sex, site of onset, and age.

CONCLUSIONI

Incidenza della SLA

↓

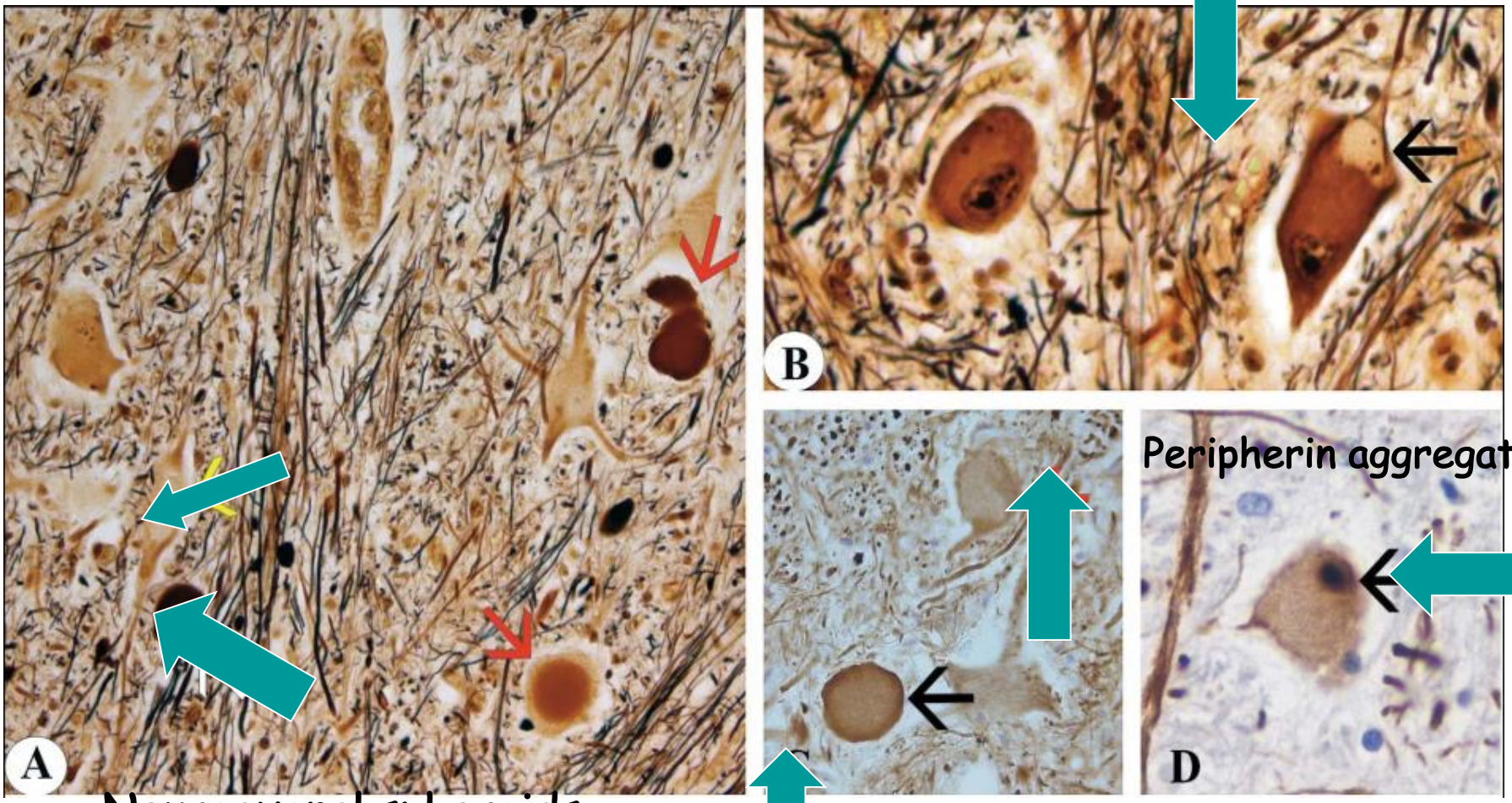
Età/sesso correlata
Variabile con il sito d'esordio
Nessun cluster temporale e geografico

Neuropatologia

- Rarefazione e degenerazione dei motoneuroni delle corna anteriori e/o dei nuclei motori del tronco encefalico con astrocitosi e atrofia dei nervi motori.
- Degenerazione del tratto piramidale associata a gliosi astrocitaria e istiocitosi.
- In alcuni casi atrofia della circonvoluzione precentrale
- Corpi di Bunina e altre inclusioni citoplasmatiche di materiale proteico di probabile origine lisosomiale e/o reticolo endoplasmatico.

Hyalinized intracellular conglomerates

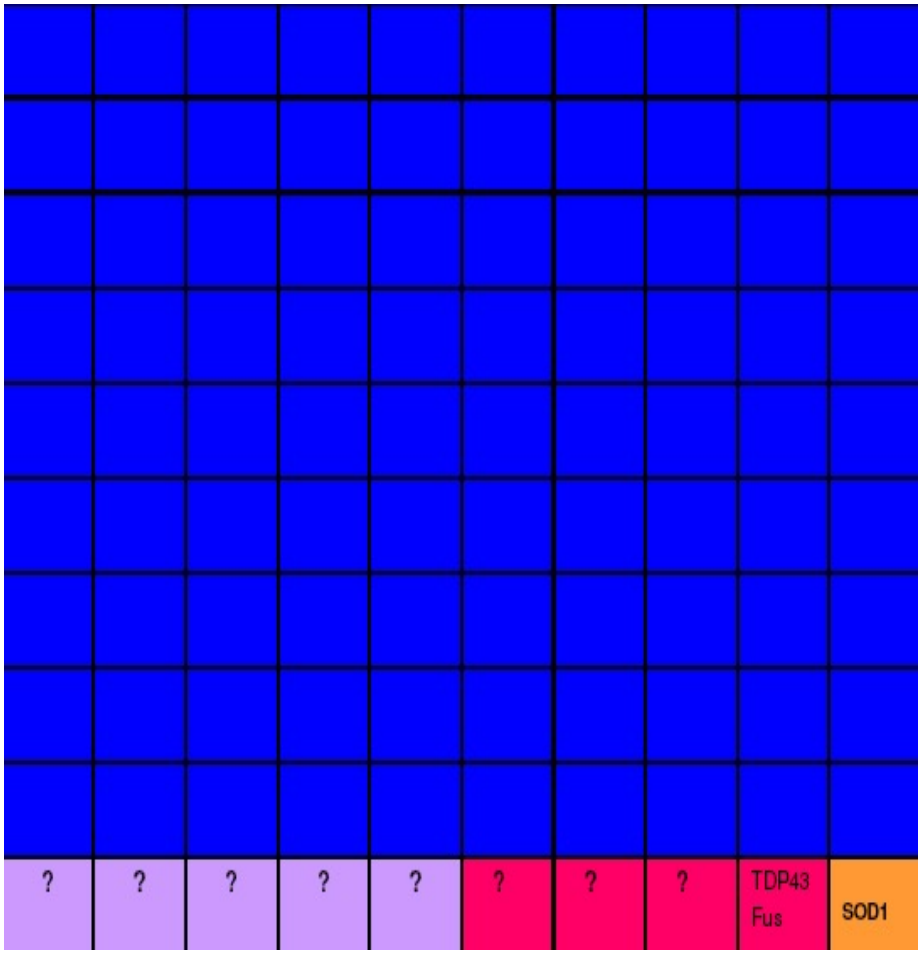
Bunina bodies



Peripherin aggregates

Neuroaxonal spheroids

Neurofilament aggregates



SLA Sporadica (SALS) 90-95%

SLA apparentemente sporadica 5%
- Anamnesi familiare incompleta
- Pedigree troppo piccolo
- Giovane età d'esordio
- Fase preclinica
- Bassa penteranza genetica
- Nuove mutazioni

SLA familiare (FALS) 5-10%

SLA familiari a trasmissione mendeliana

Nomenclatura	Frequenza dei casi	Ereditarietà	Nome della malattia	Gene	Locus	Proteina
ALS1	20%	AD/AR	SOD-FALS	SOD1	21q22.1	Cu-Zn Superossido dismutasi
ALS2	Rara	AR	ALS giovanile tipo 3	ALS2	2q33	Alsina
ALS3	Singola famiglia	AD	FALS	-	18q21	Sconosciuta
ALS4	Rara	AD	Neuropatia ereditaria distale con segni piramidali	SETX	9q34	Senatassina
ALS5	Rara	AR	ALS giovanile	SPG11	15q15.1-q21.1	Spatacsina

SLA familiari a trasmissione mendeliana

Nomenclatura	Frequenza dei casi	Ereditarietà	Nome della malattia	Gene	Locus	Proteina
ALS6	4%	AD/AR	FALS	FUS/TLS	16q12	FUS/TLS
ALS7	Singola famiglia	AD	FALS	-	20tel	Sconosciuta
ALS8	Rara	AD	SMAIV, SMA tipo Finkel (prossimale)	VAPB	20q13	VAPB
ALS9	Rara	AD?	FALS	ANG	14q11.2	Angiogenina
ALS10	8%	AD	FALS	TDP-43	1p36	TAR DNA-binding protein
ALS11	Rara	AR?	FALS	OPTN	10	Optineurina

SLA sporadiche: fattori genetici

STUDI DI AGGREGAZIONE FAMILIARE

Nelle SLA sporadiche sovrapposizione tra la SLA
e altre patologie neurodegenerative (es. FTD, Parkinson)
suggerendo l'esistenza di **GENI DI SUSCETTIBILITA'**
che aumentano il rischio di neurodegenerazione nei familiari

STUDI DI ASSOCIAZIONE SU SCALA GENOMICA

Genome-wide association study (GWAS) e collaborazioni tra gruppi di ricerca internazionali hanno permesso di identificare due loci di suscettibilità per le forme sporadiche di SLA

Genome-wide association study ientifies 19p13.3 (UNC13A)
and 9p21.2 as susceptibility loci for sporadic amyotrophic lateral sclerosis
Van Es MA et al; Nature Genetics 2009; 41: 1083-87

Due gruppi indipendenti hanno identificato una espansione della sequenza Esanucletidica ripetuta GGGGCC nel gene C9ORF72 sul cromosoma 9p21 quale difettio genetico responsabile di FTD e SLA

Neuron
Article

Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of *C9ORF72* Causes Chromosome 9p-Linked FTD and ALS

Mariely DeJesus-Hernandez,[1,10] Ian R. Mackenzie,[2,10,*] Bradley F. Boeve,[3] Adam L. Boxer,[4] Matt Baker,[1] Nicola J. Rutherford,[1] Alexandra M. Nicholson,[1] NiCole A. Finch,[1] Heather Flynn,[5] Jennifer Adamson,[1] Naomi Kouri,[1] Aleksandra Wojtas,[1] Pheth Sengdy,[6] Ging-Yuek R. Hsiung,[6] Anna Karydas,[4] William W. Seeley,[4] Keith A. Josephs,[3] Giovanni Coppola,[7] Daniel H. Geschwind,[7] Zbigniew K. Wszolek,[8] Howard Feldman,[6,9] David S. Knopman,[3] Ronald C. Petersen,[3] Bruce L. Miller,[4] Dennis W. Dickson,[1] Kevin B. Boylan,[8] Neill R. Graff-Radford,[8] and Rosa Rademakers[1,*]
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DOI 10.1016/j.neuron.2011.09.011

Neuron
Article

A Hexanucleotide Repeat Expansion in *C9ORF72* Is the Cause of Chromosome 9p21-Linked ALS-FTD

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Fattori di rischio

Pochi FATTORI DI RISCHIO supportati da evidenze epidemiologiche

- **Età**
- **Sesso maschile**
- **Fattori genetici (nelle forme familiari)**
- **Cluster geografico (ALS-Parkinsonism-Dementia complex Western Pacific)**

Numerosi FATTORI DI RISCHIO AMBIENTALI proposti

Evidenze disponibili mostrano una debole associazione

Foci endemici di SLA del Pacifico Occidentale

SLA, Guam e pipistrelli

Medical Hypothesis

Cycad neurotoxins, consumption of flying foxes, and ALS-PDC disease in Guam

Paul Alan Cox, PhD, and Oliver W. Sacks, MD

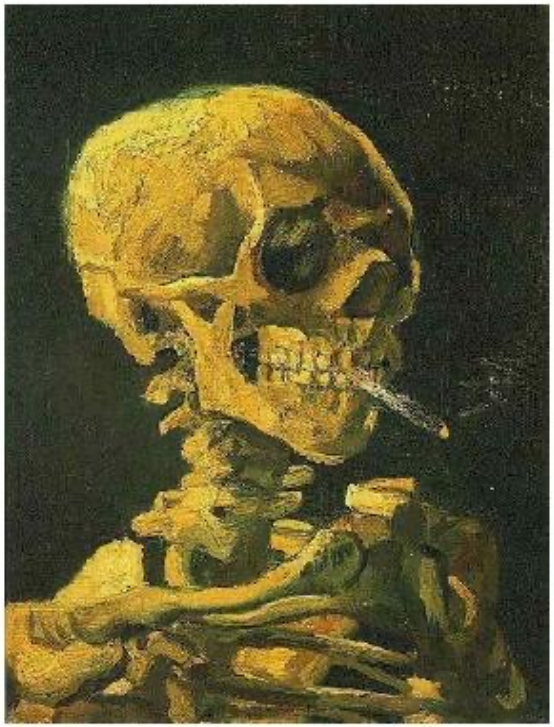
Abstract—The Chamorro people of Guam have been afflicted with a complex of neurodegenerative diseases (now known as ALS-PDC) with similarities to ALS, AD, and PD at a far higher rate than other populations throughout the world. Chamorro consumption of flying foxes may have generated sufficiently high cumulative doses of plant neurotoxins to result in ALS-PDC neuropathologies, since the flying foxes forage on neurotoxic cycad seeds.

NEUROLOGY 2002;58:956–959

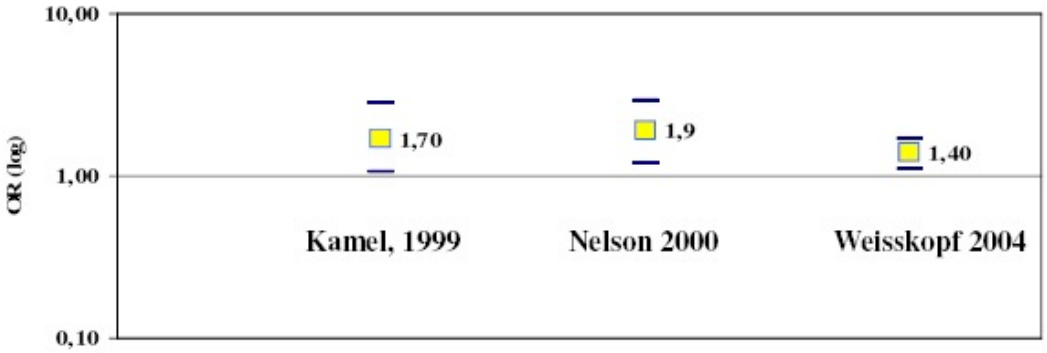
Figure 1. A flying fox of the genus Pteropus *prepared for consumption, at a Chamorro feast in Guam. After boiling in coconut milk, the animal is consumed in its entirety. Photograph by Merlin Tuttle, Bat Conservation International.*

Fumo di sigaretta

- Tre studi caso controllo hanno indicato che il fumo di sigaretta è un fattore di rischio significativo per la SLA



Vincent van Gogh, *Teschio con sigaretta accesa*, 1885



Physical activity and the association with sporadic ALS

J.H. Veldink, MD; S. Kalmijn, MD, PhD; G.J. Groeneveld, MD; M.J. Titulaer, MD; J.H.J. Wokke, MD, PhD; and L.H. van den Berg, MD, PhD

Abstract—*Objective:* To assess whether lifetime physical activity during work and leisure time is associated with an increased risk of developing ALS and to determine the association between physical activity and duration or age at onset of disease. *Methods:* Patients referred to our clinic during the 1-year period 2001 to 2002 who had definite, probable, or possible ALS according to El Escorial criteria, without a familial history of ALS, were asked to participate in the study. A case-control study was performed taking into account all occupational and leisure time activities of patients (n = 219) and controls (n = 254). Multivariate analysis included confounding factors (sex, age, level of education, body mass index, alcohol use, and smoking). Three quantitative measures of cumulative physical activity were calculated: until 1 year before the onset of disease (total physical activity), the last 10 years before the onset of disease (late physical activity), and until the age of 25 (early physical activity). In addition, a systematic review of all published data is presented. *Results:* Smoking and alcohol use were independently associated with ALS (current smoking increased risk, OR = 1.8, 95% CI = 1.0 to 3.0, $p = 0.03$, ever/current alcohol use decreased risk, OR = 0.6, 95% CI = 0.3 to 0.9, $p = 0.04$). No significant association with occupational or leisure time physical activity was found (all ORs ≤ 1.7), which was in agreement with most studies with the highest level of evidence in the systematic review. Higher leisure time activities were associated with an earlier age at onset: activity levels before age of 25 ($p < 0.001$, 7 years earlier), and activity during the last 10 years ($p < 0.001$, 3 years earlier). *Conclusions:* There is no association between physical activity and the risk of developing ALS.

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Rischio di SLA fra i calciatori professionisti

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Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players

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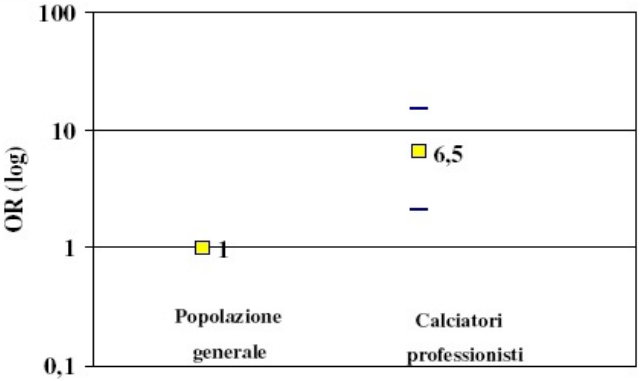


Reflection & Reaction

The sinister side of Italian soccer

Although conclusive scientific evidence of a link between amyotrophic lateral sclerosis (ALS) and soccer is lacking, new cases of the disease in soccer players are reported every month in Italian newspapers. The most high-profile fatality was that of Gianluca Signorini, a defender for Parma, Rome, and Genoa, who died in November 2002.

Aside from the sensationalism of the mass media, the Turin magistrate Raffaele Guariniello opened an inquiry in 1999 to investigate the high incidence of ALS and other diseases—such as liver tumours and leukaemia—in retired soccer players who played for top Italian clubs. Of 24 000 Italian soccer professionals who played between 1960 and 1997, eight have died from ALS. The number of cases expected in this number of people in the general population is 0·61, which indicates a ten-fold increase in risk in soccer players. The details of any current cases of ALS, diagnosed since 1997, are protected under pretrial investigation secrecy but, according to the newspapers, the number of players who have died or are affected by ALS is now more than 30. The other peculiarity of ALS in Italian soccer players is that age at disease onset is in the 40s or even earlier, whereas symptoms would typically appear in the mid 60s.

While we wait for the results of epidemiological studies in Italy, which have prompted similar studies in other European countries, it is scientifically and ethically important to speculate on the reasons for this unexpected disease risk. The potential link between ALS and soccer might offer new perspectives on the cause of this disease. The elucidation of the underlying mechanisms and cause of ALS is of overwhelming importance for finding new effective treatments.

To date, the risk factors for ALS that are supported by epidemiological observations are age, family history, male sex, and geographical clustering in the western Pacific.[1] Many environmental risk factors have also been proposed, such as exposure to metals and agricultural chemicals, rural residence, trauma, and strenuous physical activity,[2] although the available evidence is weak. Trauma and strenuous physical activity, in addition to a putative role of drug abuse that has not yet been thoroughly investigated, are suspected as possible causes of ALS in soccer professionals.

Why should soccer players be more prone to ALS? Previous studies have reported that reactive oxygen species (ROS) are generated during exercise, although most evidence for this is indirect.[3] In soccer players, an increased production of ROS may result from the combination of strenuous exercise with other factors. For example, dietary habits (eg, intake of oxidants, antioxidants, and other dietary supplements), use of drugs (many of which are pro-oxidant), and ischaemia followed by reperfusion (either due to microtraumas or to prolonged anaerobic activity followed by sudden reoxygenation) could be additional sources of oxidative stress.

The available evidence indicates that oxidative injury is one of many causative factors in several neurodegenerative diseases, including ALS. The CNS is particularly sensitive to oxidative stress for two reasons: high content of easily oxidised substrates and an inherently high production of ROS during high respiratory activity and during neurochemical reactions such as dopamine oxidation. Furthermore, metal ions, which facilitate the production of ROS, accumulate in the CNS. Oxidative stress can have detrimental effects via several interacting mechanisms, such as direct damage to crucial molecular species, increase in intracellular free calcium ions, and release of excitatory amino acids. In light of this, neuronal loss in patients with ALS might result from a complex interplay of excitotoxic stimulation, genetic factors, and dysfunction of crucial proteins and organelles (eg, mitochondria), all of which may result from oxidative stress.[4]

In ALS, the neurotoxic effect of increased ROS production seems not to be simply mediated by damage to neurons but may also involve altered function of non-neural cells. "Non-cell autonomous" death of neurons is induced by the pro-oxidant activity of a mutant form of copper/zinc superoxide dismutase (SOD) 1 in patients with familial ALS, which supports a crucial role of glia in the pathogenesis of ALS.[5,6] Several findings indicate that neuroinflammatory processes mediate ALS pathogenesis and markers of neuroinflammation, such as concentrations of cyclooxygenase-2 and prostaglandin E2, are substantially increased in ALS.[7,8] If activated glial cells participate directly in the death of motor neurons in ALS, chronic use of anti-inflammatory drugs should prevent this damage in soccer players as well as in other professional sportspeople. However, the misuse of anti-inflammatory drugs could lead to chronic inhibition of glial activation. The loss of such a physiological defence strategy may eventually contribute to pathogenetic cascades of events. Induction of protective metabolic pathways (eg, induction of molecules involved in the antioxidant defence, such as redox-sensitive transcription factors) may lead to activation of "suicide" events such as apoptosis. Indeed, evidence of the occurrence of

Putting the boot in: soccer linked to ALS?

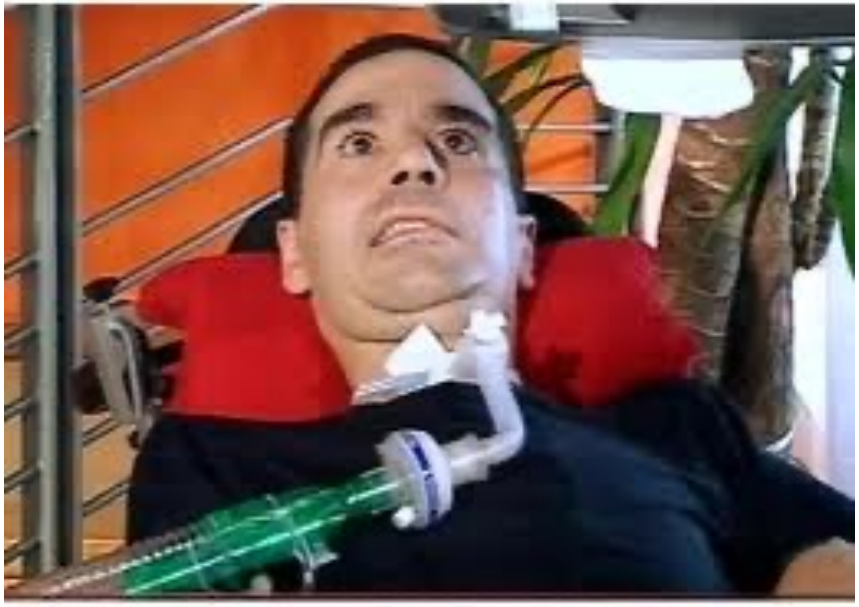
apoptotic death of neurons in ALS is accumulating,[9] but the association between inflammatory response,

SLA e attività sportiva: il calcio

Of 24 000 Italian soccer professionals who played between 1960 and 1997, eight have died from ALS.

The number of cases expected in this number of people in the general population is 0.61, which indicates a ten-fold increase in risk in soccer players. “

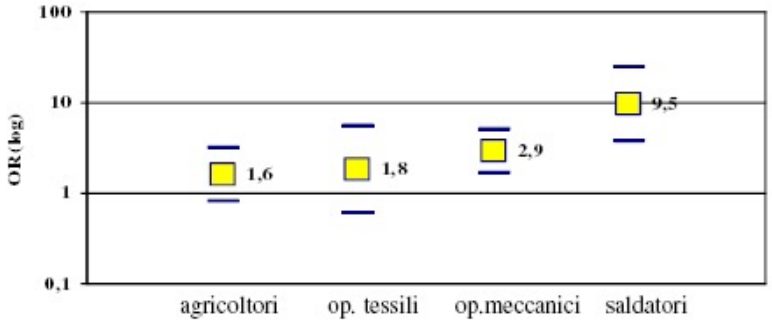
TUTTI PER STEFANO BORGONOVO



Le attività professionali

SLA e metalli: i saldatori

- In un confronto fra 220 casi e 220 controlli appaiati per sesso o ed età, con valutazione dell'attività professionale nel corso dell'intera vita, è stato osservato un significativo eccesso di saldatori, che sono a contatto con vari metalli, soprattutto manganese.



Herrero-Hernandez, comunicazione personale.

Le attività professionali

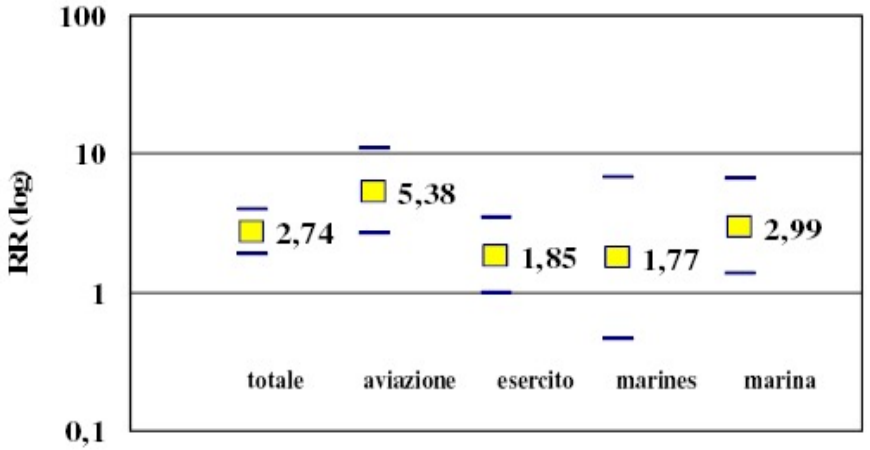
SLA e agricoltura

- Una correlazione fra SLA e agricoltura è stata identificata in vari studi caso-controllo (ad esempio lo studio di popolazione dello Stato di Washington) (McGuire et al., *Am J Epid* 1997).

- In questo studio il rischio di SLA è risultato significativamente correlato all'uso di pesticidi organofosforici e organoclorati e di erbicidi (OR 2,0, i.c. 95% 1,1-3,5) e a un'esposizione fra i 15 e i 30 anni, ma solo fra i maschi.

I reduci della Guerra del Golfo

- Studio di confronto fra 700.000 veterani del Golfo e 1.800.000 militari non impiegati nel Golfo, con un follow-up di 10 anni



Horner et al, *Neurology* 2003

Clinica

CARATTERISTICA CLINICA
principale della SLA è la presenza

Segni di interessamento del **1° motoneurone (UMN)**

Segni di interessamento del **2° motoneurone (LMN)** a livello del tronco encefalico e nelle diverse regioni di innervazione del midollo spinale

Clinica

FENOTIPO VARIABILE

Modalità di presentazione clinica dei sintomi (esordio)
Progressione della disabilità (decorso e prognosi)

Identificazione di “specifici fenotipi”
ha importanti implicazioni circa

⇩

•Prognosi e sopravvivenza
• Arruolamento dei pz.nei diversi trial clinici

Varianti fenotipiche principali

1 SLA classica:
segni di 1° e di 2°MN con coinvolgimento uniforme del tronco encefalico e delle varie regioni midollari

2 Paralisi bulbare progressiva (PBP):
prevalente interessamento della muscolatura bulbare (disartria, disfonia, disfagia) con successivo interessamento della muscolatura degli arti e tronco

3 Sclerosi Laterale Primaria (PLS)
e SLA a prevalente interessamento del 1° MN (interesamento eslcusivo o prevalente del 1° MN)

4 Atrofia Muscolare Progressiva (PMA):
interssamento eslcusivo del 2° MN)

Esordio

MODALITA' DI PRESENTAZIONE CLINICA PRINCIPALI

- **Esordio arti (superiori/inferiori)**: 70%

Forma classica

Flail arm syndrome (MN cervicali)

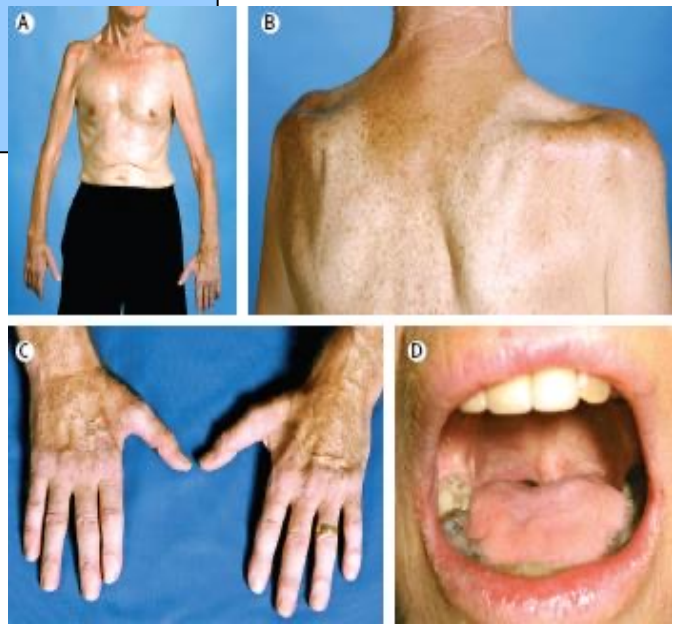
deficit cingolo scapolare

Flail leg syndrome (MN lombosacrali)

deficit muscoli loggia anterolaterale gamba

- **Esordio bulbare:** 25%
- **Esordio al tronco e respiratorio**: 5%

Successiva diffusione con coinvolgimento di altre regioni



MODALITA' DI PRESENTAZIONE CLINICA "ATIPICHE"

- Calo ponderale (scarsa prognosi)
- Crampi e fascicolazioni
- Labilità emotiva
- Deficit cognitivo (tipo frontale)

Caratteristiche cliniche

	ARTI	BULBARE
SEGNI DI 1°MONONEURONE	•Impaccio motorio alle prove di destrezza digitale •Ipostenia muscolare •Spasticità •Ipereflessia OT •Comparsa di riflessi patologici (Babinski; Hoffmann)	Paralisi pseudobulbare •Disartria spastica (eloquio lento, distorto) •Disfagia •"gag reflex" e riflesso masseterino aumentati •Riso e pianto spastici
SEGNI DI 2°MOTONEURONE	•ipostenia muscolare •atrofia muscolare •Iporeflessia OT •diminuzione del tono muscolare •fascicolazioni/crampi muscolari	Paralisi bulbare •Disartria flaccida (rinolalia, ipofonia) •tosse debole •Ipostenia, ipotrofia, fascicolazioni lingua •Difficoltà nella masticazione e disfagia

Funzioni risparmiate

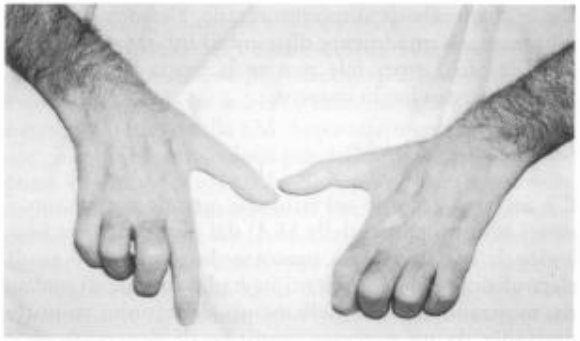
Muscoli dell'oculomozione

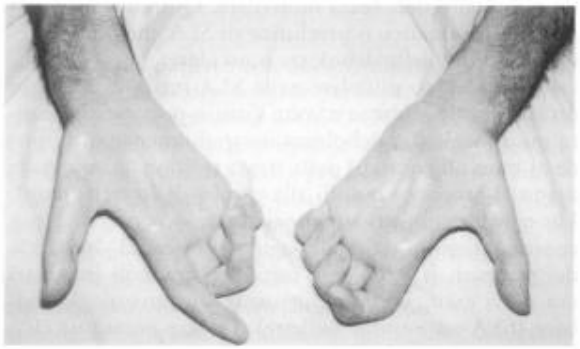
Muscoli che controllano funzioni sfinteriche (nuclei di Onuf)

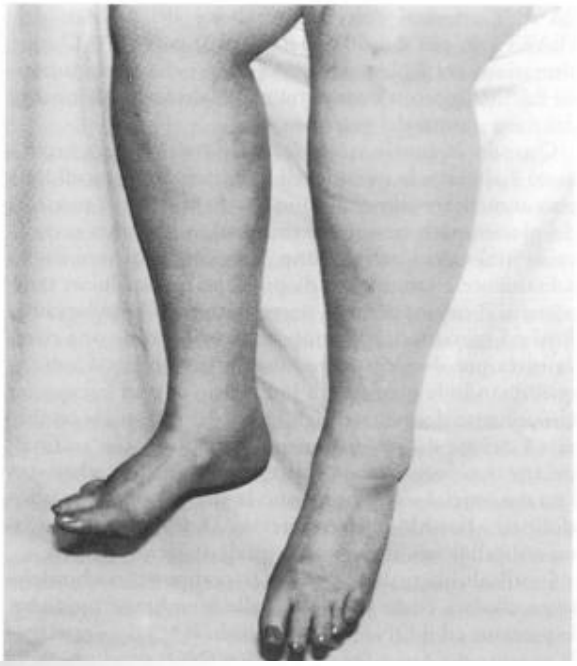
Nella SLA non sono (quasi) mai colpiti

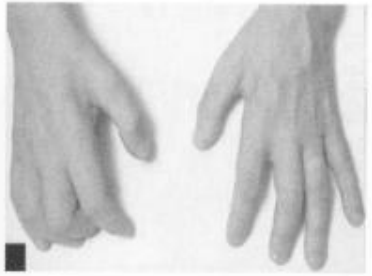
Funzioni sensitive

Quasi **mai dolore** (tranne che crampi e dolori secondari all'immobilità)









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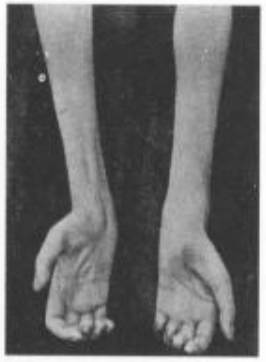
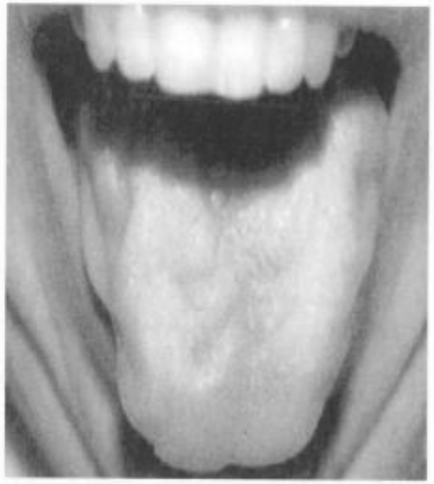


B

C



D

AXIS 1 – Defining the motor neuron disease variant
Diagnostic criteria

ALS and other motor neuron disorders 2000 1, 293–299 ISSN 1466-0822

El Escorial revisited: Revised criteria for the diagnosis of amyotrophic lateral sclerosis

Benjamin Rix Brooks[1], Robert G Miller[2], Michael Swash[3], Theodore L Munsat[4], for the World Federation of Neurology Research Group on Motor Neuron Diseases

Requirements for the diagnosis of ALS

The diagnosis of ALS requires:
(A) the **presence** of:

- (A: 1) evidence of **lower motor neuron (LMN) degeneration** by clinical, electrophysiological or neuropathologic examination,
- (A: 2) evidence of **upper motor neuron (UMN) degeneration** by clinical examination, and
- (A: 3) **progressive spread of symptoms or signs** within a region or to other regions, as determined by history or examination,

together with:
(B) the **absence** of

- (B:1) **electrophysiological or pathological evidence of other disease processes** that might explain the signs of LMN and/or UMN degeneration, and
- (B:2) **neuroimaging evidence of other disease processes** that might explain the observed clinical and electrophysiological signs.

Revised El Escorial research diagnostic criteria for ALS (summary)

Clinically definite ALS

UMN and LMN signs in three regions

Clinically definite ALS – Laboratory supported

UMN and/or LMN signs in one region *and* the patient is a carrier of a pathogenic gene mutation

Clinically probable ALS

UMN and LMN signs in two regions with some UMN signs rostral to the LMN signs

Clinically probable ALS – laboratory supported

UMN signs in one or more regions *and* LMN signs defined by EMG in at least two regions

Clinically possible ALS

UMN and LMN signs in one region, or

UMN signs in at least two regions, or

UMN and LMN signs in two regions with no UMN signs rostral to LMN signs

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Steps in the diagnosis of ALS suggested by WFN guidelines

Steps	Rationale
1. History, physical examination	Ascertain clinical findings that may suggest level of certainty of diagnosis
2. EMG examination	Ascertain findings that confirm LMN degeneration in clinically involved regions; Identify LMN degeneration in clinically uninvolved regions; Exclude other disorders
3. Neuroimaging	Ascertain findings that may exclude other disease processes
4. Clinical laboratory examinations	Ascertain possible ALS-related syndromes.
5. Neuropathologic examinations	Ascertain findings confirming/excluding ALS
6. Repetition of clinical and EMG (6 months apart)	Ascertain evidence of progression

Mitsumoto et al, 1998, 2006

EMG: modified Lambert's criteria for ALS diagnosis

- NERVE CONDUCTION STUDIES
  - normal sensory nerve conduction studies
    - amplitude may be reduced in entrapment sites and with age
  - normal motor nerve conduction studies
    - in the presence of < amplitude of CMAP, conduction velocity may be <
    - exclusion of persistent conduction block along several peripheral nerves
    - no features of diffuse demyelination (CIDP)

- NEEDLE EMG
  - active denervation (fibrillation potentials) and fasciculation potentials in upper, lower limb, and bulbar muscles
  - reinnervation of motor unit potentials (polyphasic, long duration, high amplitude) with reduced recruitment

EMG/ENG

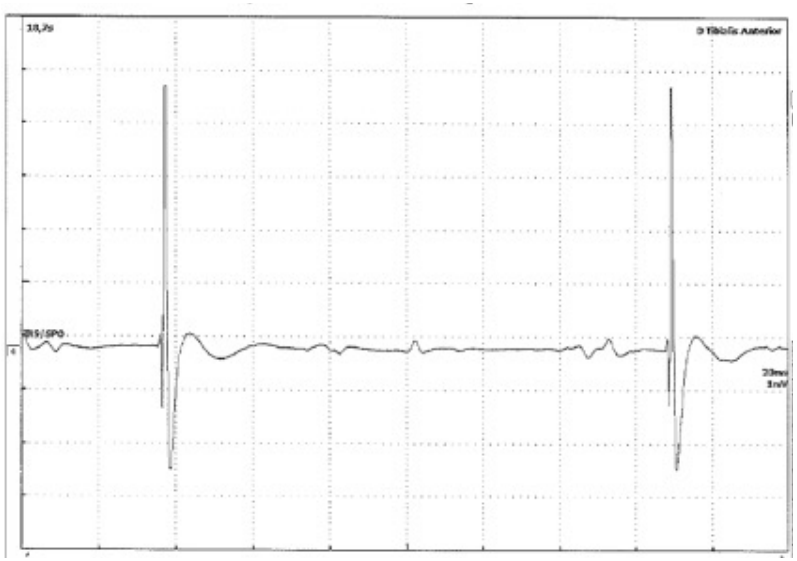
	Lesion / EMG Steps	Normal	Neurogenic Lesion		Myogenic Lesion	
			Lower Motor	Upper Motor	Myopathy	Polymyositis
1	Insertional Activity	Normal	Increased	Normal	Normal	Increased
2	Spontaneous Activity		Fibrillation Positive Wave			Fibrillation Positive Wave
3	Motor Unit Potential	0.5-1.0 mv 5-10 msec.	Large Unit Limited Recruitment	Normal	Small Unit Early Recruitment	Small Unit Early Recruitment
4	Interference Pattern	Full	Reduced Fast Firing Rate	Reduced Slow Firing Rate	Full Low Amplitude	Full Low Amplitude

MUP: motor unit potential

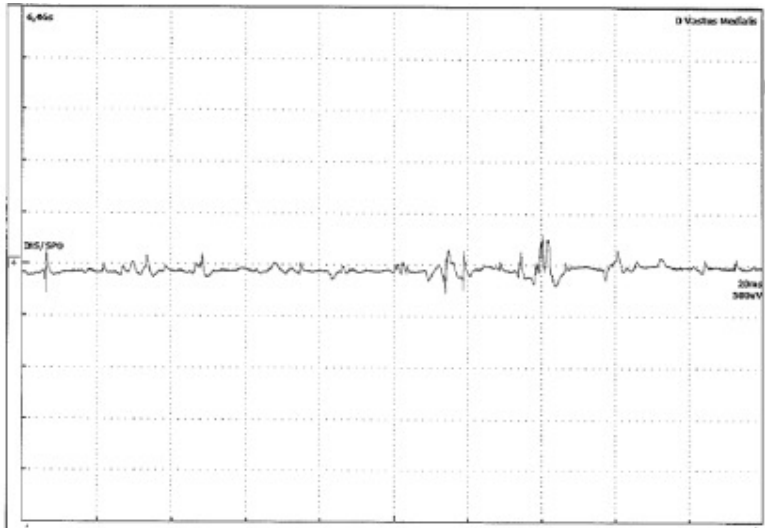
Fibs-sw: fibrillation potentials – positive sharp wave

CMAP: compound muscle action potential

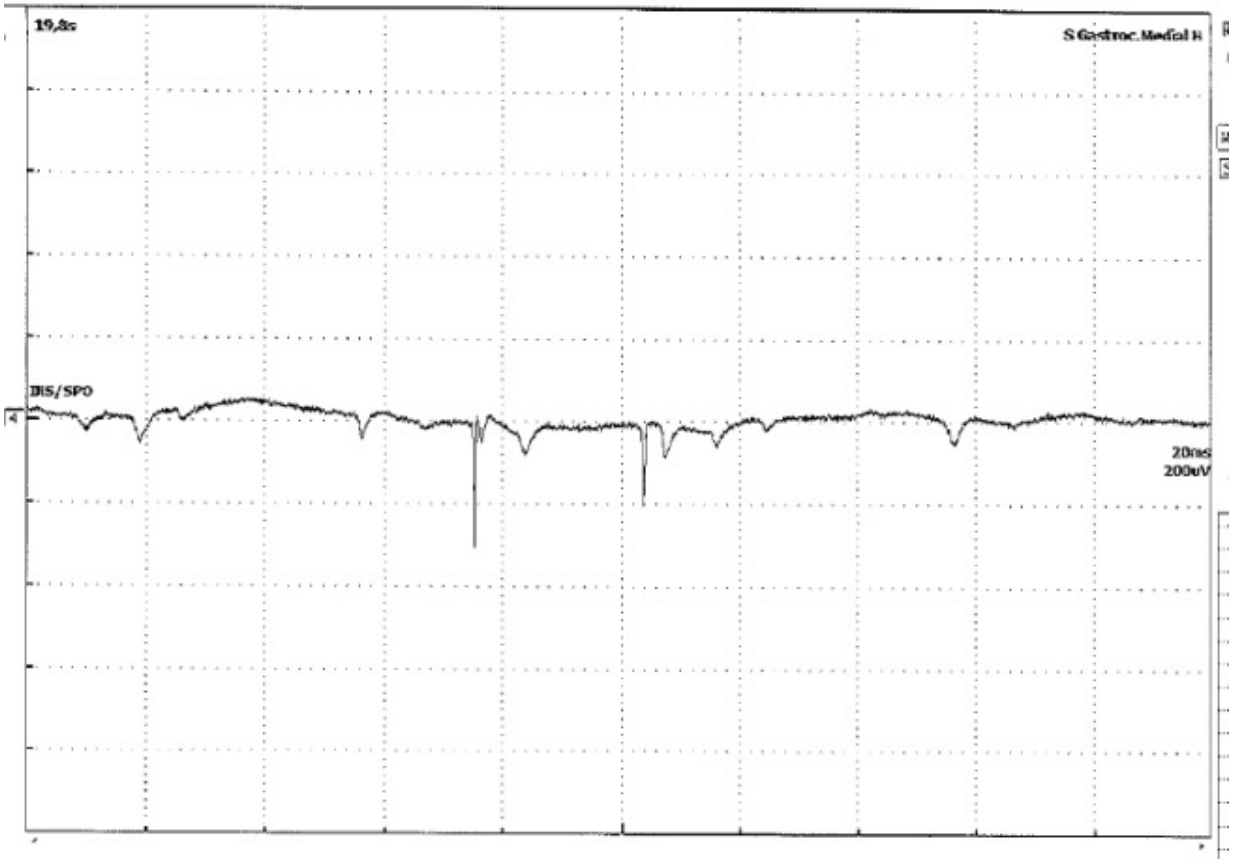
MUP neurogenic



MUP myogenic



“fibs” and ”sw”



EMG

- **A riposo**
  - **Attività spontanea patologica (fibrillazione, onde lente positive, fascicolazioni, scariche ad alta frequenza, scariche miotoniche)**
- **Lieve contrazione**
  - **Morfologia Potenziali di Unità Motoria (PUM): alterazioni quantitative e qualitative**
- **Massima Contrazione**
  - **Reclutamento PUM**

EMG

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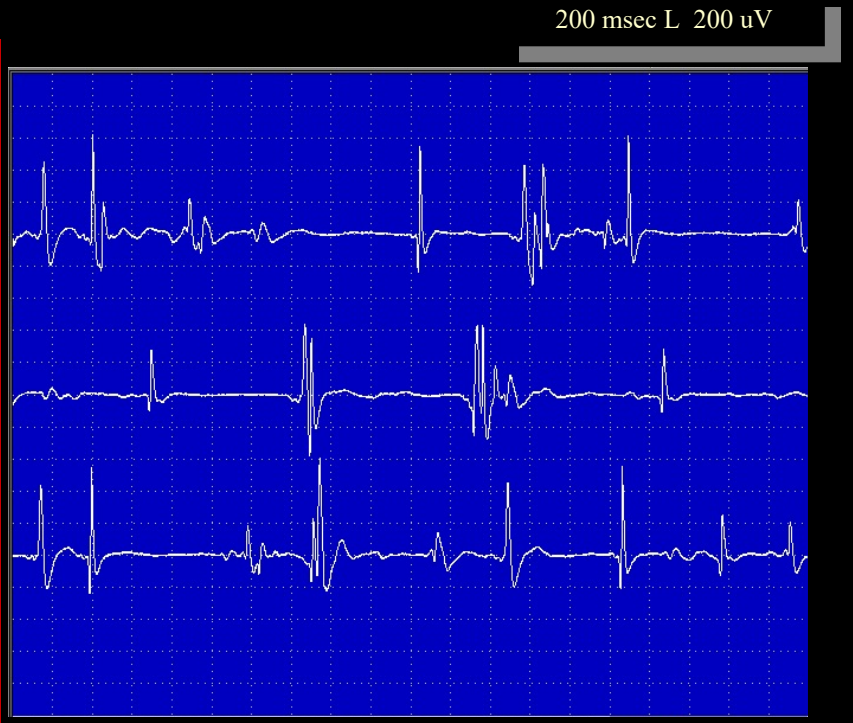

EMG

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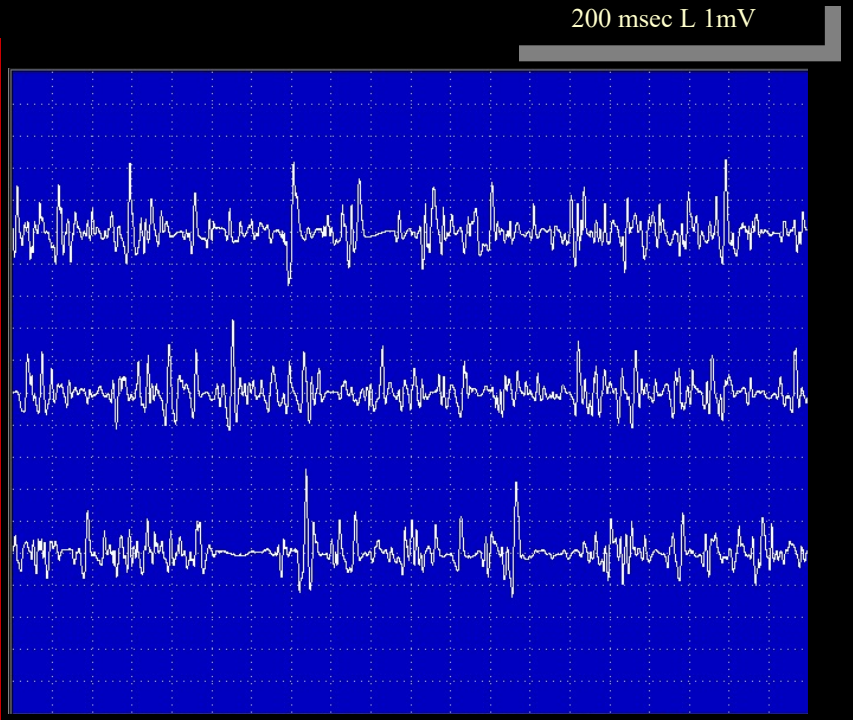
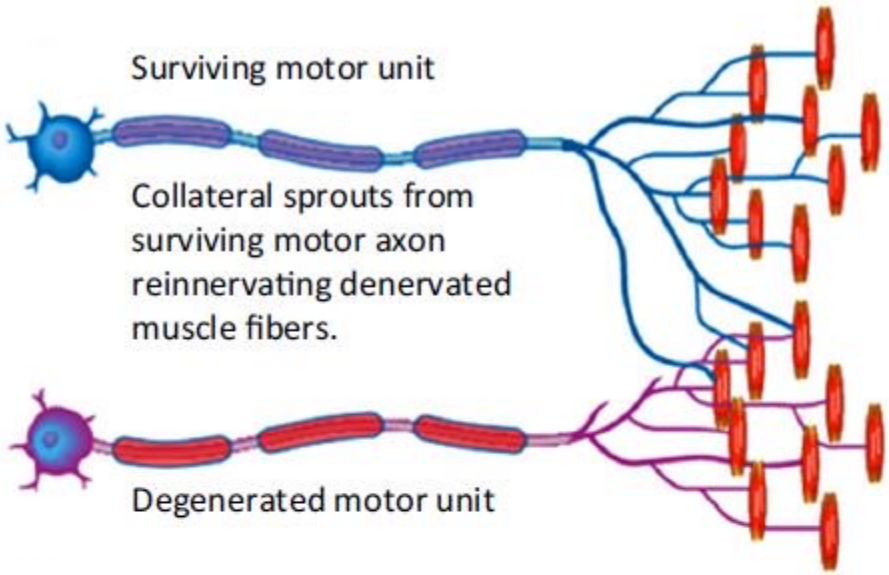
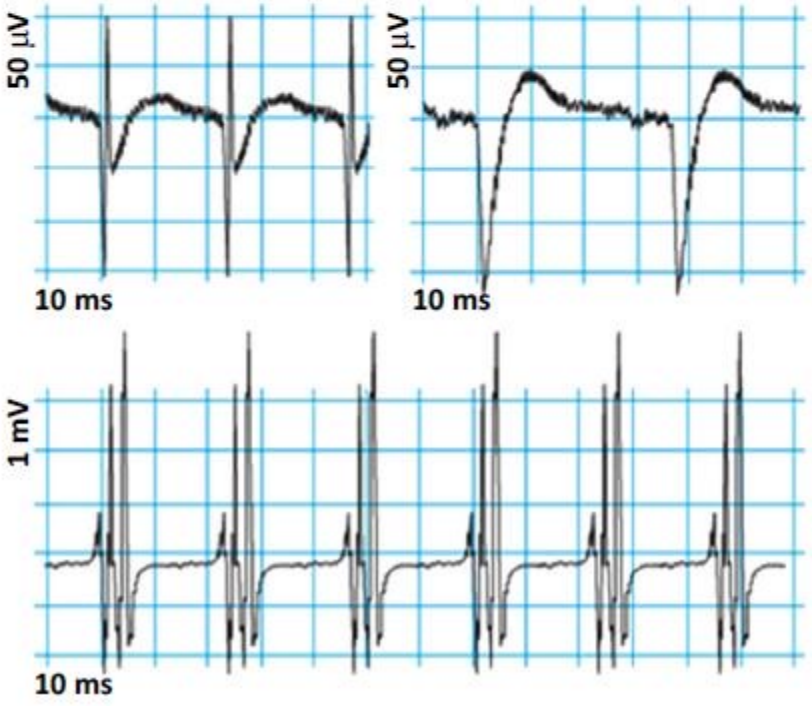


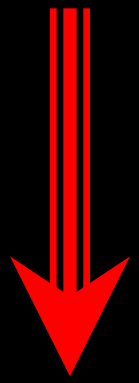




EMG: may extend the clinical findings by revealing the LMN involvement in muscles in the body regions otherwise regarded as unaffected.

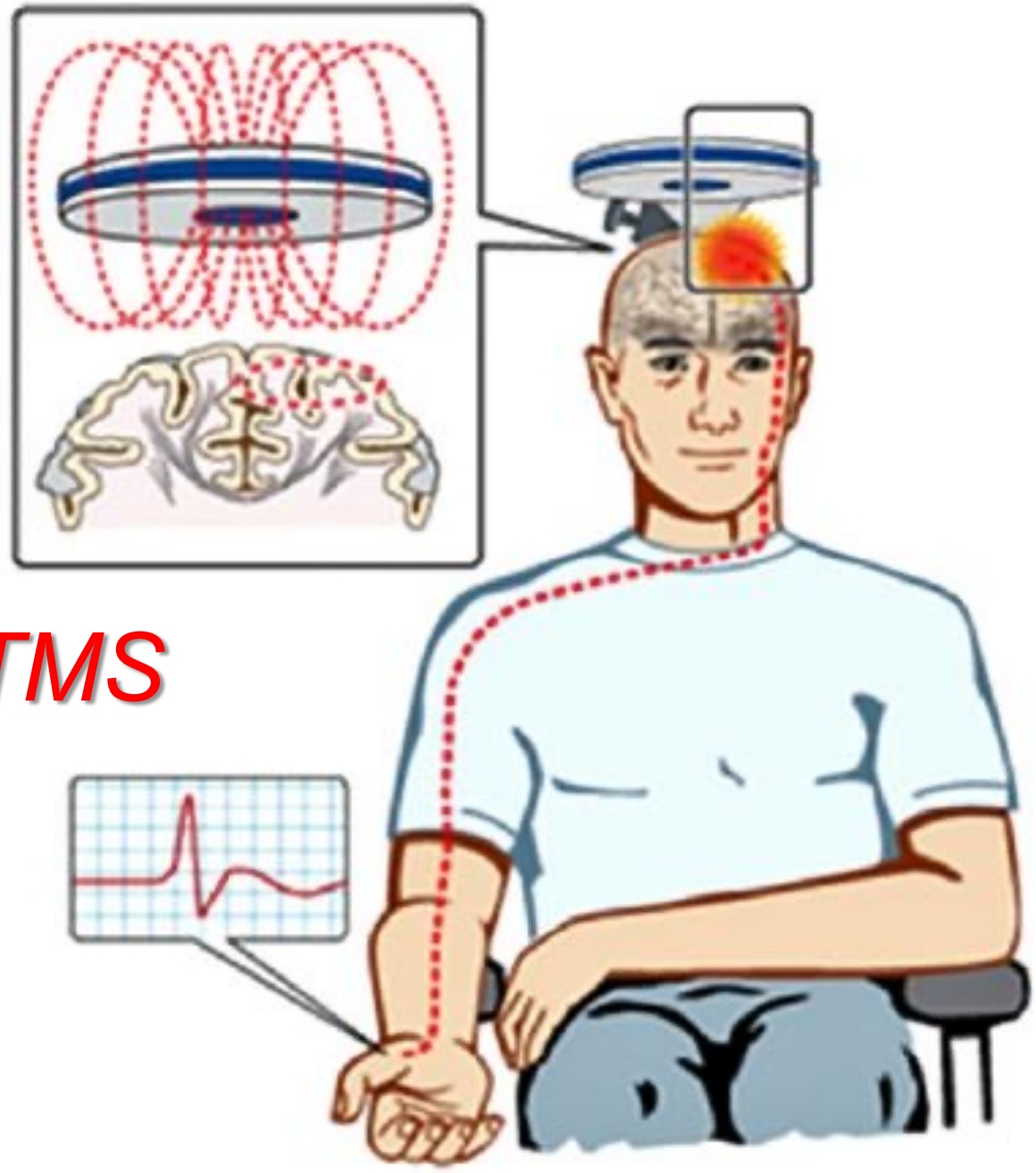
VALUTAZIONE DELLE

ALTERAZIONI DEL UMN



Potenziali Evocati Motori

UMN and TMS



- Stimolatore magnetico -

PEM

- **Nella SLA in fase iniziale**

Ampiezza Motot Evoked Potential (MEP) corticale ridotta

T.C.M.C normale

T.C.M.P. normale o lievementa aumentato

- **Nella SLA in fase avanzata**

Ampiezza MEP corticale ridotta o MEP assente

T.C.M.C aumentato

T.C.M.P. aumentato o MEP radicolare assente

FOLLOW-UP NEUROFISIOLOGICO

EMG/ENG

PEM

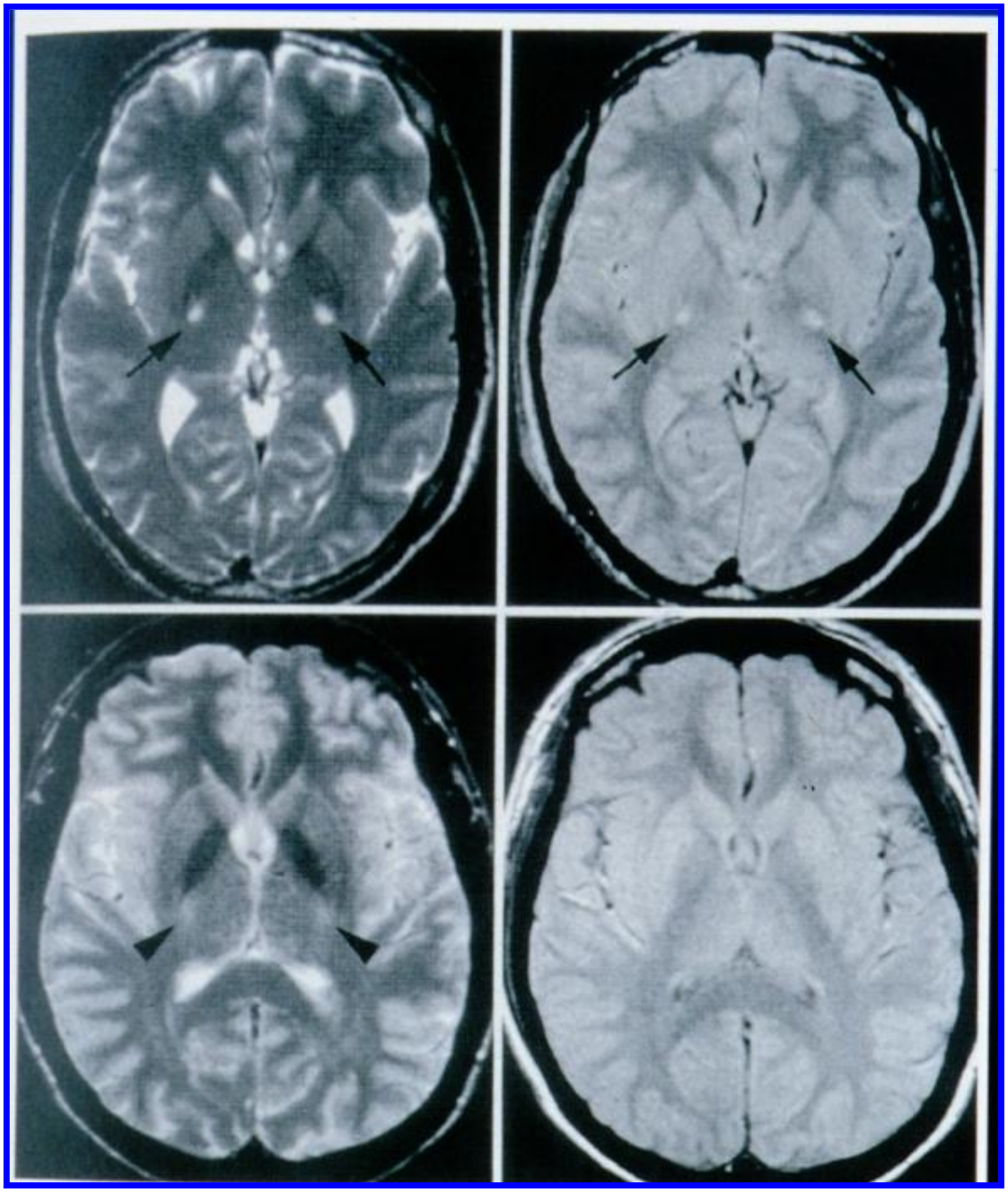
MUNE

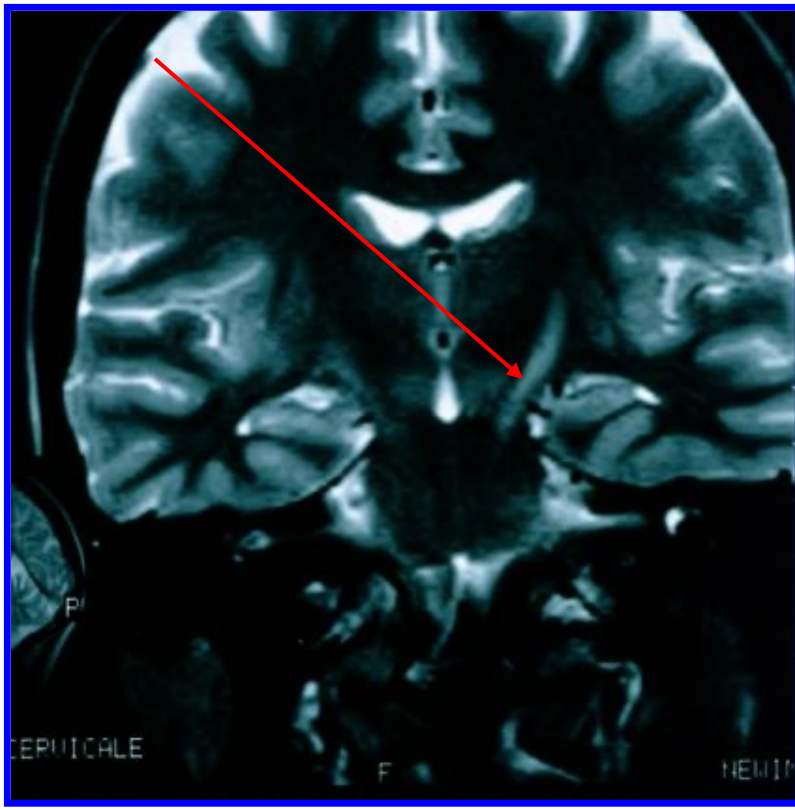
NEUROPHYSIOL. INDEX

Neuroimaging studies in the diagnosis of ALS

MRI

- Brain atrophy (parietal, insular, frontal temporal, corpus callosum).
- Spinal cord atrophy (rarely documented).
- CST hyperintensity in T_2- and proton-density weighted MRI< (usually bilateral and symmetrical, 17 to 100% in studies<).
- Neocortical hypointensity (in T_2, bilateral, in pre- and post-central gyrus, mean 52% reported).

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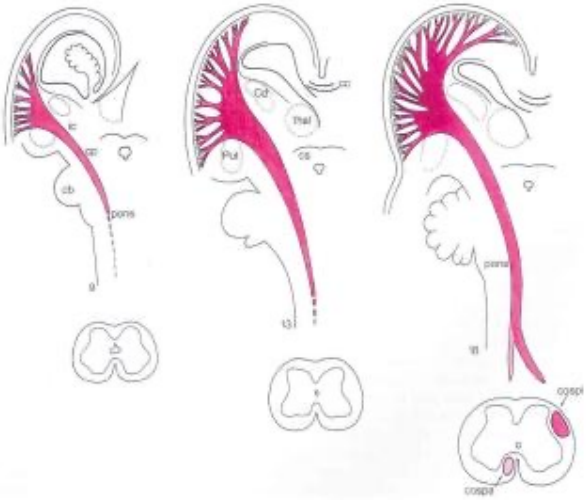
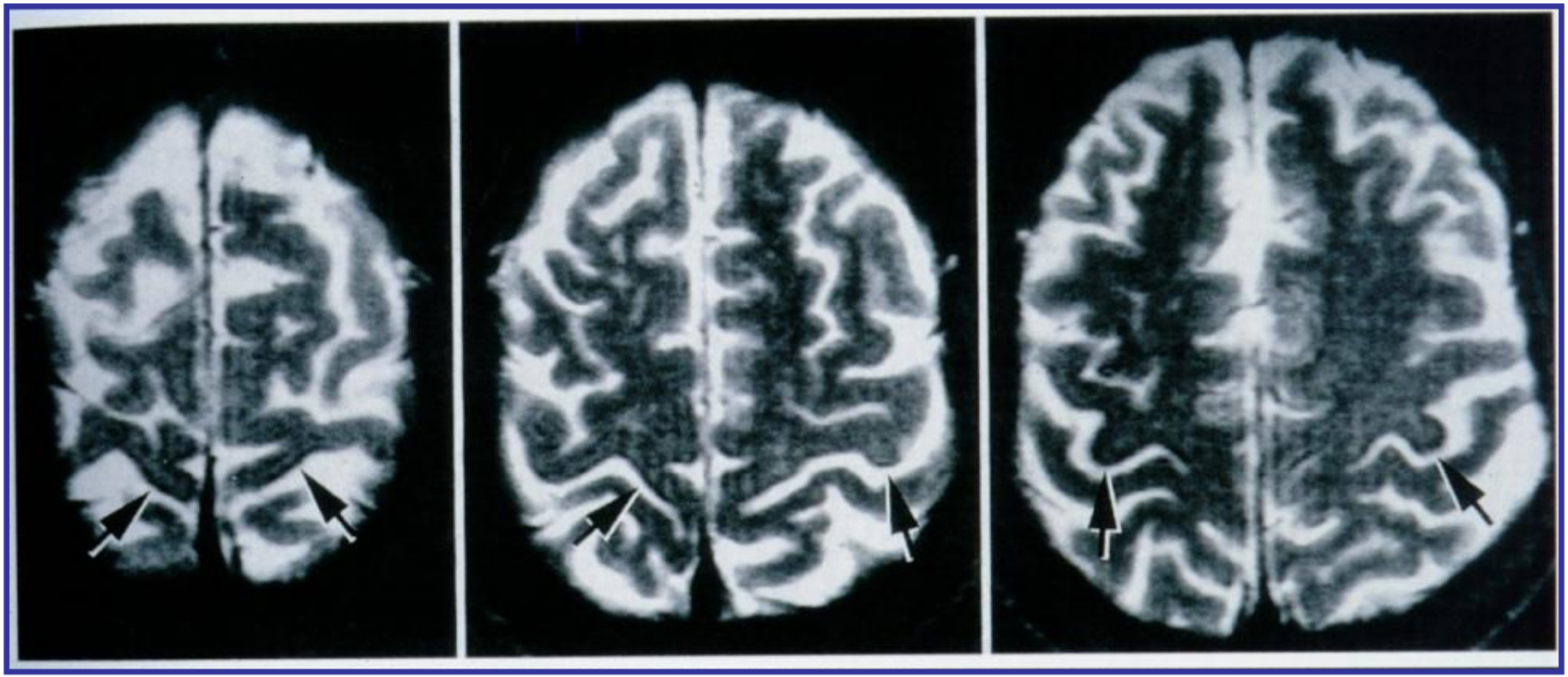
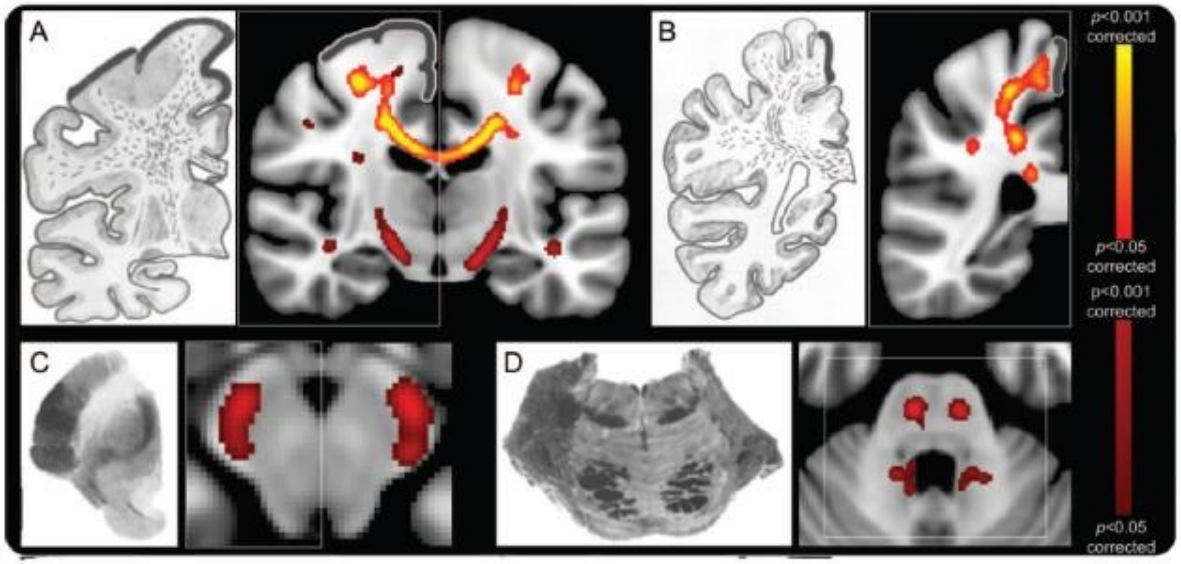




Emerging evidence of systemic diseases

Figure 1 Regional fractional anisotropy (FA) reductions in amyotrophic lateral sclerosis group whole-brain comparison with healthy controls, alongside published postmortem observations



Filippini et al., Neurology, 2010

Neuroimaging: ricerca del “biomarker”

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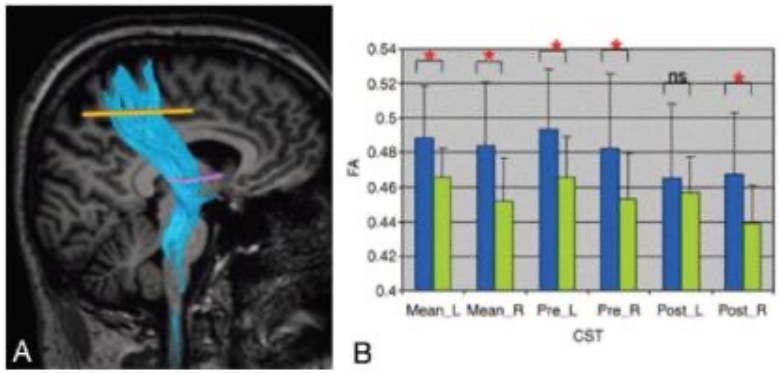
The Present and the Future of Neuroimaging in Amyotrophic Lateral Sclerosis

SUMMARY: In patients with ALS, conventional MR imaging is frequently noninformative, and its use has been restricted to excluding other conditions that can mimic ALS. Conversely, the extensive application of modern MR imaging–based techniques to the study of ALS has undoubtedly improved our understanding of disease pathophysiology and is likely to have a role in the identification of potential biomarkers of disease progression. This review summarizes how new MR imaging technology is changing dramatically our understanding of the factors associated with ALS evolution and highlights the reasons why it should be used more extensively in studies of disease progression, including clinical trials.



AJNR, 2011

Decorso

La malattia **progredisce gradualmente**, con veolocità variabile, coinvolgendo sempre nuovi gruppi muscolari

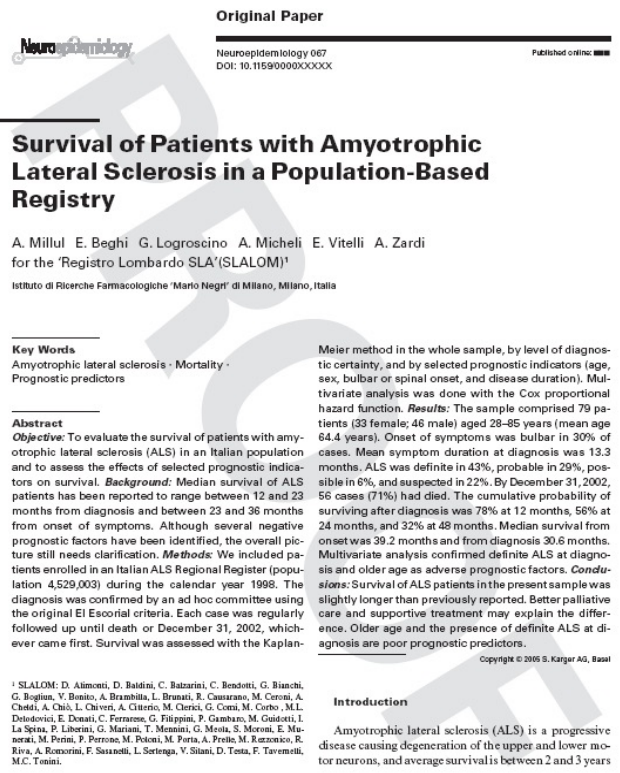
	Fase iniziale-intermedia	Fase avanzata
Muscoli • arti • collo • tronco	• Astenia • Ridotta tolleranza all'esercizio • Affaticabilità	deficit motorio progressivo sino a paralisi completa → ausili → necessità di assitenza nelle ADL
Funzioni bulbari	• Disfagia (malnutrizione, calo ponderale (scarsa prognosi) → addensanti alimentari/PEG • Diasartria/disfonia →comunicatori vocali	• Impossibilità ad alimentarsi per os • Anartria
Funzione respiratoria	• Dispnea sotto sforzo • Ortopnea • Ipoventilazione-ipercapnia • Cefalea mattutina → ventilazione assistita non invasiva (NIV)	• Insufficienza respiratoria (spesso precipitata da polmonite) → tracheotomia, ventilazione assistita • Exitus

Prognosi

Sopravvivenza mediana

- 50% 2-3 anni dall'esordio dei sintomi
  1-2 anni dalla diagnosi
- 20% 5-10 anni dall'esordio dei sintomi

- 5% “long survival” decorso lungo sino a 30 anni



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Survival of Patients with Amyotrophic Lateral Sclerosis in a Population-Based Registry

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Key Words
Amyotrophic lateral sclerosis · Mortality · Prognostic predictors

Abstract
Objective: To evaluate the survival of patients with amyotrophic lateral sclerosis (ALS) in an Italian population and to assess the effects of selected prognostic indicators on survival. ***Background:*** Median survival of ALS patients has been reported to range between 12 and 23 months from diagnosis and between 23 and 36 months from onset of symptoms. Although several negative prognostic factors have been identified, the overall picture still needs clarification. ***Methods:*** We included patients enrolled in an Italian ALS Regional Register (population 4,529,003) during the calendar year 1998. The diagnosis was confirmed by an ad hoc committee using the original El Escorial criteria. Each case was regularly followed up until death or December 31, 2002, whichever came first. Survival was assessed with the Kaplan-Meier method in the whole sample, by level of diagnostic certainty, and by selected prognostic indicators (age, sex, bulbar or spinal onset, and disease duration). Multivariate analysis was done with the Cox proportional hazard function. ***Results:*** The sample comprised 79 patients (33 female; 46 male) aged 28–85 years (mean age 64.4 years). Onset of symptoms was bulbar in 30% of cases. Mean symptom duration at diagnosis was 13.3 months. ALS was definite in 43%, probable in 29%, possible in 6%, and suspected in 22%. By December 31, 2002, 56 cases (71%) had died. The cumulative probability of surviving after diagnosis was 78% at 12 months, 56% at 24 months, and 32% at 48 months. Median survival from onset was 39.2 months and from diagnosis 30.6 months. Multivariate analysis confirmed definite ALS at diagnosis and older age as adverse prognostic factors. ***Conclusions:*** Survival of ALS patients in the present sample was slightly longer than previously reported. Better palliative care and supportive treatment may explain the difference. Older age and the presence of definite ALS at diagnosis are poor prognostic predictors.

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive disease causing degeneration of the upper and lower motor neurons, and average survival is between 2 and 3 years

[1] SLALOM: D. Altimenti, D. Baldini, C. Balzarini, C. Bendotti, G. Bianchi, G. Boglium, V. Benito, A. Brambilla, L. Brunati, R. Causarano, M. Ceroni, A. Chetdi, A. Chiò, L. Chiveri, A. Citterio, M. Clerici, G. Comi, M. Corbo , M.L. Delodovici, E. Donati, C. Ferrarese, G. Filippini, P. Gambaro, M. Guidotti, I. La Spina, P. Liberini, G. Mariani, T. Mennini, G. Meola, S. Moroni, E. Munerati, M. Perini, P. Perrone, M. Poloni, M. Porta, A. Preite, M. Renzonico, R. Riva, A. Romorini, F. Sasanelli, L. Sertenga, V. Sitani, D. Testa, F. Tavernelli, M.C. Tonini.

Registro Lombardo SLALOM
Sopravvivenza mediana

- 39 mesi sall'esordio dei sintomi
- 30 mesi dalla diagnosi

- Età avanzata e “SLA definita” alla diagnosi
  Indicatori prognostici negativi

Prognosi

NEGATIVI

- Età avanzata all'esordio
- Precoce coinvolgimento muscolatura respiratoria
- Esordio bulbare
- PBP (F, > 65 aa, segni 1° MN predominanti)

POSITIVI

- Età più giovane all'esordio
- Esordio spinale
- Ritardo diagnostico
- Flail limb syndrome
- PMA
- PLS

DIAGNOSI

In assenza di "biomarcatori" specifici per la malattia la diagnosi di SLA si basa essenzialmente sull'evidenza clinica:

1 segni di sofferenza del 1° e 2° MN nella stessa regione corporea

2 successiva progressione della malattia in altre regioni corporee

Test diagnostici paraclinici (es. di laboratorio, neurofisiologici, neuropatologici e neuroradiologici) supportano la diagnosi:

3 confermando la presenza di segni di sofferenza del 1° e 2° MN (o evidenziandone segni di interessamento subclinici)

4 escludendo altre cause che possono determinare quadri clinici simil-SLA

El Escorial, Airlie House diagnostic criteria

Consensus conference della "World Federation of Neurology Research Committee on MND (WFN)" hanno identificato dei criteri diagnostici (utilizzabili nella pratica clinica ma soprattutto in ambito di ricerca, in particolare nei trial clinici)

El Escorial criteria e Airlie House revised criteria

Segni di sofferenza del 1° e 2° Motoneurone in 4 regioni corporee

Regione	Specifici gruppi muscolari
•Bulbare	•M. facciale, palato, lingua, laringe, faringe
•Cervicale	•M. cervicale, arti superiori, diaframma
•Toracica	•M. dorsale, addominale
•Lombosacrale	•M. dorsale, arti inferiori

Livello di certezza diagnostica

El Escorial, Airlie House e Awaji diagnostic criteria

El Escorial criteria (1994)	Airlie House criteria revised (1998)	"Awaji Island criteria (2006)
Presenza di tutti i seguenti: • segni di 2° MN (esame clinico, elettrofisiologico o neuropatologico • segni di 1°MN (esame clinico) • progressione dei segni all'interno di una regione o in altre regioni	Presenza di tutti i seguenti: • segni di 2° MN (esame clinico, elettrofisiologico/neuropatologico • segni di 1°MN (esame clinico) • progressione dei segni all'interno di una regione o in altre regioni • + esami di laboratorio	• Evidenze elettrofisiologiche **equivalenti** ai segni clinci nel riconoscimento dei segni di sofferenza del 2° MN • Fascicolazioni **equivalenti** a fibrillazione e PSW nel riconoscere la denervazione in fase attiva in pz. con SLA clinicamente sospetta • Presenza di fascicolazioni "complesse" indicative di reinnervazione
• **SLA definita:** segni di 1° e 2° MN in 3 regioni • **SLA probabile**: segni di 1° e 2° MN in almeno 2 regioni con segni di 1° MN rostrali ai segni di 2° MN • **SLA possibile:** segni di 1° e 2° MN in 1 regione, solo segni di 1° MN in 2 o più regioni, o segni di 2° MN rostrali 1°MN • **SLA sospetta:** solo segni di 2° in 2 o più regioni.	• **SLA probabile "laboratory-supported":** segni clinici di 1° e 2° MN in 1 regione, solo segni di 1°MN in 1 regione con segni di 2° MN all'EMG in almeno 2 arti + esami neuroradiologici e laboratoristici che escludano altre patologie La categoria **SLA sospetta viene esclusa**	

“SLA-Mimic” Syndrome:

Sebbene rari, numerosi disturbi presentano caratteristiche cliniche simili a quelle della SLA (cosiddette forme “SLA-like”) e necessitano una accurata valutazione diagnostica:

Esami di laboratorio
Esami neuropatologici (biopsia muscolare, BOM)
Esami neurofisiologici (EMG/ENG, PEM)
Esami neuroradiologici (RM Encefalo)

Panel 2: **Differential diagnosis of ALS and appropriate investigations**

Disorders of motor neurons
- Spinal muscular atrophy (*SMN* gene deletion assay)
- X-linked spinobulbar muscular atrophy (Kennedy's disease; increased CAG repeats in DNA from blood)
- Poliomyelitis or post-polio syndrome (history, NCS, electromyography)
- Hexosaminidase A deficiency (white-cell enzyme testing)

Disorders of motor nerves
- Multifocal motor neuropathy (NCS, electromyography, ganglioside GM1 antibodies)
- Chronic inflammatory demyelinating neuropathy (NCS, lumbar puncture)
- Cramp-fasciculation syndrome (NCS, electromyography)
- Neuromyotonia (antibodies to voltage-gated potassium channels)
- Hereditary spastic paraparesis plus (gene mutation testing)
- Hereditary motor neuropathy with pyramidal features
- Radiculoplexopathy (NCS, electromyography, MRI)
- Paraneoplastic syndrome (serum markers, imaging, bone marrow biopsy sample)
- Heavy metal poisoning (urine or blood screens)
- Mononeuritis multiplex (NCS, electromyography, vasculitic screen, serology)

Disorders of neuromuscular junction
- Myasthenia gravis (acetylcholine receptor antibodies, MuSK antibodies, repetitive stimulation, single-fibre electromyography)
- Lambert-Eaton myasthenic syndrome (repetitive stimulation)

Structural CNS and spinal lesions
- Syringomyelia or syringobulbia (MRI)
- Tabes dorsalis (syphilis serology)
- Multiple sclerosis (MRI, oligoclonal bands, evoked responses)
- Monomelic spinal muscular atrophy (Hirayama's disease; electromyography, MRI)
- Lyme disease (Lyme serology)
- Human T-lymphotropic virus-1 (HIV)

Myopathy
- Inclusion body myositis (electromyography, CK, muscle biopsy sample)
- Polymyositis (electromyography, CK, muscle biopsy sample, autoimmune screens)
- Dermatomyositis (electromyography, CK, skin, and muscle biopsy sample)
- Polyglucosan body disease (NCS, electromyography, muscle or nerve biopsy sample)

Endocrine
- Thyrotoxicosis (thyroid function tests, electromyography, muscle biopsy sample)
- Hyperparathyroidism (calcium ion and parathyroid testing)
- Subacute combined degeneration (vitamin B_{12} concentrations)
- Coeliac disease (serum testing, bowel biopsy sample)

ALS=amyotrophic lateral sclerosis. CK=creatine kinase. NCS=nerve conduction studies. MuSK=muscle-specific tyrosine kinase.

Test di laboratorio

- FT3, FT4, TSH, PTH
- Screening per connettiviti
- Elettroforesi sieroproteica e Immunofissazione
- Ab Anti GM-1
- Esame Liquor CS
- Agoaspirato midollare
- Ab paraneoplastici (anti Hu-Yo-Ri-amfifisina-CV2)
- Dosaggio β-esosaminidasi
- Ab anti HIV 1-2, HTLV 1
- Analisi genetica M.Kennedy (triplette CAG rec.androgeni)
- Dosaggio sierico degli acidi grassi a lunga catena
- Biopsia di muscolo e nervo

Test neurofisiologici

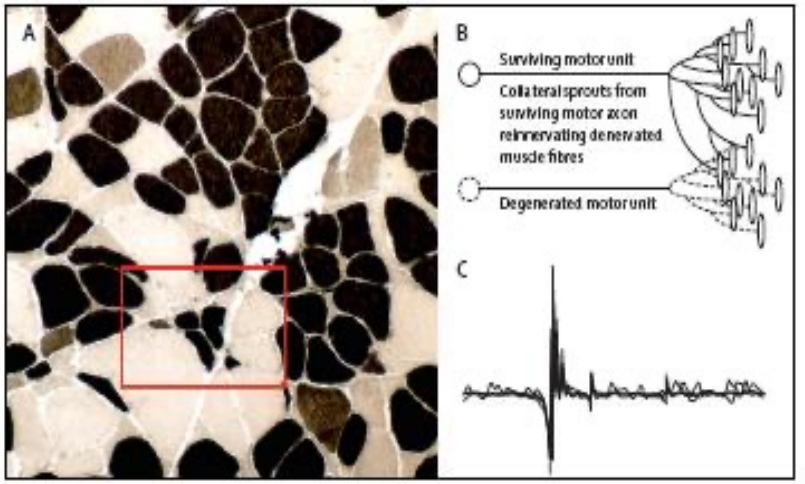


Figure 4: Investigation findings in ALS
(A) Biopsy sample of the left vastus lateralis muscle from a patient with ALS, stained with ATPase pH 9·4. The biopsy sample highlights grouped atrophic fibres with both type I and type II fibres (mixed-type fibres, encompassed by red box). (B) Pathophysiology of motor unit degeneration and reinnervation; with superimposition (C) of ten traces demonstrating the typically large, polyphasic, unstable (complex) motor units observed in established ALS (sweep duration 50 ms), with late components, indicating some re-innervation. ALS=amyotrophic lateral sclerosis.

➢ENG: studio conduzione nervosa sensitivo-motoria

➢EMG (esame ad ago):→ 2° MN

•Potenziali di **fibrillazione e positive sharp wave** (denervazione in fase attiva)
•Segni di sofferenza neurogena cronica (PUM di ampiezza e durata incrementata, ridotto pattern di reclutamento volontario)
•Potenziali di **fascicolazione** (denervazione cronica-reinnervazione)
(scariche spontanee delle unità motorie che sopravvivono,visibili clinicamente come "guizzi" muscolari involontari; a livello della lingia sono molto specifiche)

➢PEM (stimolazione magnetica transcranica) → 1° MN

Test neuroradiologici

- A lungo le tecniche di neuroimaging, nell'ambito del percorso diagnostico della SLA, sono state utilizzate per dimostrare reperti NEGATIVI, e quindi escludere altre cause, più che evidenziare reperti POSITIVI specifici della malattia

- Tecniche di neuroimaging multimodale→ SLA disturbo neurodegenerativo multisistemico

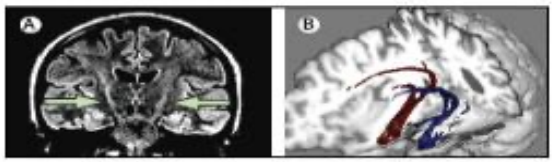


Figure 5: Standard and experimental MRI sequences in patients with ALS
(A) T2-weighted FLAIR sequence shows hyperintense corticospinal tracts in a patient with ALS on this coronal view (arrows), but this feature is neither sensitive nor specific in the absence of other more obvious clinical symptoms. (B) Diffusion tensor tractography is a research-based MRI technique that has potential to study extramotor and motor neuronal pathway involvement in ALS (superior oblique cut-out brain section viewed from left). In this patient with an unusual ALS phenotype that included prominent aphasia, reconstruction of the temporal lobe white matter projection fibres indicated that there were fewer fibres on the left (blue) compared with the right (red) side. ALS=amyotrophic lateral sclerosis. FLAIR=Fluid-attenuated inversion-recovery.

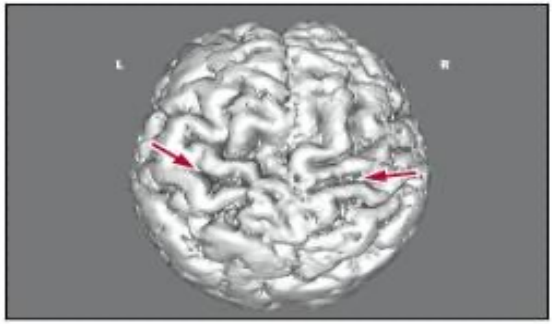


Figure 6: 3-Dimensional MRI of a brain of a patient with primary lateral sclerosis, as shown from above
Arrows show visibly widened precentral sulci with relative atrophy of the adjacent gyri, notably the motor strips. Macroscopic atrophy as seen here is rare in patients with typical ALS, but is more frequently noted in those with primary lateral sclerosis, who have a predominantly upper motor neuron burden of disease. This figure highlights the late stage of a corticomotoneuronal process postulated to be inherent in ALS more generally. ALS=amyotrophic lateral sclerosis.

Panel 3: Key neuroimaging findings in ALS

MRI corticospinal tract hyperintensity

Hyperintensity of the corticospinal tracts as seen on MRI can be prominent in ALS,[85,87] but this feature is not specific to the disease (figure 5A).

Cerebral atrophy detection with MRI

Voxel-based morphometry has quantified grey and white matter to detect cerebral atrophy in patients with ALS[84] linked to cognitive impairment,[91] with notable differences in regional emphasis between patients with sporadic disease and those with familial disease who have a longer life expectancy.[100] 3-Dimensional rendering of the brain by use of MRI might also serve to highlight focal abnormality (figure 6).

Magnetic resonance spectroscopy

The measurement of proton-containing metabolites such as N-acetylaspartate (expressed as a ratio with creatine/phosphocreatine or choline) has served as a marker of neuronal loss. Patients with ALS have a reduced primary motor cortex N-acetylaspartate to creatine ratio compared with controls,[101] and use of magnetic resonance spectroscopy seems particularly sensitive in the detection of upper motor neuron dysfunction, distinguishing patients with progressive muscular atrophy from those with ALS.[102]

Diffusion tensor imaging

Diffusion tensor imaging can be used to exploit the sensitivity of MRI to identify the direction of water diffusion, which is expected to be restricted (ie, anisotropic) within intact neuronal pathways and more diffuse (isotropic) in regions of reduced integrity. Quantifiable measures such as fractional anisotropy and mean diffusivity are powerful surrogate markers of neuronal pathological changes,[103] and inter-connectivity between neuronal pathways can be mapped using the allied technique of tractography (figure 5B).[104] Use of diffusion tensor imaging can detect reduced fractional anisotropy within the corticospinal tract of patients with ALS.[105]

Functional studies

Results of PET activation studies with 2-^{18}fluoro-2-deoxy-D-glucose and $H_2{}^{15}O$ have indicated widespread extramotor changes in patients with ALS,[106] with frontal deficits linked to neuropsychological impairment,[107] providing clear application to the emerging clinicopathological overlap between ALS and FTD.[108] Non-invasive study of brain activation by functional MRI exploits differences in the resonant properties of oxyhaemoglobin versus deoxyhaemoglobin (blood oxygenation level dependent [BOLD]-functional MRI). By analysing whole-brain BOLD-functional MRI activity in the resting state, functionally interconnected brain regions can be identified.[109] Results from studies in patients with ALS have shown both "default mode" and sensorimotor network activation changes.[110] This technique has the potential to further delineate the extramotor cerebral pathological changes in patients with ALS.

Molecular imaging

Receptor ligand PET has been used to study molecular mechanisms in ALS. Data from ^{11}C-flumazenil PET have indicated reduced inhibitory GABAergic cortical effects in ALS,[111] in keeping with the hypothesis of cortical hyperexcitability as a fundamental aspect of ALS pathogenesis.[112] Use of the benzodiazepine receptor PET ligand ^{11}C-PK11195 revealed widespread microglial activation in ALS,[113] supported by the finding of inflammatory biomarkers in the cerebrospinal fluid.[114] The pronounced frontotemporal reductions in the binding of the 5-HT1A receptor ligand ^{18}C-WAY100635 in patients with ALS,[115] and data from neuropathological receptor studies that revealed similar changes in FTD,[116] suggest that serotonergic mechanisms warrant further study in relation to pathogenesis. Finally, paramagnetic properties of small particles of iron oxide, which can be used as intravenous contrast agents, might indicate the start of the era of molecular MRI,[117] with potential to understand inflammatory mechanisms[118] and therapeutic stem-cell tracking.[119]

Detection of presymptomatic markers of disease

The poor definition of the population at risk for sporadic ALS impedes attempts to identify an early, presymptomatic diagnostic biomarker. Results from a diffusion tensor imaging study of presymptomatic patients with a highly penetrant dominant SOD1 gene mutation revealed changes in the posterior limb of the internal capsule not seen in healthy controls, which might be among the earliest detectable changes.[120]

ALS=amyotrophic lateral sclerosis. FTD=frontotemporal dementia.

Biomarcatore “ideale” per la SLA

Elevata sensibilità e specificità

Differenziare fenotipi clinici

Facilmente accessibile ed economico

Facilmente ripetibile

Misurabile in fase preclinica

Buon indicatore di progressione di malattia

Poco invasivo e facilmente misurabile in pz. con elevata disabilità fisica

Ad oggi non ancora individuato

- **EMG** (indici quantitativi)

- **Tecniche RM non convenzionali**

RM spettroscopica (1H-RMS)
Voxel-Based morphometry (VBM)
RM con tensore di diffusione (DTI-MRI)
RM funzionale (fMRI)

- **Numerose molecoleindagate nel LCS e sangue periferico dei pz. con SLA** (legate ai principali meccanismi fisiopatologici) indagate nel LCS e sangue periferico dei pz. con SLA

Markers di stress ossdativo
Fattori di crescita
Markers di neuroinfiammazione
Markers di danno assonale (NF-L, NF-H)→possibili biomarkers di diagnosi, progressione e severità di malattia

Diagnosi

1 ANAMNESI e OBIETTIVITA' NEUROLOGICA

- ricerca di segni di sofferenza del 1 e/o 2 motoneurone nelle 4 regioni del SNC
- criteri di El Escorial revisionati/Awaji Island

2 NEUROFISIOLOGIA

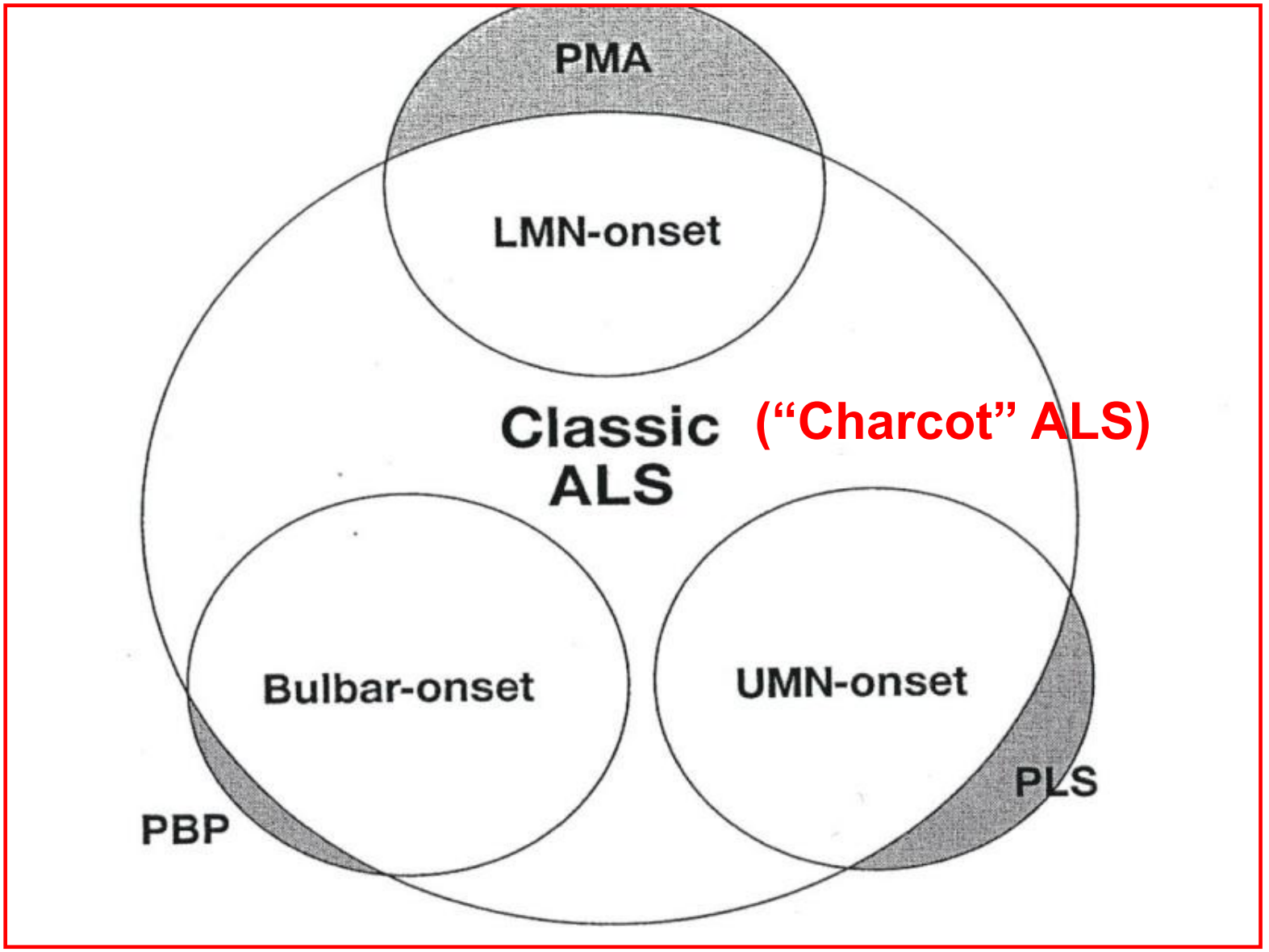
- conferma della sofferenza del 2 motoneurone nelle regioni clinicamente affette o evidenza di sofferenza in regioni clinicamente non ancora coinvolte
- esclusione di altre malattie

3 NEURORADIOLOGIA

- esclusione di altre malattie
- Nessun test diagnostico anche se: RMN T2 pesate iperintesità dei tratti corticospinali e ipointensità della corteccia motoria; nuove tecniche di neuroimaging

4 TESTS DI LABORATORIO

- Esclusione di altre malattie


PMA
LMN-onset
Classic ALS
("Charcot" ALS)
Bulbar-onset
UMN-onset
PLS
PBP

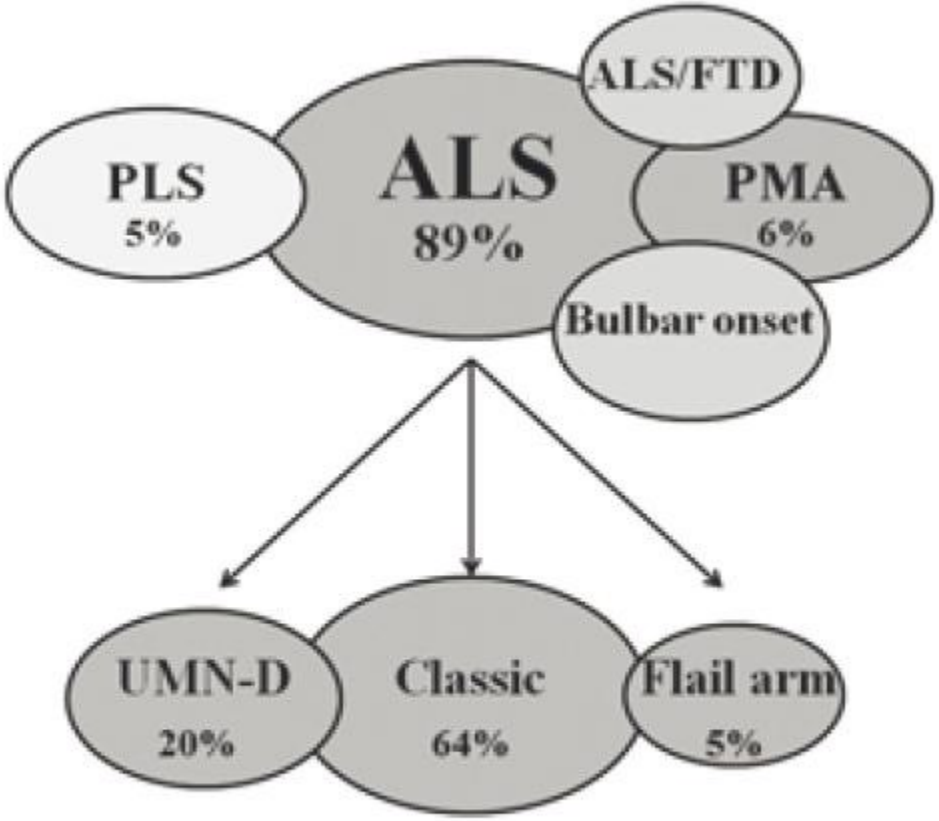
Clinical syndromes of ALS

Syndrome	Main clinical features	Prognosis
Classic ("Charcot") ALS	Limb onset (spinal); bulbar involvement usual; UMN + LMN signs; M:F ratio 3:2.	60-70% of all cases at presentation; median survival 3-4 yrs.
Progressive bulbar palsy (PBP)	Onset with dysarthria, then progressive speach and swallowing difficulties; limb involvement follows (months or yrs); M:F ratio: 1:1 (PBP > common in older women).	20% of all case at presentation; median survival 2-3 yrs.
Progressive muscular atrophy (PMA)	Almost always limb onset; > 50% develop UMN signs; 85% develop bulbar symptoms; heterogeneous condition but majority are ALS; M:F ratio 3-4.	10% all cases at presentation; overlap with "flail arm" and "flail leg" syndromes; median survival 5 yrs; more long survivors (>10 yrs).
Primary Lateral Sclerosis (PLS)	Clinically progressive pure UMN syndrome; after few yrs may convert to ALS.	10 yrs or more.

Clinical syndromes of ALS (cont.)

Syndrome	Main clinical features	Prognosis
"Flail arm syndrome"; man in a barrel syndrome; Vulpian-Bernhard syndrome	Syndrome of predominantly LMN weakness of both arms; UMN signs develop in 50-70%; often slow progression; pathology is that of ALS.	About 10% of all cases; M:F ratio 9:1; prognosis better than in ALS syndrome more common in African and Asian patients.
"Flail leg syndrome"; "pseudopolyneuritic form" of ALS; Patrikios syndrome	Syndrome of progressive leg weakness, predominantly LMN.	Rare; slow progression; DD difficult.
Monomelic forms of ALS	Rare variants of ALS with slowly progressive focal (upper > lower limb UMN and LMN syndrome); Distinct LMN form most common in Asia (monomelic juvenile onset amyotrophy; Hirayama's syndrome); DD with multifocal motor neuropathy.	Juvenile onset form progressive over months or several yrs and then stabilises; does not generalises; pathology unknown.
ALS-dementia syndrome (ALS-D)	Dementia of fronto-temporal type present in 5% of all ALS cases; 20-40% ALS patients have subtle cognitive changes of "frontal" type; ALS-D may present first with dementia or ALS progressing to dementia, or with combination of both; about 50% familial.	Usually 2 to 5 yrs.

Different clinical phenotypes !



Clinical phenotypes in our population of 850 patients with sporadic motor neuron disease.

Sabatelli et al., 2013

JNNP Online First, published on March 14, 2011 as 10.1136/jnnp.2010.235952

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†

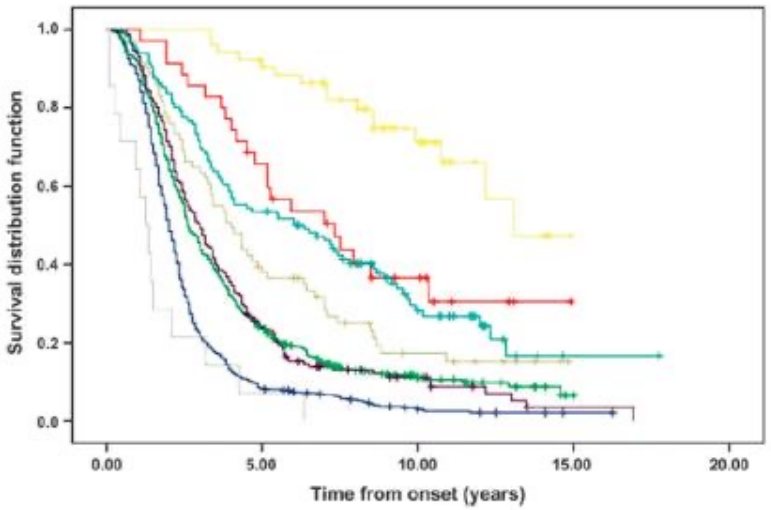


Figure 3 Tracheostomy free survival, according to amyotrophic lateral sclerosis (ALS) phenotype. Yellow, PUMN; red, PLMN; light blue, pyramidal ALS; grey, flail arm; violet, classic ALS; green, flail leg; blue, bulbar; cyan, respiratory. Crosses are censored patients. PLMN, pure lower motor neuron phenotype;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

Diseases that can masquerade as ALS/MND

Anatomical abnormalities/compression syndromes:
Arnold-Chiari-1 and other hindbrain malformations
Cervical, foramen magnum or posterior fossa region tumors
Cervical disc herniation with osteochondrosis
Cervical meningeoma
Retropharyngeal tumour
Spinal epidural cyst
Spondylotic myelopathy and/or motor radiculopathy
Syringomyelia

Acquired enzyme defects
Adult GM2 gangliosidosis (hexosaminidase-A or B- deficiency)
Familial amyloid polyneuropathy (FAP)
Polyglucosan body disease

Autoimmune syndromes:
Monocloncal gammopathy with motor neuropathy
Multifocal motor neuropathy with/without conduction bloks (MMN)
Dysimmune LMN syndromes (with GM1, GD1b, and asialo-GM1 antibodies)
Other dys-immune LMN syndrome including CIDP
Multiple sclerosis
Myastenia gravis

Endocrine abnormalities
Diabetic "amyotrophy"
Insulinoma causing neuropathy
Hyperthyroidism with myopathy
Hyperparathyroidism
Hypokalemia (Conn's syndrome)

Exogenous toxins
Lead (?), mercury (?), cadmium, aluminum, arsenic, thallium, manganese, organic, pesticides, neurolathyrism, konzo

EFNS Task Force, 2005

Diseases that can masquerade as ALS/MND (cont.)

Infections:
Acute poliomyelits
Post-poliomyelitis progressive muscular atrophy
HIV-1 (with vacuolar myelopathy)
HTLV-1cassociated myelopathy (HAM, tropical spastic paraplegia)
Neuroborreliosis
Spinal encephalitis lethargica, varicells-zoster, brucellosis, cat-scratch disease,neuro-syphilis, prion disorders

Myopathies:
Cachectic myopathy
Carcinoid myopathy
Dystrophin-deficient myopathy
Inclusion body myositis (IBM)
Inflammatory myopathies
Polymyositis
Sarcoid Myositis

Neoplastic syndromes:
Chronic lymphocytic leukemia
Intramedullary glioma
Lymphoproliferative disorders with paraproteinemia and/or oligoclonal bands in the CSF
Pancoast tumor syndromes
Paraneoplastic Encephalomyelitis (PEM) with anterior horn cell involvement
Stiff-Person-Plus syndromes

Physical injury:
Electric shock neuronopathy
Radiation-induced radiculo-plexopathies and/myelopathy

Vascular Disorders:
Arterioveneous malformation
Dejerine anteriori bulbar artery syndrome
Stroke
Vasculitis

EFNS Task Force, 2005

Diseases that can masquerade as ALS/MND (cont.)

Other neurological conditions:

Wester pacific atypical forms of MND/ALS (Guam, New Guinea, Kii Peninsula Japan)
Carribean atypical forms of MND-dementia-PSP (Guadeloupe)
Madras-form of juvenile onset MND/ALS (South India)
Frontotemporal dementia with MND/ALS (FTD, including Pick's disease with amyotrophy)
Multiple System Atrophy (MSA)
Olivo-ponto cerebellar atrophy (OPCA/SCA) syndromes
Primary lateral sclerosis (PLS; some subtypes not related to ALS)
Progressive supranuclear palsy (PSP)
Hereditary spastic paraplegia (HSP; many variants, some subtypes with distal amyotrophy)
Progressive spinal muscular atrophy (PMA; some subtypes not related to ALS)
Spinobulbar muscular atrophy with/without androgen receptor mutation (SBMA)
SMA I-IV
Brown-Vialetto-van Laere syndrome (early onset bulbar and spinal ALS with sensorineural deafness
Fazio-Londe syndrome (infantile PBP)
Harper-Young syndrome (laryngeal and distal SMA)
Monomelic sporadic spinal muscular atrophy (BFA, including Hirayama Syndrome)
Polyneuropathies with dominating motor symptoms (HMSN type 2)
Benign fasciculations
Myokymia

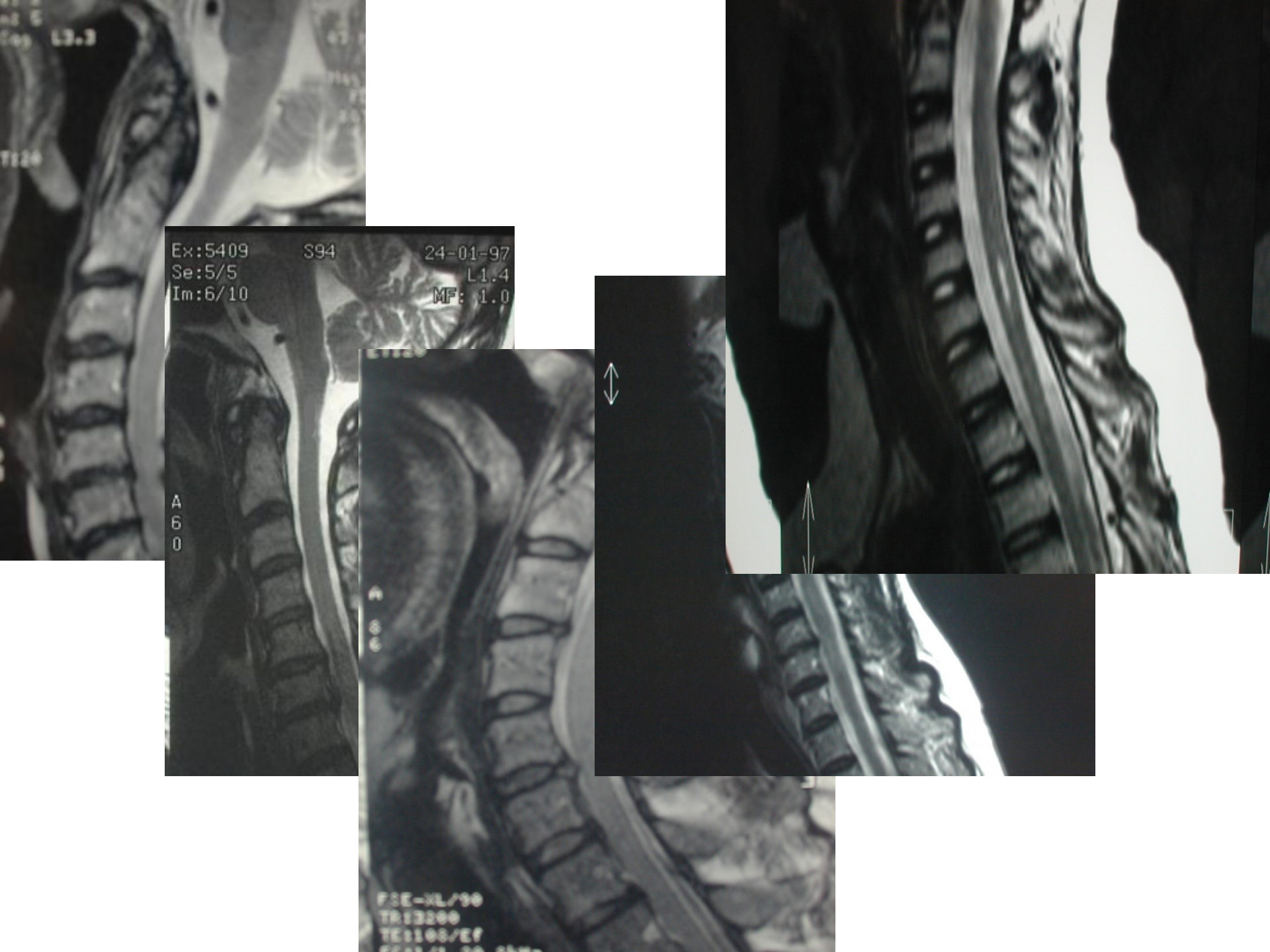
EFNS Task Force, 2005

The majority of patients with adult-onset motor neuron disease will be found to have

IDIOPATHIC ALS

The most important of the acquired diseases of the spinal cord in simulating ALS:

Spondylotic Myelopathy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Honesty and hope: announcement of diagnosis in ALS

Vincenzo Silani, MD; and Gian Domenico Borasio, MD

Article abstract—Informing patients and their families about a diagnosis such as amyotrophic lateral sclerosis (ALS) is a daunting task for any physician. The way the diagnosis is communicated will have a major impact on the physician–patient relationship and the attitude of the patient toward the disease and toward symptomatic treatment measures. Breaking the news can be truly defined as the starting point of palliative care in ALS. It is an ongoing information process which, by its nature, escapes narrow definitions or standardization attempts. Nevertheless, a number of techniques exist to facilitate the process and ease the burden for physicians, patients, and families. We believe that the terminal phase should be discussed at the latest when first respiratory symptoms appear, to prevent unwarranted fears of "choking to death."

NEUROLOGY 1999;53(Suppl 5):S37–S39

Riconsiderare la diagnosi se:

1. Storia atipica
2. Mancata progressione dei sintomi
3. Comparsa di segni atipici (sensibilità, sfinteri)
4. Follow-up neurofisiologico e neuroradiologico

Non esiste un test diagnostico specifico per SLA: la clinica insieme alla negatività delle indagini strumentali supportano la diagnosi

LA PROGRESSIONE DELLA MALATTIA E' UN REQUISITO INDISPENSABILE ALLA DIAGNOSI

TRATTAMENTO DELLA SLA: principi ispiratori

- Approccio moltidisciplinare
- Rispetto del principio di autonomia del paziente
- Tempestività degli interventi
- Facilitazione dell'accesso ai servizi
- Aiuto all'utilizzazione dei servizi disponibili
- Formazione e informazione dei pazienti e delle famiglie

Miglioramento della qualità di vita

Interventi 'terapeutici' nella SLA

- Comunicazione della diagnosi
- Approccio clinico multidisciplinare
- Trattamenti 'neuroprotettivi'
- Trattamenti sintomatici
- Consulenza genetica
- Trattamenti respiratori
- Trattamenti nutrizionali
- Comunicazione alternativa/aumentativa
- Intervento psicologico
- Interventi sulla famiglia
- Terapie palliative e di fine vita

Comunicazione della diagnosi

La comunicazione della diagnosi è un momento molto delicato e deve essere affrontato nei tempi e nei modi più adeguati per il singolo paziente ed i membri della famiglia, sempre con **estrema sensibilità**

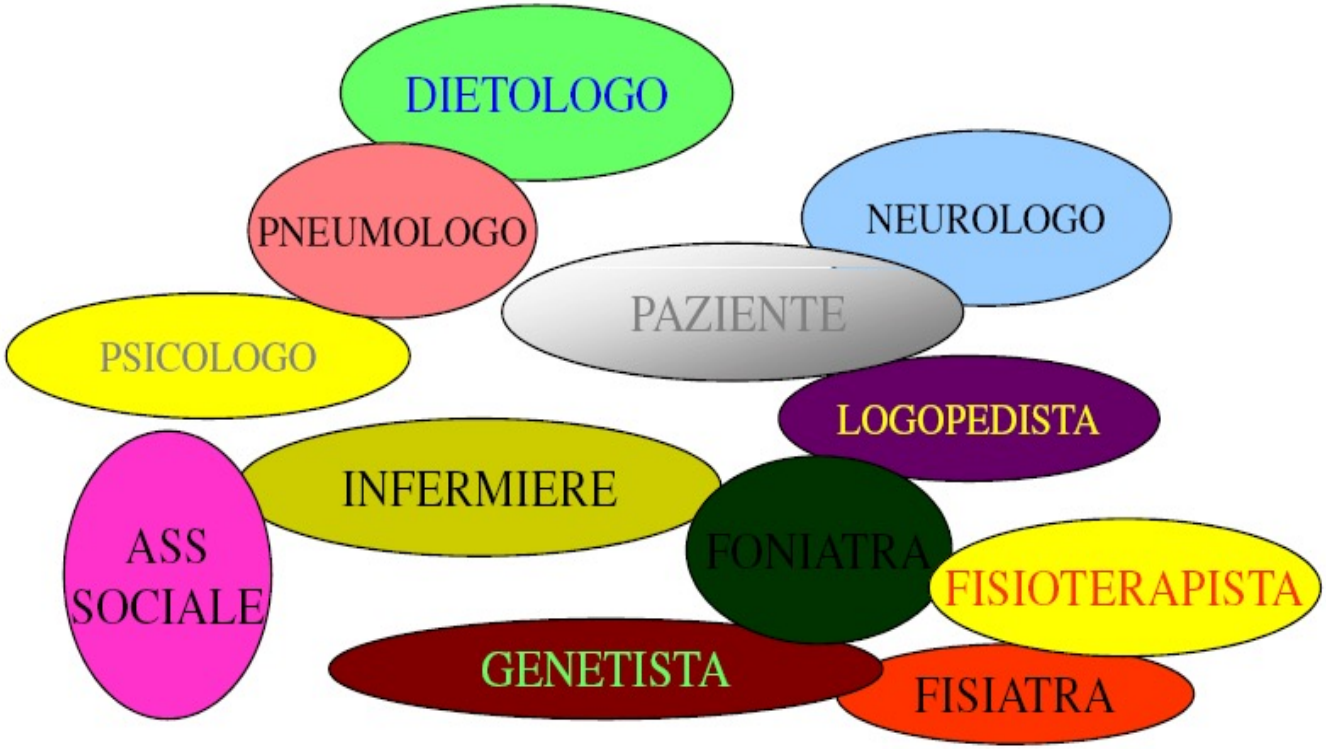
Il carico emotivo di una diagnosi comunicata in maniera scorretta può accompagnare il paziente e la famiglia lungo l'intero decorso della malattia ed influenzare il processo di accettazione della prognosi, infausta, della malattia

Team multidisciplinare

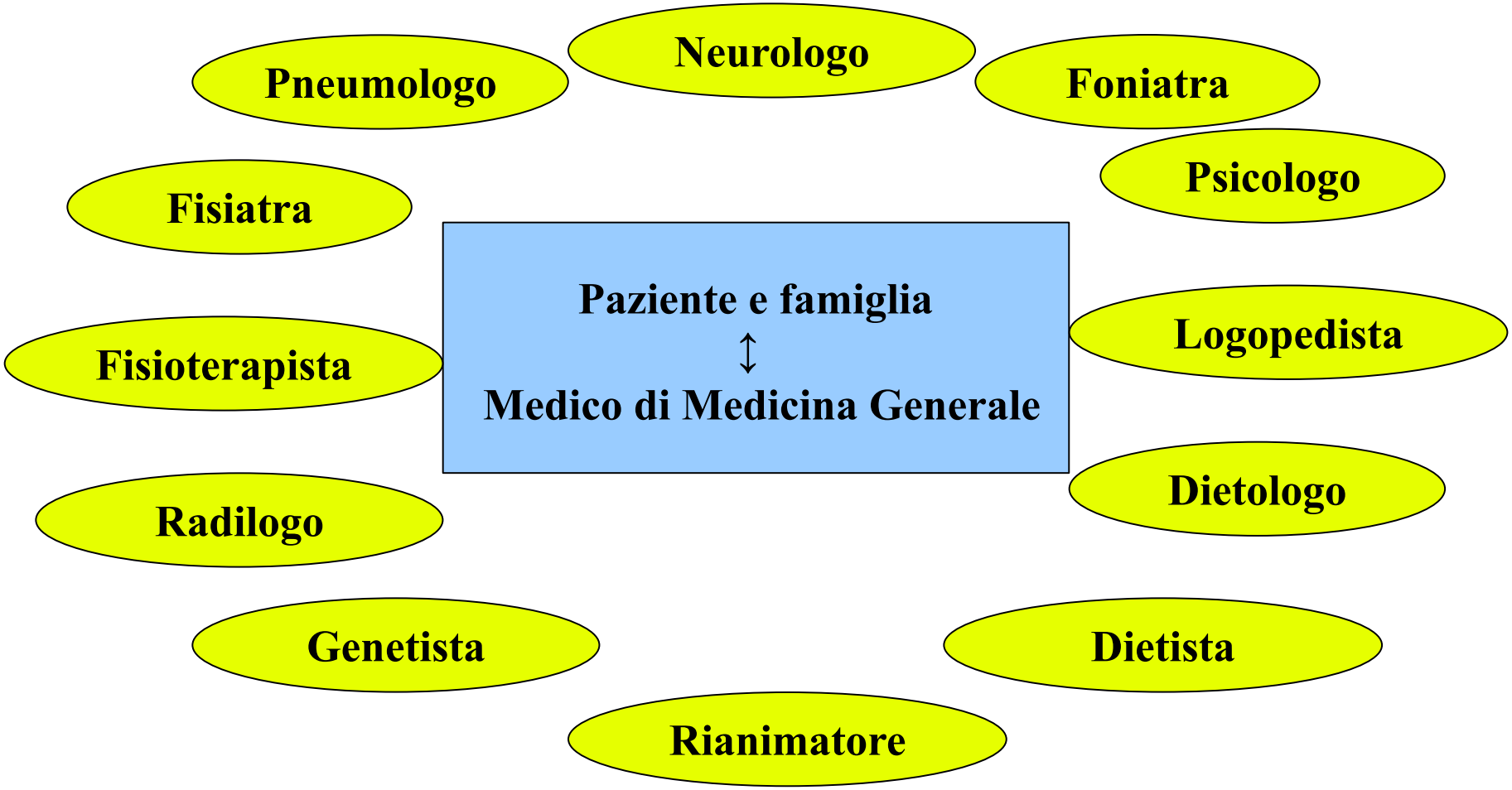
- Presa in carico da parte di un gruppo multidisciplinare, che include, oltre al neurologo, fisiatra, fisioterapista, dietologo, dietista, psicologo, neuropsicologo, pneumologo, etc.
- Visite ogni 2-3 mesi
- Possibilità per il paziente di avere contatti 'intercorrenti'
- Stretto collegamento con il territorio (medico di base, assistenti sociali, servizi territoriali di fisioterapia, logopedia, etc.)

"to cure rarely, to treat often, to care always"

Modello assistenziale tradizionale



Modello assistenziale multidisciplinare



Terapia neuroprotettiva

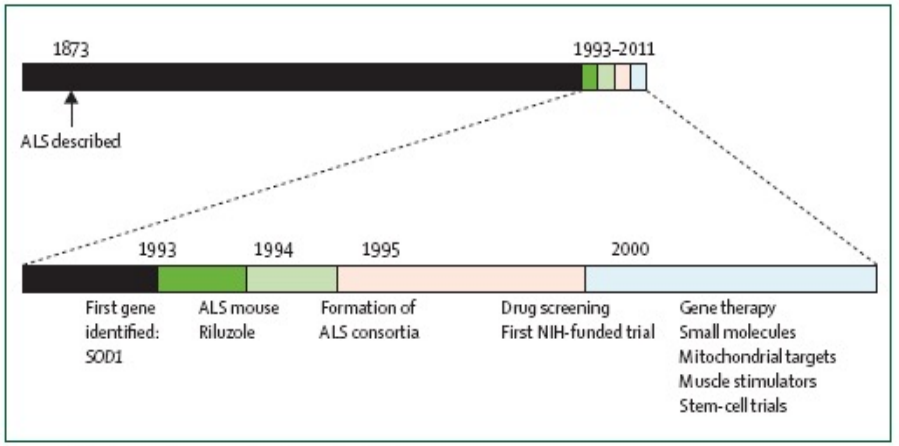


Figure 1: The increasing pace of advances in ALS
ALS=amyotrophic lateral sclerosis. NIH=National Institutes of Health.

RILUZOLO (Rilutek), inibitore del rilascio del glutammato, unico farmaco "disease-modifying" che ha dimostrato in 2 grossi RCT aumentare la sopravvivenza di 3-6 mesi

Table 5 Summary of the most important controlled therapeutic studies in ALS

Completed trials
N-acetylcysteine*
Brain-derived neurotrophic factor (BDNF)*
Branched-chain amino acids*
Celecoxib*
Ciliary neurotrophic factor (CNTF)* (two trials)
Creatine* (three trials)
Cyclosporine*
Dextromethorphan*
Gabapentin*
Glial-derived neurotrophic factor (GDNF)*
Indinavir*
Interferon beta-1a*
Insulin-like growth factor (IGF-1)*
Lamotrigine* (two trials)
Lymphoid irradiation*
Nimodipine*
ONO-2506*
Pentoxifylline*
Riluzole
Selegiline*
TCH-346*
Topiramate*
Verapamil*
Vitamin E* (two trials)
Xaliproden*
Ongoing phase II/III trials (summer of 2005)
Arimoclomol
Ceftriaxone
IGF-1 polypeptide
Minocycline
Phase III trials being planned or considered
AEOL 10150
Celastrol
Coenzyme Q10
Copaxone
IGF-1 – viral delivery
Memantine
NAALADase inhibitors
Nimesulide
Scriptaid
Sodium phenylbutyrate
Talampanel
Tamoxifen
Thalidomide
Trehalose

*No therapeutic benefit was observed.

Edaravone - Razionale

Radicut, Radicava

- *Farmacocinetica*

  emivita 4.5-6 h
  metabolismo epatico (glucuronazione)

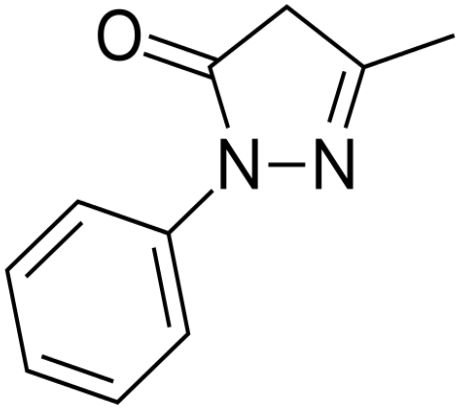
- *Farmacodinamica*

  eliminazione perossinitriti
  inattivazione ROS
  sintesi prostacicline

- *Applicazioni*

  neuroprotezione nell'ictus ischemico
  studi su PD, AD

- *Aumento sporavvivenza nel topo wobbler*



1-fenil-3-metil-5-pirazolone

Edaravone – MCI186-12

Amyotrophic Lateral Sclerosis. 2006; 7: 247–251

Taylor & Francis

ORIGINAL ARTICLE

Investigation of the therapeutic effects of edaravone, a free radical scavenger, on amyotrophic lateral sclerosis (Phase II study)

HIIDE YOSHINO[1] & AKIO KIMURA[2]

[1]*Department of Neurology, Kohnodai Hospital, National Center of Neurology and Psychiatry, Chiba, and* [2]*Department of Neurology, Gifu University Hospital, Yanagido, Gifu-city, Japan*

- *open label*
- *20 pazienti (30 e 60 mg/die)*
- *somministrazione i.v. a cicli*
- *ALSFRS-R: 4.7 vs 2.3 (p=0.036)*
- ↓ *3-nitrotirosina in CSF*

Table II. Effect of edavarone on decline of ALSFRS-R score.

Group	No. of cases excluding dropouts	Total ALSFRS-R: Score at 6 months before start of treatment	Total ALSFRS-R: Score prior to 1st cycle of administration	Total ALSFRS-R: Score after 6th cycle of administration	Change in the 6 months before the start of treatment	Change in the 6 months after the start of treatment	Difference in rate of decline*	Wilcoxon signed rank test
30 mg	4	39.3±8.0	32.0±9.6	27.0±9.6	−7.3±2.8	−5.0±3.6	2.3±3.9	0.500
60 mg	12	42.7±6.3	38.0±6.0	35.8±7.3	−4.7±2.1	−2.3±3.6	2.4±3.5	0.039

* Difference in rate of decline=change of ALSFRS-R score in the six months before the start of treatment minus change of ALSFRS-R score in the six months after the start of treatment (i.e. during treatment with edavarone).

Edaravone – MCI186-16

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2014; 15: 610–617

informa
healthcare

ORIGINAL ARTICLE

Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients

KOJI ABE[1], YASUTO ITOYAMA[2], GEN SOBUE[3], SHOJI TSUJI[4], MASASHI AOKI[2], MANABU DOYU[5], CHIKUMA HAMADA[6], KAZUOKI KONDO[7], TAKATOMO YONEOKA[7], MAKOTO AKIMOTO[7] & HIIDE YOSHINO[8]; ON BEHALF OF THE EDARAVONE ALS STUDY GROUP

[1]*Department of Neurology, Okayama University Hospital, Okayama,* [2]*Department of Neurology, Tohoku University Hospital, Sendai (Yasuto Itoyama is currently affiliated with International University of Health and Welfare, Ohtawara, Japan),* [3]*Department of Neurology, Nagoya University Hospital, Nagoya,* [4]*Department of Neurology, The University of Tokyo Hospital, Tokyo,* [5]*Department of Neurology, Aichi Medical University Hospital, Nagakute,* [6]*Faculty of Engineering, Tokyo University of Science, Tokyo,* [7]*Development Division, Mitsubishi Tanabe Pharma Corporation, Tokyo, and* [8]*Yoshino Neurology Clinic, Ichikawa, Japan*

- *RCT vs placebo (199 pts.)*
- *20-75 yrs.; D, P, PLS; onset < 36 mo.*
- *FVC>70%, JALS 1-2*
- *declino ALSFRS-R: 1-4 p in 12 sett.*

Table II. Change in endpoints during treatment.

	Change in endpoints during treatment (ANCOVA)				Repeated-measures analysis			
	Adjusted mean change LS Mean ± S.E.		Inter-group difference in adjusted mean change LS Mean ± S.E. (95% C.I.)	p value	Adjusted mean LS Mean ± S.E.		Inter-group difference in adjusted mean LS Mean ± S.E. (95% C.I.)	p value
	Placebo	Edaravone			Placebo	Edaravone		
Primary endpoint								
ALSFRS-R	−6.35 ± 0.84 (99)	−5.70 ± 0.85 (100)	0.65 ± 0.78 (−0.90 – 2.19)	0.411	37.43 ± 0.46	38.08 ± 0.47	0.65 ± 0.44 (−0.22 – 1.52)	0.141
Secondary endpoint								
%FVC	−17.49 ± 2.39 (99)	−14.57 ± 2.41 (100)	2.92 ± 2.24 (−1.49, 7.33)	0.193	87.30 ± 1.56	88.56 ± 1.59	1.26 ± 1.46 (−1.63, 4.15)	0.390
Grip strength	−5.71 ± 0.69 (99)	−4.81 ± 0.69 (100)	0.89 ± 0.64 (−0.37, 2.16)	0.165	13.22 ± 0.42	13.83 ± 0.43	0.60 ± 0.40 (−0.18, 1.38)	0.130
Pinch strength	−1.03 ± 0.15 (99)	−0.83 ± 0.15 (100)	0.20 ± 0.14 −0.08, 0.48)	0.165	2.62 ± 0.11	2.83 ± 0.11	0.21 ± 0.10 (0.01, 0.41)	0.038
Modified Norris scale	−16.15 ± 2.00 (97)	−14.12 ± 2.05 (95)	2.03 ± 1.89 (−1.69, 5.75)	0.284	NA	NA	NA	NA
ALSAQ40	19.13 ± 3.79 (95)	19.60 ± 3.82 (95)	0.48 ± 3.50 (−6.44, 7.39)	0.892	NA	NA	NA	NA

ALSFRS-R: interaction between treatment group and period ($p = 0.915$). ALSFRS-R: the revised amyotrophic lateral sclerosis functional rating scale. NA: not applicable. For Modified Norris scale and ALSAQ40, repeated measures analysis was not conducted

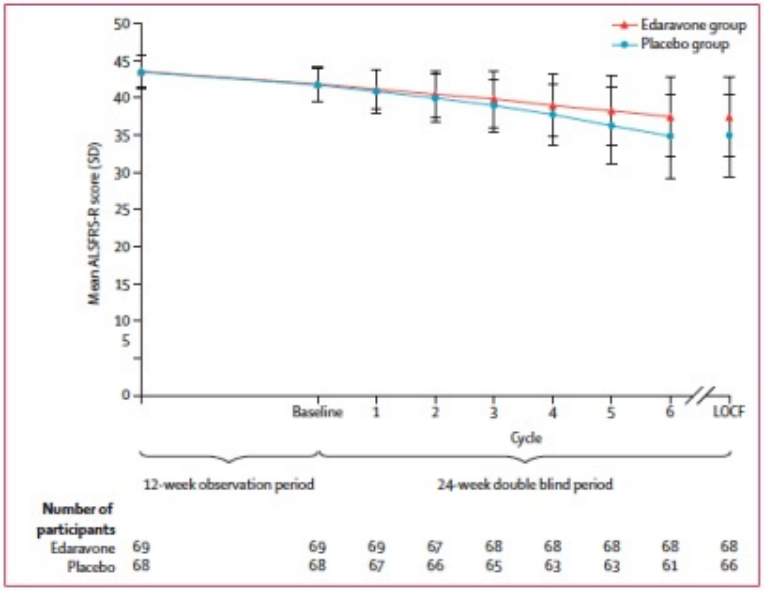
Edaravone – MCI186-19

Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial

The Writing Group* on behalf of the Edaravone (MCI-186) ALS 19 Study Group†

- *RCT vs placebo (137 pts.)*
- *20-75 yrs.; D, P, ~~PLS~~; onset < 24 mo.*
- *FVC>80%, JALS 1-2*
- *item 1-9 ALSFRS-R >2, item 10-12 = 4*
- *declino ALSFRS-R: 1-4 p in 12 sett.*

	Least-squares mean change		Least-squares mean difference	p value*
	Edaravone (n)	Placebo (n)		
Primary endpoint				
ALSFRS-R score	-5·01, 0·64 (68)†	-7·50, 0·66 (66)†	2·49, 0·76 (0·99 to 3·98)	0·0013
Secondary endpoints				
FVC (%)	-15·61, 2·41 (67)†‡	-20·40, 2·48 (66)†	4·78, 2·84 (-0·83 to 10·40)	0·0942
Modified Norris Scale scores				
Total	-15·91, 1·97 (68)†	-20·80, 2·06 (63)†‡	4·89, 2·35 (0·24 to 9·54)	0·0393
Limb scale	-11·47, 1·61	-14·91, 1·68	3·44, 1·92 (-0·36 to 7·24)	0·0757
Bulbar scale	-4·44, 0·76	-5·89, 0·79	1·46, 0·90 (-0·33 to 3·24)	0·1092
ALSAQ-40 score	17·25, 3·39 (68)†	26·04, 3·53 (64)†‡	-8·79, 4·03 (-16·76 to -0·82)	0·0309
Grip strength (kg)§	-4·08, 0·54 (68)†	-4·19, 0·56 (66)†	0·11, 0·64 (-1·15 to 1·38)	0·8583
Pinch strength (kg)§	-0·78, 0·14 (68)†	-0·88, 0·14 (66)†	0·10, 0·16 (-0·23 to 0·42)	0·5478



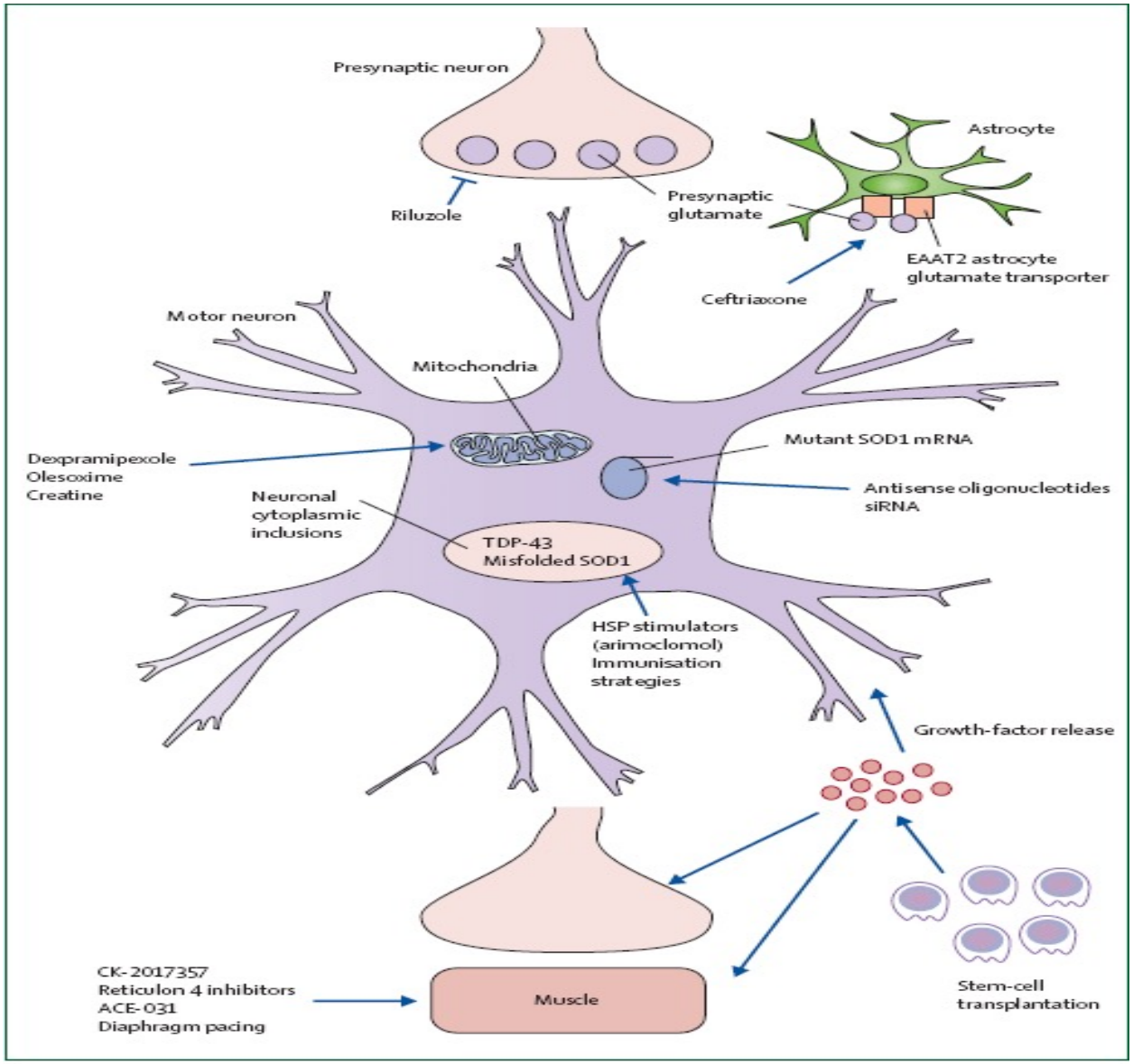


Figure 2: **Novel therapeutic targets in ALS**

Table 3 Recent trials

Drug	Phase	Number of patients, duration	Design	Primary outcome	Results
Valproic acid [64]	III	163, interim analysis	Randomized sequential trial	Survival	Negative
CoQ10 [65]	II	185, 9 months	Futility trial	Decline in ALS-FRSr	Negative
Talampanel [66]	II	59, 9 months	Randomized control trial	Decline in isometric arm strength	Negative
Dextromethorphan + quinidine [67]	III	326 (not only ALS), 12 weeks	Randomized control trial	Pseudo-bulbar symptoms	Positive
THC [68]	III	27, 12 weeks	Randomized crossover, control trial	Cramps	Negative
Memantine [69]	II	63, 12 months	Randomized control trial	Decline in ALS-FRS	Negative
Lithium [63]	III	84, interim analysis	Futility trial	Decline in ALS-FRS	Negative
Lithium [70]	III	171, interim analysis	Single-blind, randomized, dose-finding trial	Survival or severe loss of autonomy	Negative

ALS, amyotrophic lateral sclerosis; ALS-FRS, ALS functional rating scale; ALS-FRSr, revised ALS functional rating scale; TCH, tetrahydrocannabinol.

	Proposed mechanism	Stage of development	Preliminary results and comments
Glutamate targets			
Ceftriaxone[a]	Decreases synaptic glutamate	Phase 3 study	Criteria for tolerability met; study in stage 3 and more than two-thirds of patients recruited
Protein misfolding			
Arimoclomol[b]	Amplifies HSP gene expression	Phase 2/3 study in FALS	Human placebo-controlled study showed safety and CSF penetration[c]
Immunisation	Removes misfolded SOD1	Preclinical studies	Promising preclinical data in SOD1 transgenic mouse model[d,e]
RNA targets			
Antisense SOD1 oligonucleotides (ISIS 333611)[f]	Lowers concentrations of mutant SOD1	Phase 1 study in FALS	Concentrations of mutant messenger RNA reduced with antisense oligonucleotides and small inhibitory RNA molecules, leading to slowed disease progression in the mutant SOD1 transgenic mouse model[g–i]
Mitochondrial targets			
Olesoxime (TRO19622)[j,k]	Mitochondrial pore modulation	Phase 2/3 study	Preclinical studies showed in-vitro and in-vivo efficacy[k]
Dexpramipexole[l,m]	Increases mitochondrial function	Phase 3 study	Phase 2 study of 102 patients with ALS showed safety and tolerability, and motor decline lessened and survival improved in a dose-response manner
Growth factors			
VEGF (sNN0029)[n,o]	Angiogenesis and neuroprotection	Phase 1/2 study of intracerebroventricular administration	Preclinical animal data showed efficacy[n,o]
Stem-cell therapy			
Bone marrow or embryonic stem cells into CNS[p–r]	Neuroprotection	Phase 1 study	For both strategies, additional preclinical and safety data required Optimum cell-type, dose, cofactor requirements, and location of transplantation unknown
IPS cells in SC	Neuroprotection	Phase 1 study pending	
Muscle targets			
Diaphragm pacing[s]	Diaphragm contraction	Phase 1 study	Safety and efficacy reported[s] FDA approval for humanitarian designation exemption pending
Skeletal muscle troponin activator (CK-2017357)[t]	Increases muscle force	Phase 2 study completed	Fatigue, strength, and pulmonary function improved in a dose-response manner[t]
GDF-8 (myostatin) inhibitor (ACE-031)[u]	Promotes musde growth	Phase 1 study in postmenopausal women	Future studies in ALS expected
Reticulon 4 (Nogo-A) inhibitor (GSK1223249)[v]	Promotes neurite growth	Phase 1 study	Study to be completed in 2011

ALS=amyotrophic lateral sclerosis. HSP=heat shock protein. FALS=familial ALS. VEGF=vascular endothelial growth factor. iPS=induced pluripotent stem. SC=spinal cord. FDA=US Food and Drug Administration.

Table 1: Summary of ALS therapeutic targets being tested in clinical trials

Panel 6: Controversy in ALS—alternative and off-label treatments

Given the terminal nature of ALS, the fact that patients are often willing to experiment with unproven therapies is not surprising. Popular alternative and off-label treatments have included insulin-life growth factor-1, lithium carbonate,[70] minocycline,[3,66] and stem-cell therapy. Patients should take caution when starting alternative and off-label treatments. As identified by some ALS clinical trials, some treatments can accelerate the progression of muscle weakness and negatively affect survival.

To keep the ALS community informed of available alternative and off-label treatments, an internet-based initiative, ALSUntangled, has been established recently.[3,65] ALSUntangled enables the exchange of information about new alternative and off-label treatments between patients with ALS and clinicians. Patients with ALS are encouraged to share newly hypothesised alternative and off-label treatments, as the goal of this initiative is to consolidate and convey information about cost, scientific and ethical basis, and potential benefits and risks of every so-called treatment.

ALS=amyotrophic lateral sclerosis.

Terapie sintomatiche

- Scialorrea
- Secrezioni bronchiali
- Sintomi affettivi pseudobulbari
- Crampi
- Spasticità
- Dolore
- Insonnia
- Depressione
- Ansia

Panel 5: Symptomatic care in ALS

Weakness and disability
- Orthotics (eg, ankle foot orthosis, neck collars)
- Physiotherapy
- Adaptive aids (eg, walking frame, wheelchair)

Dysphagia
- Assessment by speech therapist and dietitian
- Safe swallowing techniques and modified diet
- Insertion of gastrostomy tube

Dyspnoea and poor cough
- Ventilatory support
- Morphine or benzodiazepines
- Chest physiotherapy
- Suction machine
- Manually assisted coughing techniques

Pain (ie, musculoskeletal pain and cramps, fasciculations and spasticity, skin pressure pain caused by immobility)
- Physiotherapy, NSAIDs
- Muscle relaxants (baclofen, botulinum toxin)
- Anticonvulsants (eg, gabapentin)
- Re-positioning and pressure area care
- Opioid drugs
- Pressure-relieving cushions and mattress

Dysarthria
- Assessment by speech pathologist
- Communication aids
- Educate family and caregivers

Cognitive changes (frontal lobe dysfunction or dementia)
- Explain symptomatology to caregivers and family
- Antidepressant therapies

Sialorrhoea
- Anticholinergic antidepressants (eg, amitriptyline)
- Anticholinergic drugs (eg, glycopyrronium bromide)
- Botulinum toxin injections
- Radiation of salivary glands
- Mouth-care products
- Suction

Thickened saliva
- Natural remedies (eg, papaya)
- Ensure adequate hydration
- Saline nebulisers; nebulised *N*-acetylcysteine
- Suctioning of the mouth
- Mouth care

Emotional lability
- Educate patients with ALS and caregivers
- Amitriptyline
- Benzodiazepines
- Dextromethorphan hydrobromide/quinidine sulfate

Depression and anxiety
- Counselling
- Benzodiazepines
- Antidepressants

Sleep disturbance
- Treat underlying problem
- Respiratory review, non-invasive ventilation
- Benzodiazepines, tricyclic antidepressants

Constipation
- Dietary changes (eg, increase fluid and fibre intake)
- Use formulations high in bran, bulk, or fibre
- Regular oral aperients (Movicol [Norgine, the Netherlands] or suppositories).

ALS=amyotrophic lateral sclerosis. Data from Andersen and colleagues[43] and Miller and colleagues.[213]

Riabilitazione

Obiettivo:

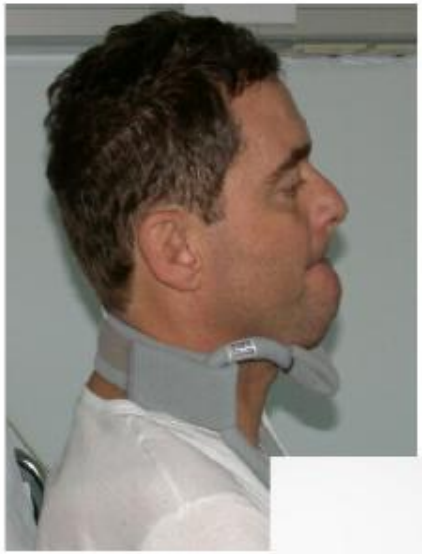
Limitare i danni secondari dovuti alla perdita di mobilità

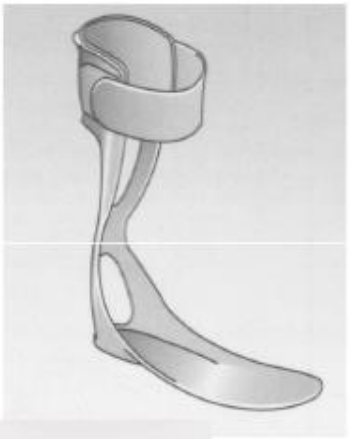
L'immobilità può essere causa di retrazioni muscolo-tendinee, limitazioni o rigidità articolari che a lungo andare possono evolvere in forme dolorose. Dedicare un po' di tempo ad un programma quotidiano di mobilizzazione attiva, attiva-assistita o passiva, abbinato al mantenimento di posizioni corrette a letto, seduti, in piedi può ovviare a questi inconvenienti. Ogni programma chinesiterapico deve tener conto di due regole fondamentali:

- non superare la soglia dell'affaticamento
- non superare la soglia del dolore

Addestrare i parenti alla corretta assistenza, ai passaggi posturali e ai trasferimenti

Ausili



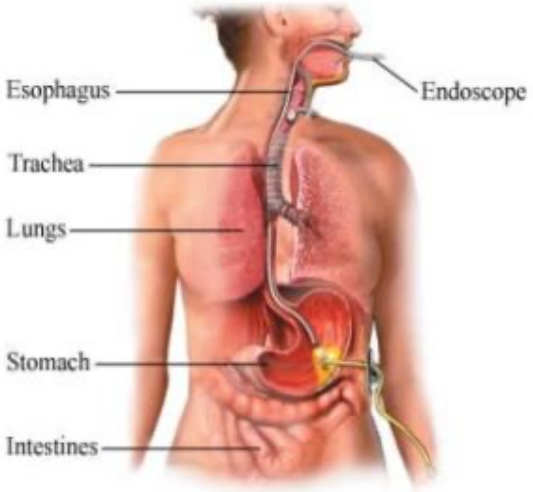


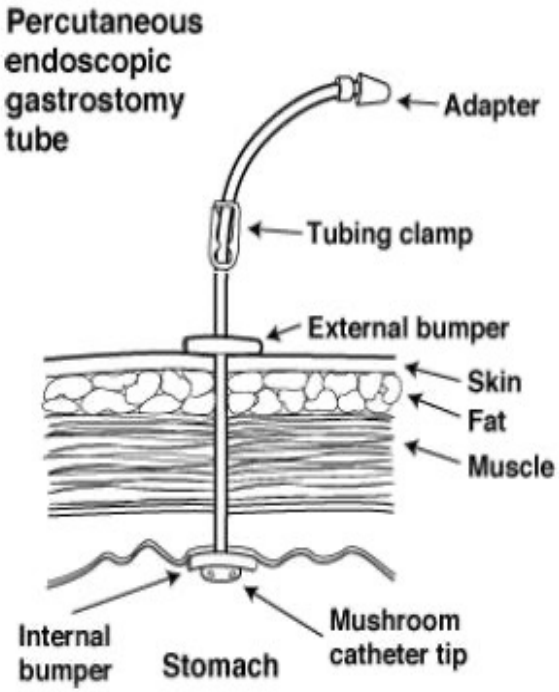
La nutrizione

Trattamento della disfagia

- Consigli comportamentali
- Modificazione della consistenza della dieta
- Nutrizione enterale PEG/RIG

PEG





La respirazione

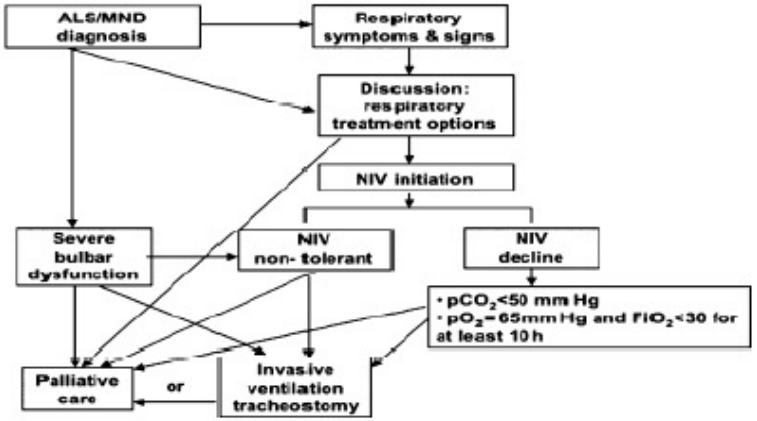
Interventi sulla funzione respiratoria

- Ginnastica respiratoria
- Insufflator-exsufflator (colpo di tosse indotto)
- Ventilazione non invasiva
- Ventilazione mediante tracheostomia

Table 9 Proposed criteria for NIV [modified from Leigh *et al.* (2003)]

1 Symptoms related to respiratory muscle weakness. At least one of the following:
  (a) Dyspnoea
  (b) Orthopnoa
  (c) Disturbed sleep not because of pain
  (d) Morning headache
  (e) Poor concentration
  (f) Loss of appetite
  (g) Excessive daytime sleepiness (ESS > 9)
2 Signs of respiratory muscle weakness (FVC < 80% or SNP < 40 cm H_2O)
3 Evidence of either:
  (a) Significant nocturnal desaturation on overnight oximetry, *or*
  (b) Morning blood-gas pCO2 >6.5 Kpa.

ESS, Epworth Sleepiness Score.

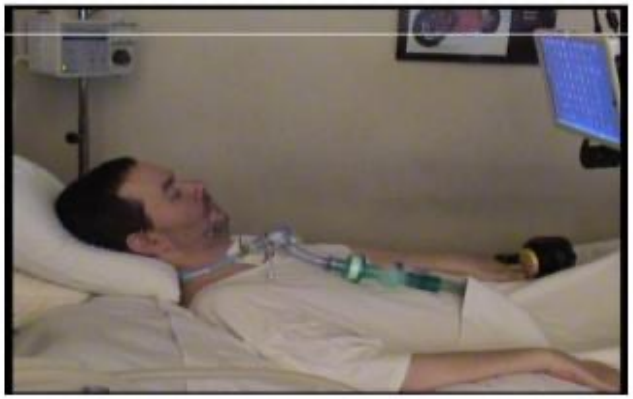


Comunicazione aumentativa/alternativa

- La disartria evolve fino alla perdita completa di una fonazione utile (anartria)

- La comunicazione può essere mantenuta attraverso accorgimenti che vanno dall'uso di carta e penna a comunicatori computerizzati

Strumenti di comunicazione ad alta tecnologia



Il supporto psicologico

- Assistenza psicologica individuale per i pazienti e i familiari che ne facciano richiesta
- Organizzazione di gruppi di auto-aiuto rivolti ai familiari
- Organizzazione di corsi informativi sulla malattia per pazienti, parenti, medici di base, etc.
- Incontri di supervisione con i medici coinvolti nell'attività per la SLA

Scelte di fine vita

- Tracheostomia
- Testamento biologico
- Interventi palliativi di sollievo della fase finale di soffocamento

Assistenza nelle fasi terminali

Presa incarico del paziente SLA in fase terminale da parte d di 'UO Cure Palliative

Gestione del paziente preferenzialmente al domicilio

Se necessario ricovero in Hospice

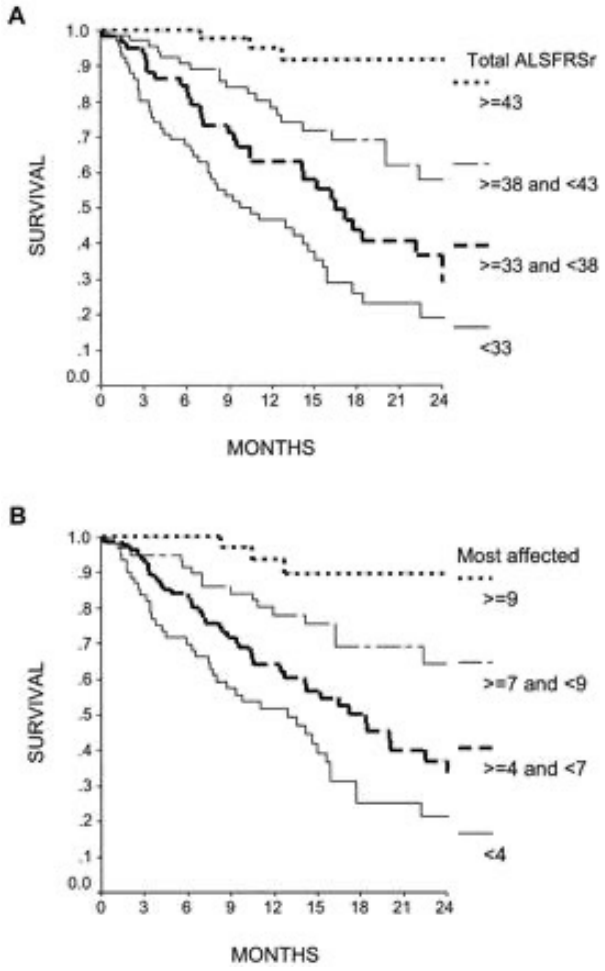
ALSFRS-R

ALS Functional Rating Scale

Patient_____**Pt #**_____

Rate each task on a five-point scale from **0 = can't do**, to **4 = normal ability**. Individual item scores are summed to produce a reported score of between **0 = worst** and **48 = best**.

Domain	Level of Functional Impairment	Score
Speech	4- Normal speech processes 3- Detectable speech disturbance 2- Intelligible with repeating 1- Speech combined with non-vocal communication 0- Loss of useful speech	
Salivation	4- Normal 3- Slight but definite excess of saliva in mouth; may have nighttime drooling 2- Moderately excessive saliva; may have minimal drooling 1- Marked excess of saliva with some drooling 0- Marked drooling; requires constant tissue or handkerchief	
Swallowing	4- Normal eating habits 3- Early eating problems; occasional choking 2- Dietary consistency changes 1- Needs supplemental tube feeding 0- NPO (exclusively parenteral or enteral feeding)	
Handwriting	4- Normal 3- Slow or sloppy; all words are legible 2- Not all words are legible 1- Able to grip pen but unable to write 0- Unable to grip pen	
Cutting Food	4- Normal 3- Somewhat slow and clumsy, but no help needed 2- Can cut most foods, although clumsy and slow; some help needed 1- Food must be cut by someone, but can still feed slowly 0- Needs to be fed	
Dressing and Hygiene	4- Normal function 3- Independent and complete self-care with effort or decreased efficiency 2- Intermittent assistance or substitute methods 1- Needs attendant for self-care 0- Total dependence	
Turning in Bed	4- Normal 3- Somewhat slow and clumsy, but no help needed 2- Can turn alone or adjust sheets, but with great difficulty 1- Can initiate, but not turn or adjust sheets alone 0- Helpless	



King's Staging System

Stadiazione clinica utilizzante la diffusione

STADIO 1 : Prima regione interessata

STADIO 2 : Seconda regione interessata

STADIO 3 : Terza regione interessata

STADIO 4 : Necessità di Intervento

STADIO 4A Gastrostomia | *STADIO 4B NIV*

STADIO 5 : Decesso

RESEARCH PAPER

The MITOS system predicts long-term survival in amyotrophic lateral sclerosis

Irene Tramacere,[1] Eleonora Dalla Bella,[2] Adriano Chiò,[3] Gabriele Mora,[4] Graziella Filippini,[1] Giuseppe Lauria,[2] on behalf of the EPOS Trial Study Group

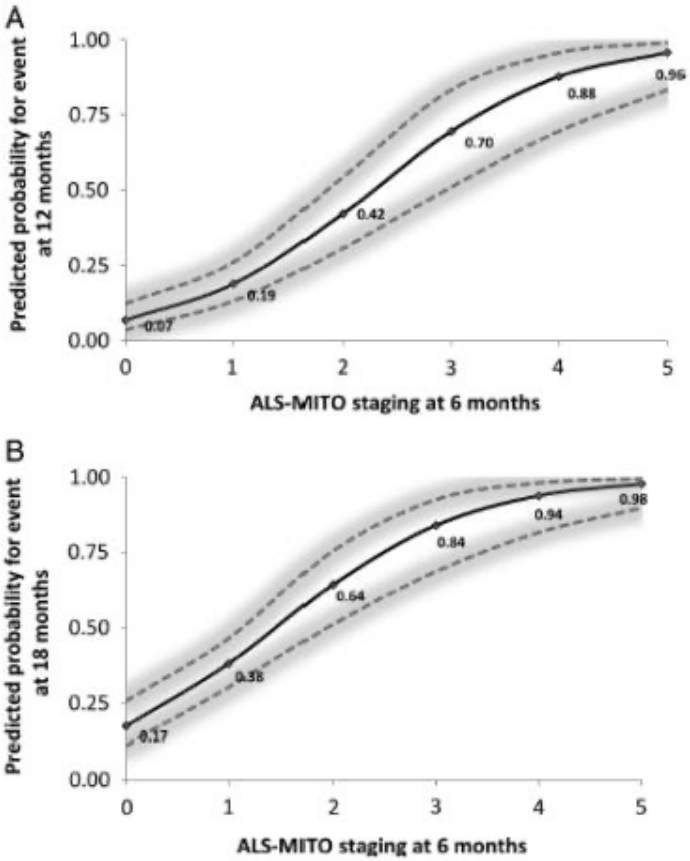


Figure 4 Predicted probability with the corresponding 95% CI of ALS-MITO staging at 6 months for event at 12 months (A) and at 18 months (B). ALS, amyotrophic lateral sclerosis; ALS-MITO, ALS Milano-Torino.

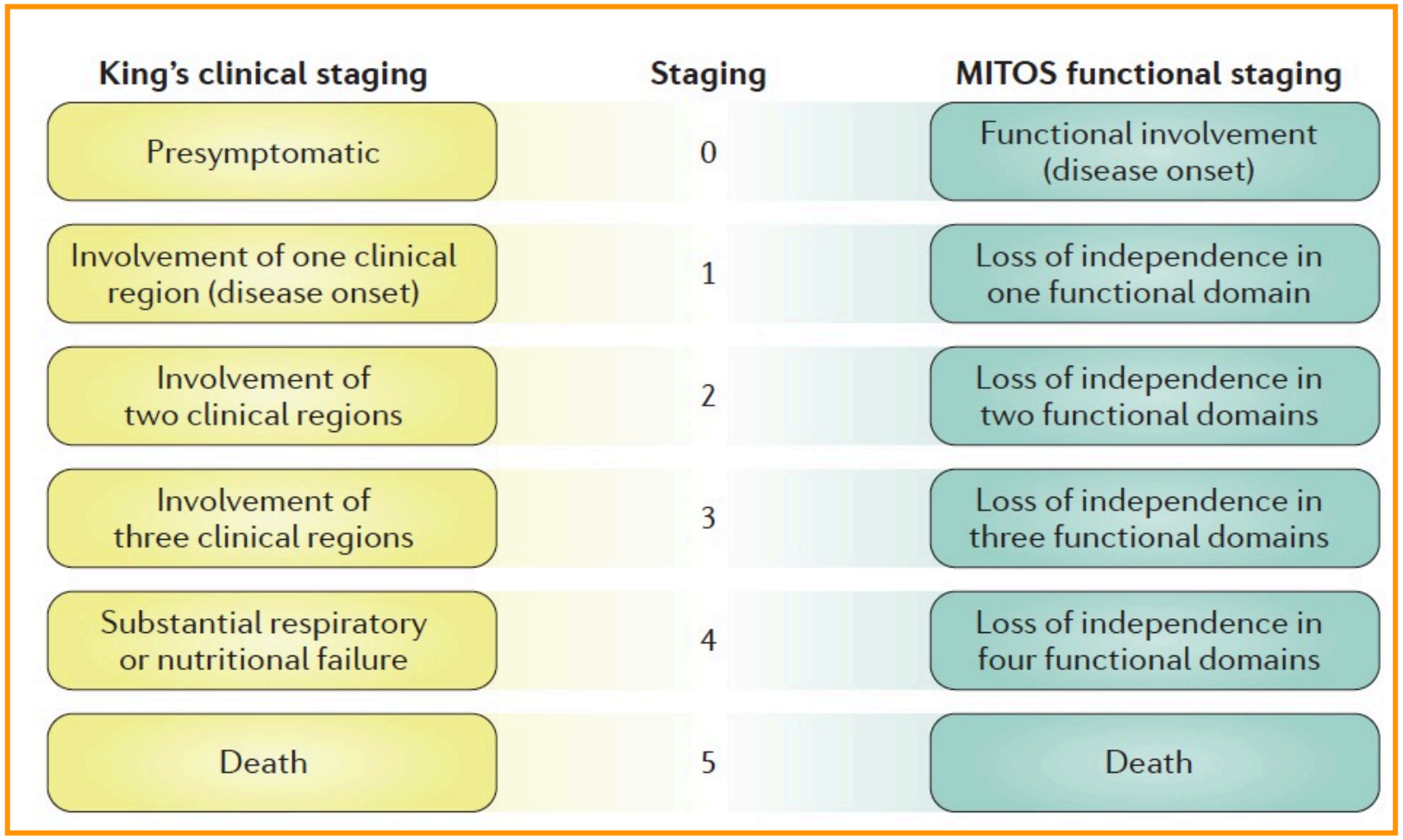
RESEARCH PAPER

Development and evaluation of a clinical staging system for amyotrophic lateral sclerosis

Adriano Chiò,[1] Edward R Hammond,[2] Gabriele Mora,[3] Virginio Bonito,[4] Graziella Filippini[5]

Table 1 Functional domains and stages

ALSFRS domain	Item	Score	Functional score*
Movement (walking/self-care)†	8	4 Normal	0
	Walking	3 Early ambulation difficulties	
		2 Walks with assistance	
		1 Non-ambulatory functional movement only	1
	OR	0 No purposeful leg movement	
	6	4 Normal function	0
	Dressing and hygiene	3 Independent and complete self-care with effort or decreased efficiency	
		2 Intermittent assistance or substitute methods	
		1 Needs attendant for self-care	1
		0 Total dependence	
Swallowing	3	4 Normal eating habits	0
	Swallowing	3 Early eating problems; occasional choking	
		2 Dietary consistency changes	
		1 Needs supplemental tube feeding	1
		0 NPO (exclusively parenteral or enteral feeding)	
Communicating†	1	4 Normal speech processes	0
	Speech	3 Detectable speech with disturbances	
		2 Intelligible with repeating	
		1 Speech combined with non-vocal communication	1
	AND	0 Loss of useful speech	
	4	4 Normal	0
	Handwriting	3 Slow or sloppy; all words are legible	
		2 Not all words are legible	
		1 Able to grip pen but unable to write	1
		0 Unable to grip pen	
Breathing†	10	4 None	0
	Dyspnea	3 Occurs when walking	
		2 Occurs with one or more of: eating, bathing, dressing	
		1 Occurs at rest, difficulty breathing when either sitting or lying	1
	OR	0 Significant difficulty, considering using mechanical respiratory support	
	12	4 None	0
	Respiratory insufficiency	3 Intermittent use of NIPPV	
		2 Continuous use of NIPPV during the night	1
		1 Continuous use of NIPPV during the night and day	
		0 Invasive mechanical ventilation by intubation or tracheostomy	
ALS-MITOS	Stage	Functional domains lost	
	0	None	
	1	1 domain	
	2	2 domains	
	3	3 domains	
	4	4 domains	
	5	Death	



Hardiman et al., 2017

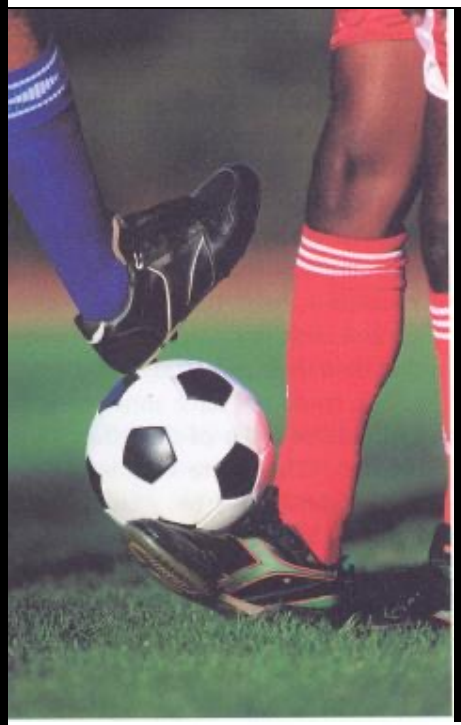
Valutazione del grado di disabilità nelle malattie neurologiche ad interessamento neuromuscolare

Funzioni		**I colonna** (stadio A)	**II colonna** (stadio B)	**III colonna** (stadio C)	**IV colonna** (stadio D)
Principali	*Secondarie*	Deficit moderato (34 – 66%)	Deficit medio-grave (67 – 80%)	Deficit grave (81 – 99%)	Deficit completo (100%: accompagnamento)
Motricità	Deambulazione	Autonoma ma rallentata e faticosa	Rallentata e con necessità di appoggio di sicurezza	Perdita sub-completa della capacità di camminare autonomamente	Perdita completa della capacità di camminare
	Vestizione	Autonoma e completa, ma imprecisa e difficoltosa	Non sempre autonoma e con necessità di assistenza occasionale	Necessità di assistenza sub-continua	Dipendenza totale
Comunicazione	Scrittura	Rallentata e/o imprecisa ma comprensibile	Rallentata e imprecisa, talora difficilmente comprensibile	Perdita della capacità di scrivere a mano	Perdita della capacità di scrivere su tastiera
	Parola	Dislalia occasionale, linguaggio comprensibile	Dislalia sub-continua, linguaggio talora difficilmente comprensibile	Dislalia continua con linguaggio incomprensibile	Perdita della verbalizzazione
Alimentazione		Disfagia occasionale o sporadica	Disfagia con necessità di modificazioni della consistenza della dieta	Necessità di nutrizione enterale con gastrostomia	Nutrizione esclusivamente enterale o parenterale
Respirazione		Dispnea in attività fisiche moderate	Dispnea in attività fisiche minimali (necessita di assistenza ventilatoria intermittente e/o notturna)	Dispnea a riposo (necessita di assistenza ventilatoria intermittente e/o notturna)	Dipendenza assoluta dal respiratore

Classificazione Regione Lombardia

Reflection & Reaction

The sinister side of Italian soccer



- 24.000 Italian soccer professional (1960-1997)
- 8 ALS
- cases expected: 0.61
- ten-fold increase in risk
- details of cases after 1997 protected under pretrial investigation
- 30 ALS cases reported by newspapers
- in 7.325 soccers (1970-2001) SMR 6.5, 5 cases vs 0,77 expected (Chiò et al., 2005)

THE LANCET Neurology Vol 2 November 2003


Other side of the coin...

Istituto psichiatrico e neuropatologico della R. Università di Napoli
diretto dal Prof. L. BIANCHI

I DISTURBI PSICHICI

NELLA SCLEROSI LATERALE AMIOTROFICA

NOTA CLINICA

DEL

dott. O. FRAGNITO
Libero docente e aiuto

Annali di Neurologia, 25, 273-287, 1907

Ospedale Psichiatrico Provinciale di Roma
Direttore Prof. Dott. Francesco Bonfiglio

Un caso di sclerosi laterale amiotrofica con demenza.

Contributo allo studio delle lesioni corticali nella malattia di Charcot

Dott. Diego de Caro - Assistente

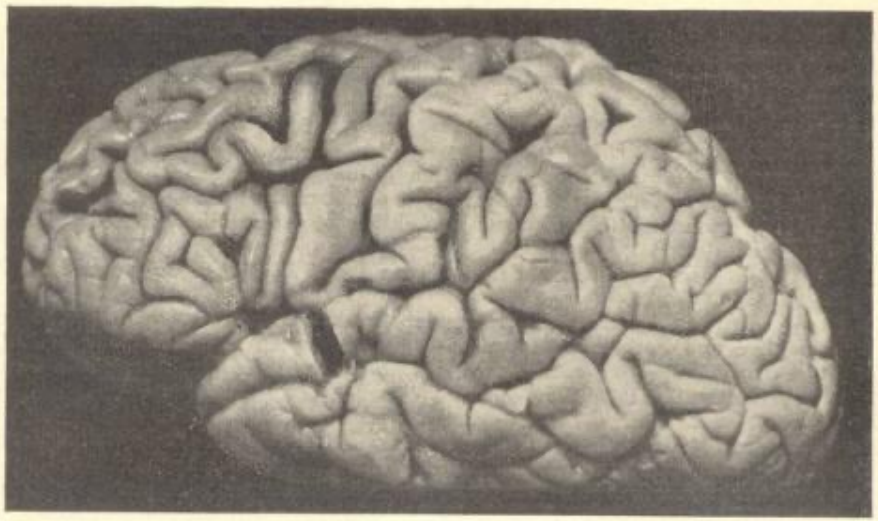


Fig. 1
Emisfero sinistro del cervello. È evidente l'atrofia del lobo prefrontale. La circonvoluzione frontale ascendente è normalmente sviluppata.

Journal of Neurology, Neurosurgery, and Psychiatry 1984;**47**:953–959

Presenile dementia with motor neuron disease in Japan: clinico-pathological review of 26 cases

YOSHIO MITSUYAMA

From the Department of Psychiatry, Miyazaki Medical College, Miyazaki, Japan

SUMMARY The clinico-pathological findings of 26 cases of presenile dementia with motor neuron disease in Japan are reviewed. The characteristic features include: (1) Progressive dementia with slowly progressive onset in the presenile period. (2) Neurogenic muscular wasting during the course of illness. (3) A duration of illness to death of from one to three years. (4) Absence of extrapyramidal symptoms and definite sensory deficits. (5) No characteristic abnormalities in the CSF or EEG. (6) No known parental consanguinity of familial occurrence. (7) Non-specific mild degenerative changes throughout the CNS without evidence of cerebrovascular disease or primary degenerative dementia, but with the presence of pathological findings of motor neuron disease. The possibility that this is a new disease entity is suggested.

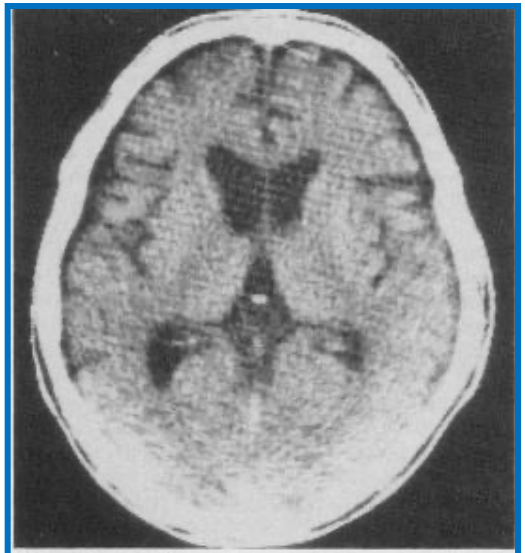


Fig 6 *Case 3; CT scan shows moderate cerebral atrophy.*

ALS-FTSD: clinical continuum (2017)

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2016; 1–22

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

Amyotrophic lateral sclerosis - frontotemporal spectrum disorder (ALS-FTSD): Revised diagnostic criteria

MICHAEL J. STRONG[1], SHARON ABRAHAMS[2], LAURA H. GOLDSTEIN[3], SUSAN WOOLLEY[4], PAULA MCLAUGHLIN[5], JULIE SNOWDEN[6], ENEIDA MIOSHI[7], ANGIE ROBERTS-SOUTH[8], MICHAEL BENATAR[9], TIBOR HORTOBÁGYI[10], JEFFREY ROSENFELD[11], VINCENZO SILANI[12], PAUL G INCE[13] & MARTIN R. TURNER[14]

Table 2. Application of Axis I and Axis II diagnostic classification for ALS and ALS-FTSD (modified from Strong et al., 2009) (2).

Heading	Subheadings	Existing, synonymous terms within the literature	Characteristics
Axis I. Motor neuron disease variant			
ALS	Sporadic ALS	sALS, classic ALS, Charcot disease, motor neuron disease	A progressive motor system disorder with both UMN and LMN involvement, with the degree of diagnostic certainty further defined by either the El Escorial criteria (revised) (6) or the Awaji criteria (9).
	genetic ALS	gALS; familial ALS (fALS)	As indicated for sporadic ALS with the additional components: 1. Confirmed ALS associated genetic mutation, or 2. Clinical evidence of autosomal dominant, autosomal recessive, or X-linked inheritance
	Western Pacific ALS	Lytico bodig	ALS arising within a hyper-endemic region of the western Pacific (e.g., Kii Peninsula, Guam, Rota)
Axis II. Neuropsychological characterisation			
ALSbi			A diagnosis of ALSbi requires: 1. The identification of apathy with or without other behaviour change OR 2. meeting at least two non-overlapping supportive diagnostic features from the Rascovsky criteria (37)
ALSci			A diagnosis of ALSci depends on evidence of either executive dysfunction (including social cognition) or language dysfunction or a combination of the two.
			OR 3. The presence of at least 2 of those behavioural/cognitive symptoms, together with loss of insight and/or psychotic symptoms OR 4. The presence of language impairment meeting criteria for semantic dementia/ semantic variant PPA or non-fluent variant PPA. This may co-exist with behavioural/ cognitive symptoms as outlined above.
ALS-dementia		ALS-D*	ALS with dementia, not typical of FTD
	ALS-AD		ALS in association with Alzheimer's disease
	ALS-vascular dementia		ALS in association with vascular dementia (185)
	ALS-mixed dementia		ALS in association with a mixed dementia (e.g., AD-vascular dementia)
FTD-MND-like			A neuropathological diagnosis in which FTLD is the primary diagnosis but in which there is neuropathological evidence of motor neuron degeneration, but insufficient to be classified as ALS
ALS-Parkinsonism-dementia-complex		Western Pacific variant of ALS; lytico Bodig	ALS concurrent with dementia and/or Parkinsonism occurring in hyperendemic foci of the western Pacific

Strong et al., 2017

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2016; 1–10

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

The validation of the Italian Edinburgh Cognitive and Behavioural ALS Screen (ECAS)

BARBARA POLETTI[1]*, FEDERICA SOLCA[1]*, LAURA CARELLI[1], FABIANA MADOTTO[2], ANNALISA LAFRONZA[1], ANDREA FAINI[3], ALESSIA MONTI[4], STEFANO ZAGO[5], DANIELA CALINI[1], CINZIA TILOCA[1], ALBERTO DORETTI[1,6], FEDERICO VERDE[1,6], ANTONIA RATTI[1,6], NICOLA TICOZZI[1,6], SHARON ABRAHAMS[7]* & VINCENZO SILANI[1,6]*

EDINBURGH COGNITIVE AND BEHAVIOURAL ALS SCREEN – ECAS

Versione Italiana - Poletti et al. (2016)

Data dell'esame: .....
Anni di scolarità: .....
Professione: .....
.....
Lateralità manuale: .....

Nome: .....
Data di nascita: .....
Indirizzo e numero di telefono: .....
.....
.....

Italian parallel versions B and C (Poletti et al, 2017)

Executive dysfunction is a negative prognostic indicator in patients with ALS without dementia

M. Elamin, MRCP
J. Phukan, PhD
P. Bede, MRCP
N. Jordan, MSc
S. Byrne, MRCP
S. Pender, PhD
O. Hardiman, FRCPI, FAAN

ABSTRACT

Background: The prognostic implications of cognitive impairment in amyotrophic lateral sclerosis (ALS) are not established.

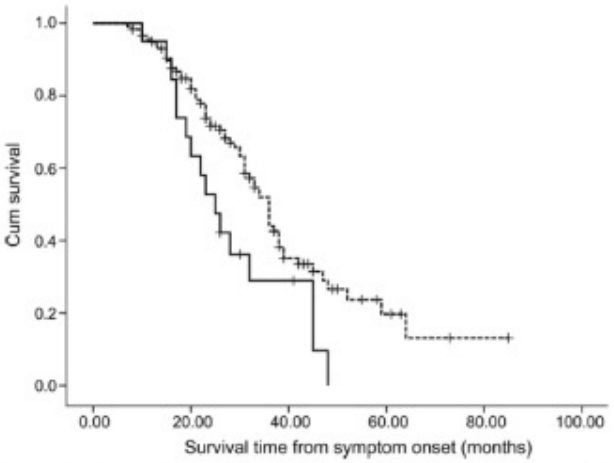
Objective: To investigate the survival effect of the comorbid frontotemporal dementia (FTD) and to determine whether, in the absence of dementia, impairment in different cognitive domains affects outcome.

Methods: A prospective population-based study of incident cases of ALS in the Republic of Ireland included home-based neuropsychological assessments using age-, sex-, and education-matched controls. Four cognitive domains were evaluated: executive function, memory, language, and visuospatial skills.

Results: Mean age of the participants (n = 128) was 63.3 years; 61.2% were male and 31.3% had bulbar onset ALS. Factors associated with shorter survival included age more than 60, severe disability at baseline, shorter delay to diagnosis, and early respiratory involvement. Comorbid FTD was associated with significantly shorter survival time (hazard ratio [HR] 2.67, 95% confidence interval [CI] 1.04–6.85, $p = 0.041$). In patients with ALS without dementia, the presence of executive dysfunction was significantly associated with shorter survival. This was confirmed in a multivariate model that included age, delay to diagnosis, disease severity at baseline, education, and respiratory status (HR 3.44, 95% CI 1.45–8.16, $p = 0.005$). In the absence of executive dysfunction, single or multi-domain impairment in other cognitive domains had no significant effect on survival.

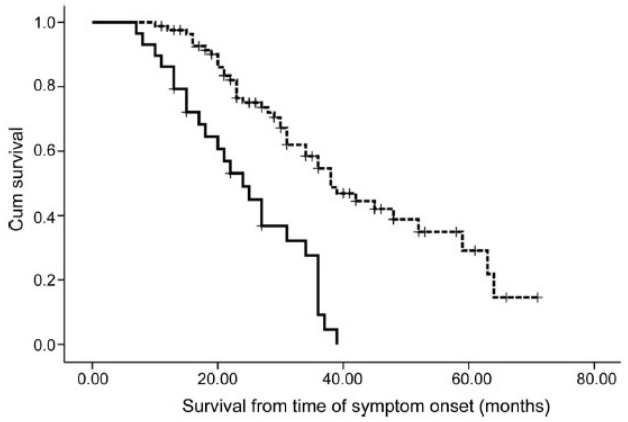
Conclusions: Comorbid frontotemporal dementia is a negative prognostic indicator. In patients with ALS without dementia, executive dysfunction, but not impairment in other cognitive domains, is an important negative prognostic indicator. Neurology® 2011;76:1263–1269

Figure 2 Kaplan-Meier plots of survival probabilities for 136 patients with amyotrophic lateral sclerosis (ALS) stratified by presence of comorbid frontotemporal dementia



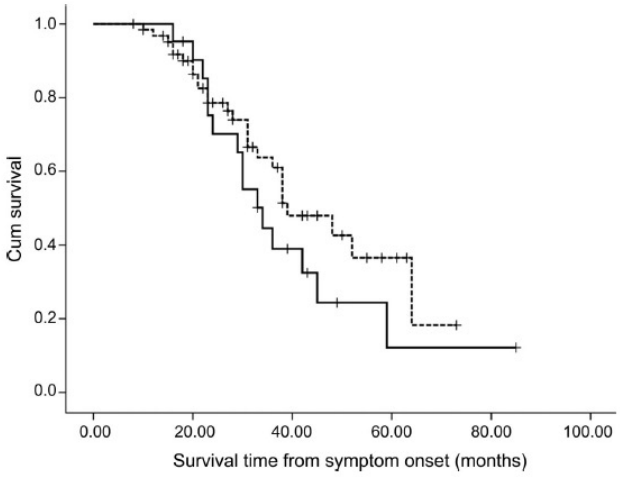
Log-rank test for equality of survival functions, $p = 0.026$. Black line: ALS with comorbid frontotemporal dementia; dotted line: ALS with no evidence of dementia; +: censored cases.

Figure 3 Kaplan-Meier plots of survival probabilities for 113 patients with amyotrophic lateral sclerosis stratified by presence of executive dysfunction



Log-rank test for equality of survival functions, $p < 0.0001$. Black line: patients with executive dysfunction (n = 29); dotted line: patients without executive dysfunction (n = 84); +: censored cases.

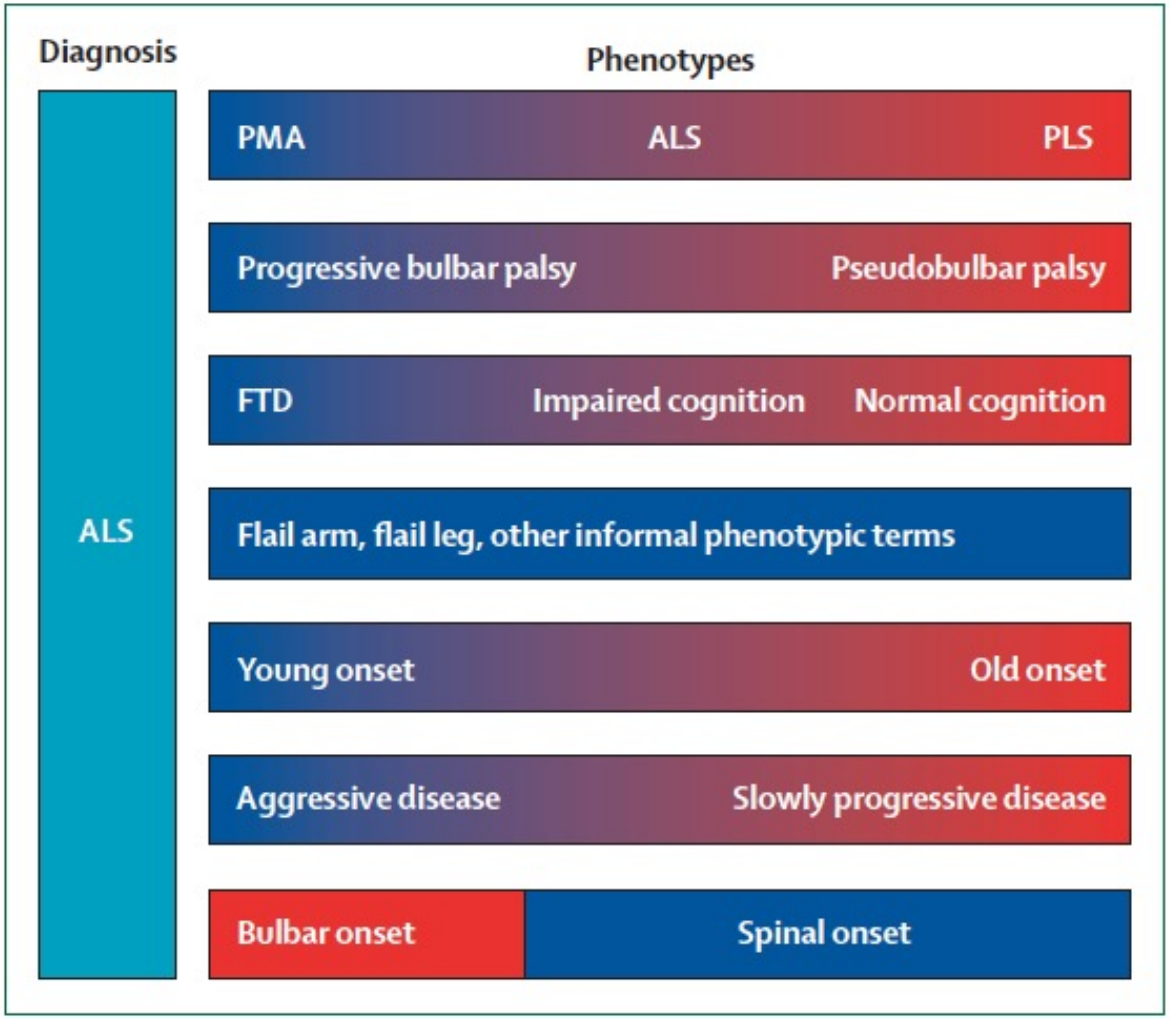
Figure 4 Kaplan-Meier plots of survival probabilities for 84 patients with amyotrophic lateral sclerosis stratified by presence of nonexecutive cognitive impairment



Amyotrophic lateral sclerosis: moving towards a new classification system

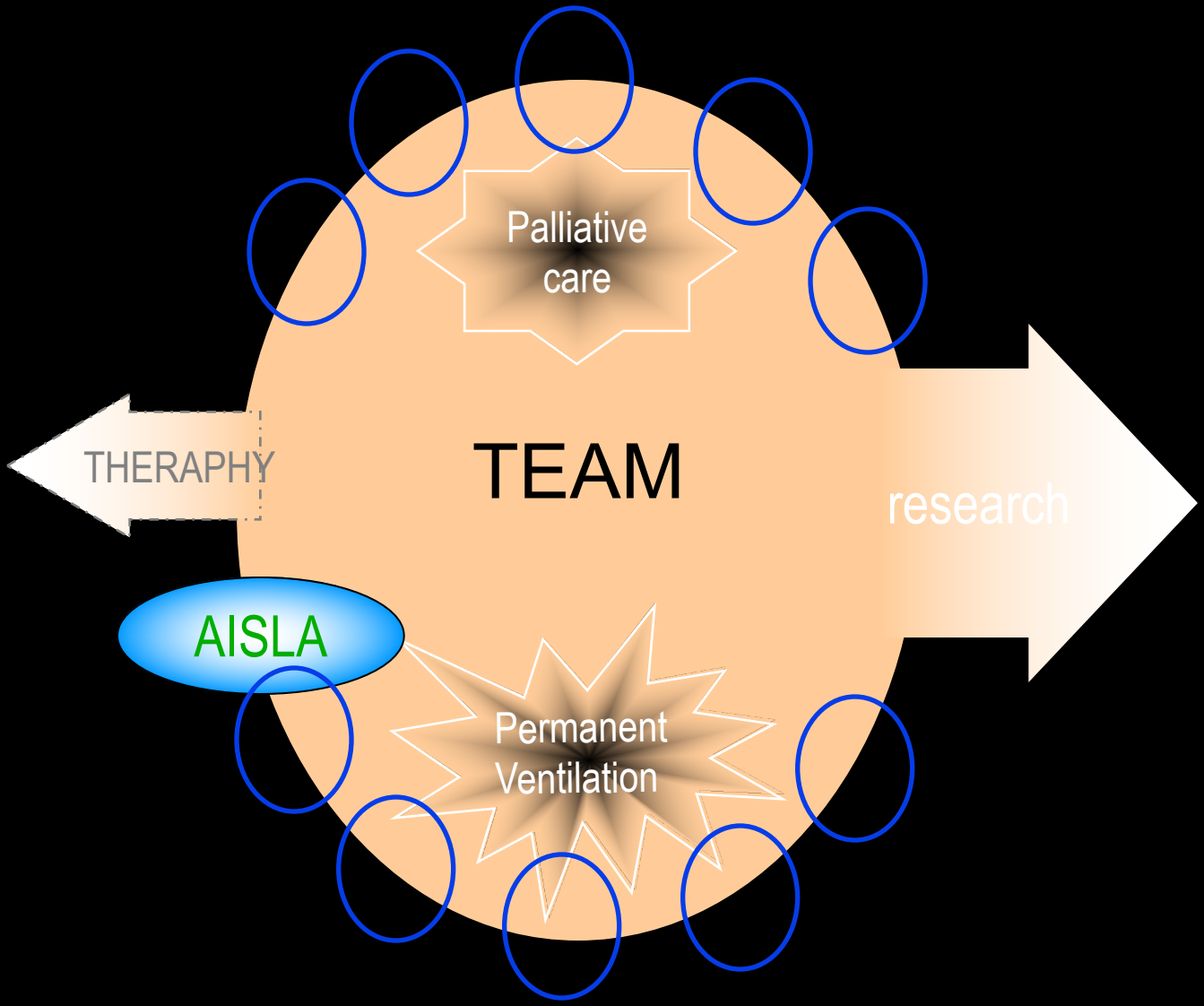
Ammar Al-Chalabi, Orla Hardiman, Matthew C Kiernan, Adriano Chiò, Benjamin Rix-Brooks, Leonard H van den Berg

Lancet Neurol 2016; 15: 1182–94



Diagnosis and phenotypes of amyotrophic lateral sclerosis

e COMUNQUE, per il paziente…..



J Neurol (1998) 245 [Suppl 2]: S13–S19

Vincenzo Silani
Edward J. Kasarskis
Nobuo Yanagisawa

Nutritional management in amyotrophic lateral sclerosis: a worldwide perspective

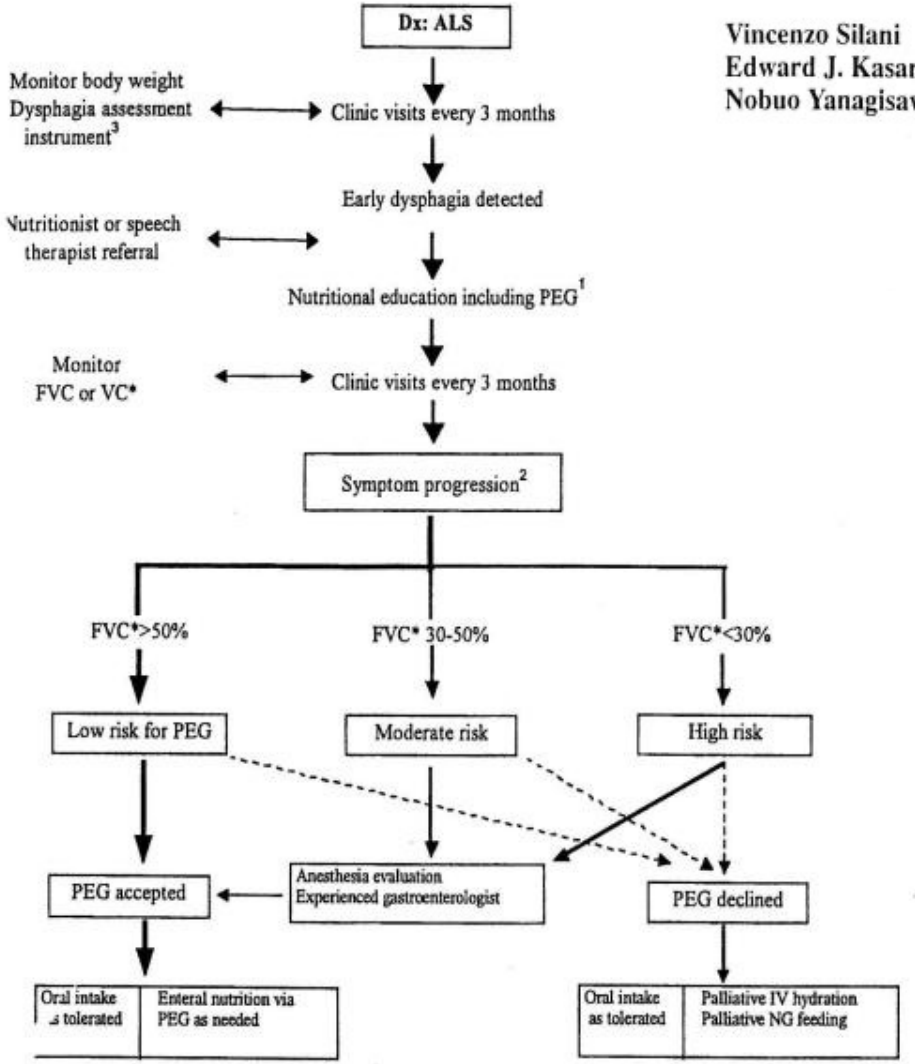


*Figure 2. Algorithm for nutrition management. [1]Rule out contraindications. [2]Prolonged mealtime, ending meal prematurely because of fatigue, accelerated weight loss due to poor caloric intake, family concern about feeding difficulties. *Forced vital capacity (FVC) or vital capacity (VC) can be used. VC may be more accurate in patients with bulbar dysfunction. [3]For example, Colorado Dysphagia Disability Inventory, bulbar questions in the ALS Functional Rating Scale, or other instrument. Dx = diagnosis; PEG = percutaneous endoscopic gastrostomy.*

ENTERAL NUTRITION

NFT

55% prescribed EN, 90% failures

PEG

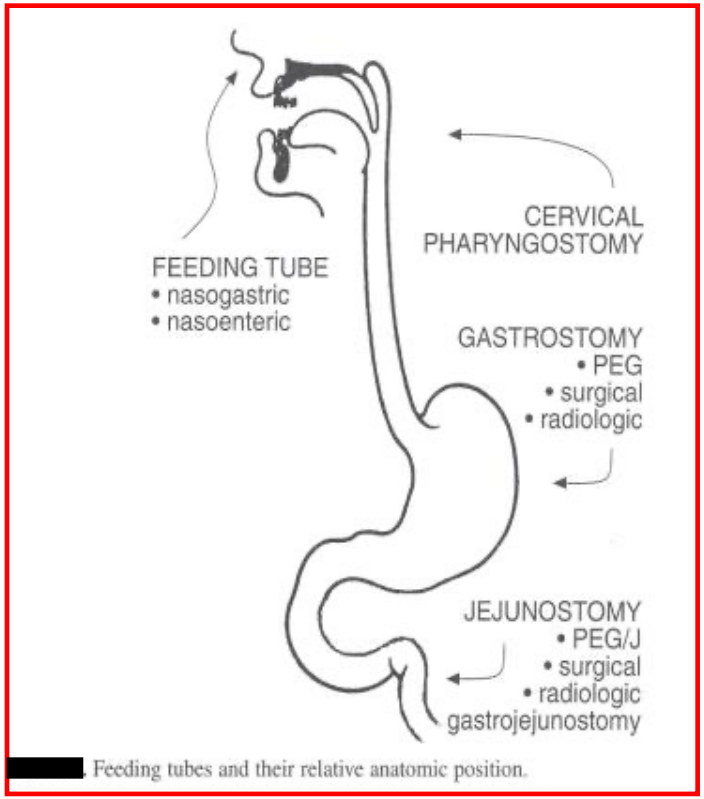
93% prescribed EN, no failure

PEJ

Alternative strategy

RIG/PRG

Better tolerated



[redacted]. Feeding tubes and their relative anatomic position.

Neurology 1999;52:1311–1323

Practice parameter: The care of the patient with amyotrophic lateral sclerosis (an evidence-based review)

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

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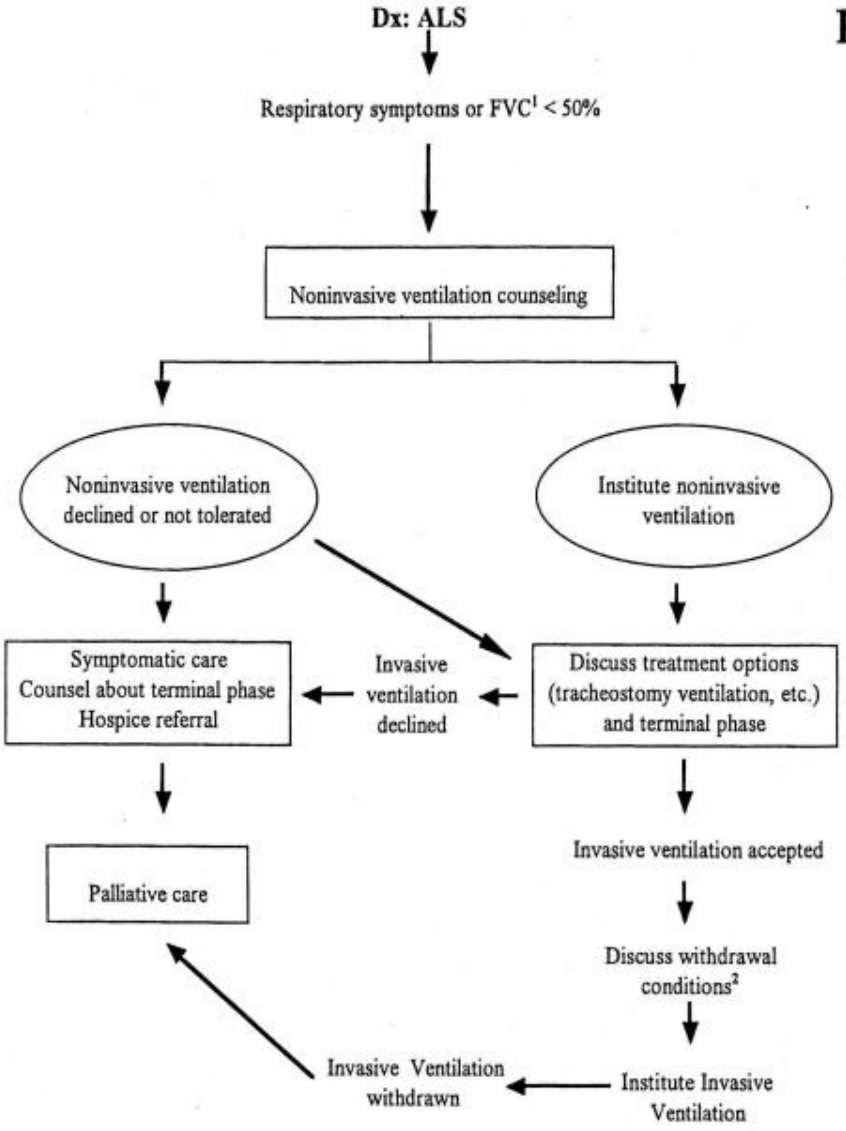
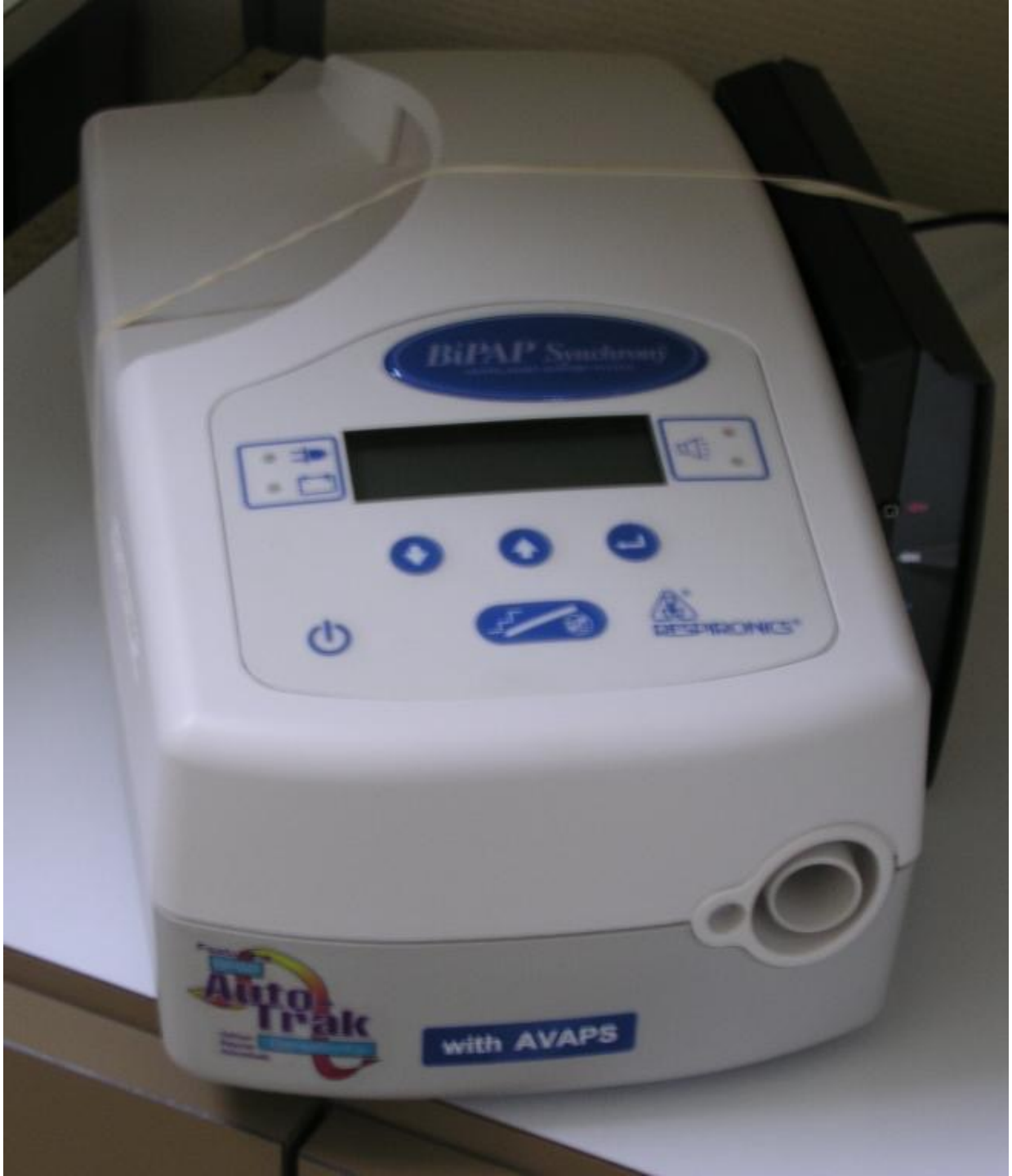
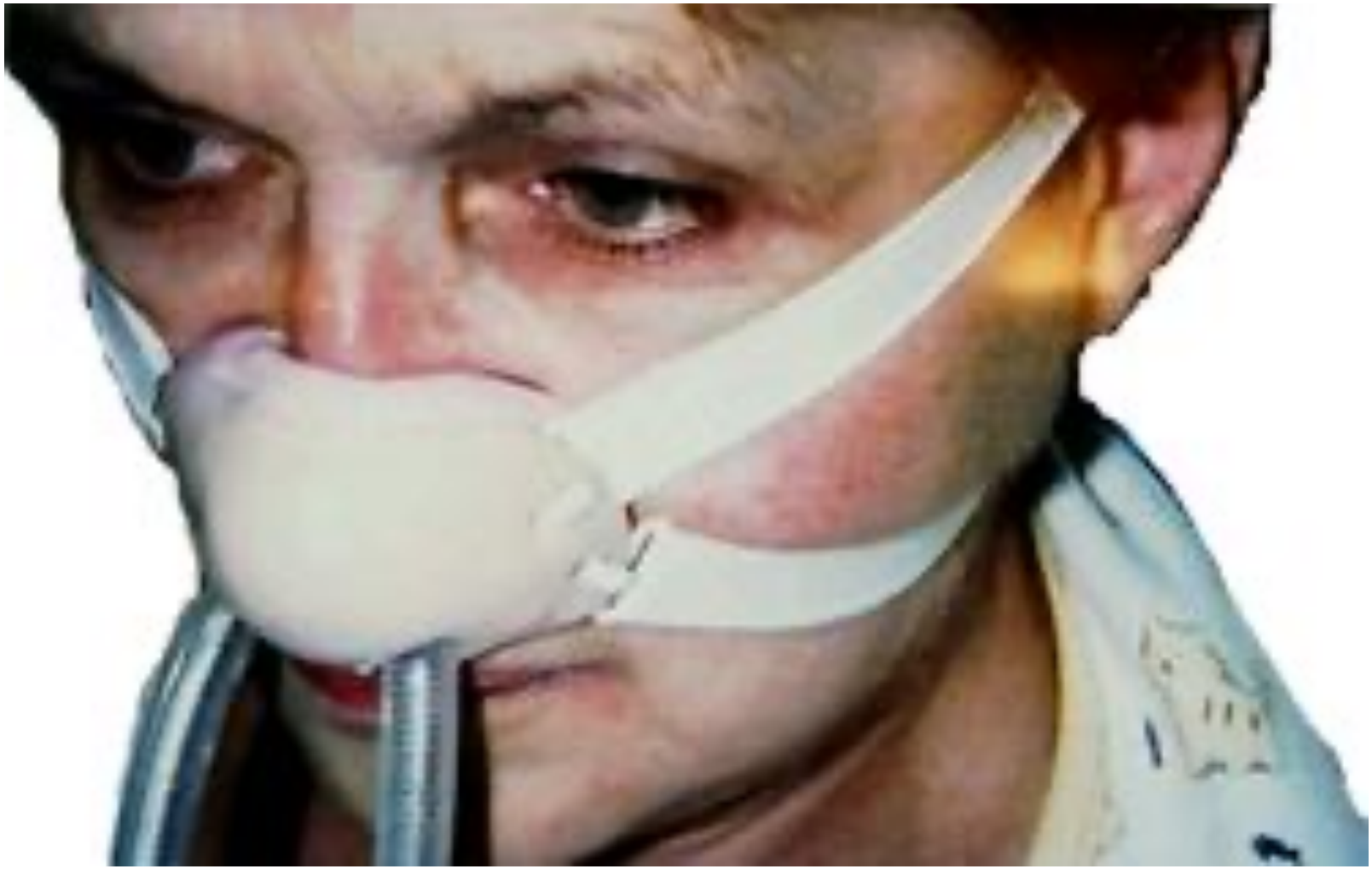
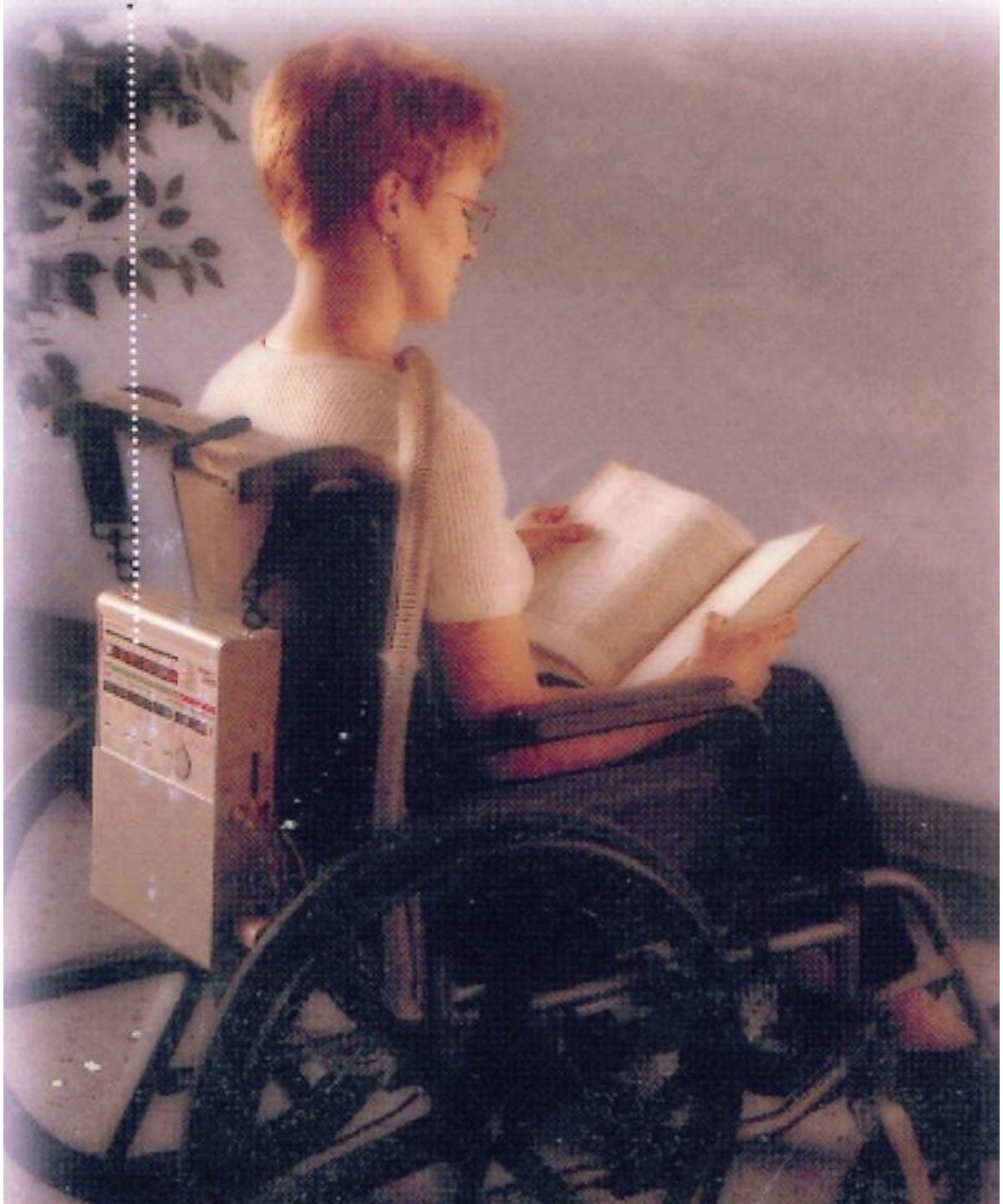


Figure 3. Algorithm for respiratory management. [1]Forced vital capacity (FVC) or vital capacity (VC) can be used. VC may be more accurate in patients with bulbar dysfunction. [2]Agreement needed for conditions of withdrawal prior to or concurrent with instituting invasive ventilation (e.g., locked in state, coma, etc.). Dx = diagnosis.


BiPAP Synchrony
RESPIRONICS
Auto Trak
with AVAPS

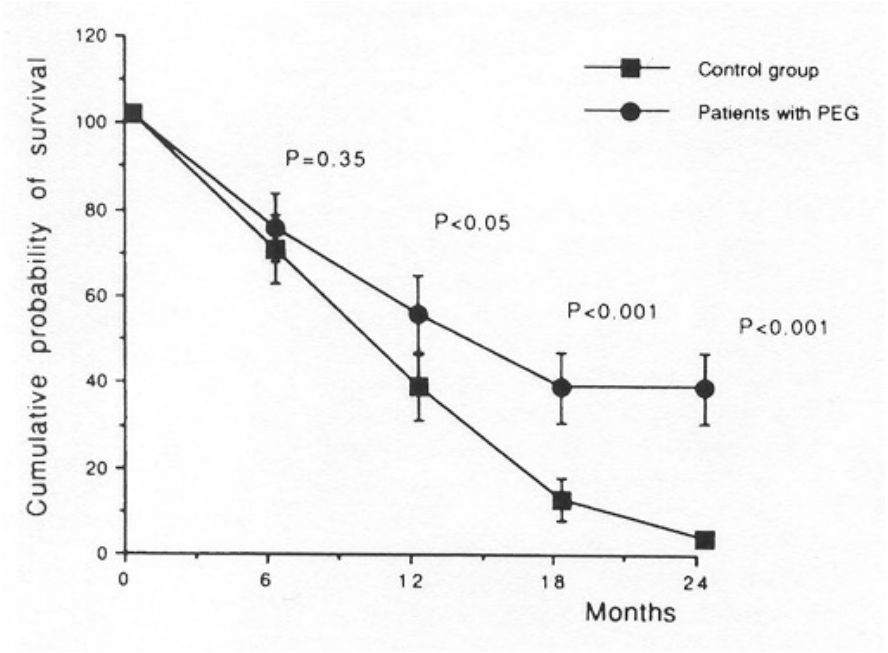


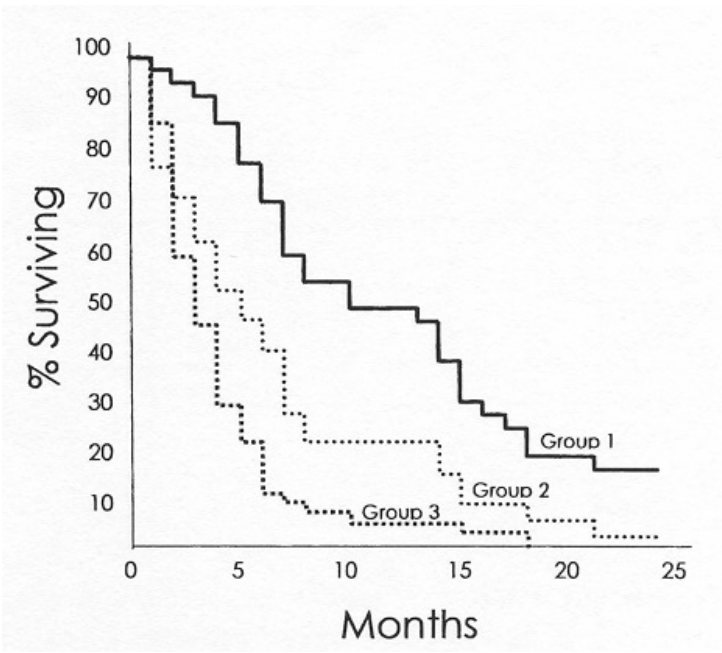


Nutrition and Respiration

Both have potentially profound effects on survival:

PEG (left, from Mazzini et al) and BiPAP (right, from Kleopa et al.)





Symptomatic treatment

- *Scialorrea*

  - Amitriptiline 25-50 mg oral x 3 a day
  - Atropine drops (IV) 0.25-0.75 mg x 3 a day
  - Glycopyrrolate (nebulized or iv form)
  - Scopolamine (oral or dermal patch)
  - Scopolamine transdermal (1.5 mg every 5 days (II)
  - Benztropine (I)
  - Botulinum toxin type A (IV)
  - No study in type B
  - Radiological intervention (IV): external irradiation or low dosage palliative radiation of single fraction of 7-8 Gy

Symptomatic treatment

- *Bronchial secretion*
  - Portable home suction device
  - Mucolytic (guafemesin, N-acetylcysteine)
  - Beta-R antagonist (metoprolol, propanolol)
  - Anticholinergic bronchodilator (ipratropium, theophylline, furosemide)
  - Mechanical cough asisting device (insufflator-exsufflator) via a face mask

Good practice points

1. Teach the patient and carers the technique of assisting expiratory movements using a manual assisted cough (can also be performed by a physical therapist).
2. Provide a portable home suction device and a room humidifier.
3. Consider using a mucolytic like N-acetylcysteine, 200–400 mg three times daily.
4. If these measures are insufficient, try a nebulizer with saline and a β-receptor antagonist and/or an anti-cholinergic bronchodilator and/or a mucolytic and/or furosemide in combination.
5. The use of a mechanical insufflator-exsufflator may be helpful, particularly in the setting of an acute respiratory infection.

Symptomatic treatment

- *Pseudobulbar emotional lability*

  - Dextromethorphan and quinidine (IA)
  - Fluvoxamine
  - Amitriptyline
  - Citalopram
  - Dopamine
  - Lithium

Symptomatic treatment

- *Cramps*

  – Quinine sulphate 200 mg x 2 and vitamin E (I)
  – Physiotherapy
  – Carbamazepine
  – Diazepam
  – Phenytoin
  – Verapamil
  – Gabapentin

Symptomatic treatment

- *Spasticity*

  - Physical therapy (IIB)
  - Hydroterapy in heated pool (III)
  - Cryoterapy
  - Oral baclofen (up to 80 mg daily)
  - Intrathecal baclofen
  - Gabapentin (900-2400 mg daily)
  - Tizanide (6-24 mg daily)
  - Memantine (10-60 mg daily)
  - Dantrolene (25-100 mg daily)
  - Diazepam (10-30 mg daily)
  - Botulin toxin A

Symptomatic treatment

- *Depression, anxiety, and insomnia*
  - Amitriptyline
  - Sertraline
  - Fluoxetine
  - Paroxetine
  - Zolpidem
  - Diazepam
  - Sub-lingual lorazepam

Symptomatic treatment

- *Pain*
  - Paracetamol
  - Weak opioids (tramadol)
  - Strong opioids (morphine or ketobemidon)

Good practice point
Treat pain in ALS following accepted guidelines.

Venous thrombosis
Patients with leg paralysis have an increased risk of venous thrombosis.

Good practice points
Physiotherapy, limb elevation, compression stockings can be used. Prophylactic treatment with anti-coagulants is not recommended.

Palliative and end-of-life care

A palliative care approach should be incorporated into the care plan for patients and carers from the time of diagnosis (Borasio *et al.*, 2001b, class III recommendation). Early referral to a specialist palliative care team is often appropriate.

The aim of palliative care is to maximize quality of life of patients and families by relieving symptoms, providing emotional, psychological and spiritual support as needed, removing obstacles to a peaceful death, and supporting the family in bereavement (Oliver *et al.*, 2000).

8 For symptomatic treatment of dyspnea and/or pain of intractable cause use opioids alone or in combination with benzodiazepines if anxiety is present. Titrating the dosages against the clinical symptoms will almost never result in a life-threatening respiratory depression (Sykes and Thorns, 2003, class IA recommendation).

9 For treating terminal restlessness and confusion because of hypercapnia neuroleptics may be used, (e.g. chlorpromazine 12.5 mg every 4–12 h po, iv or pr).

Good practice points

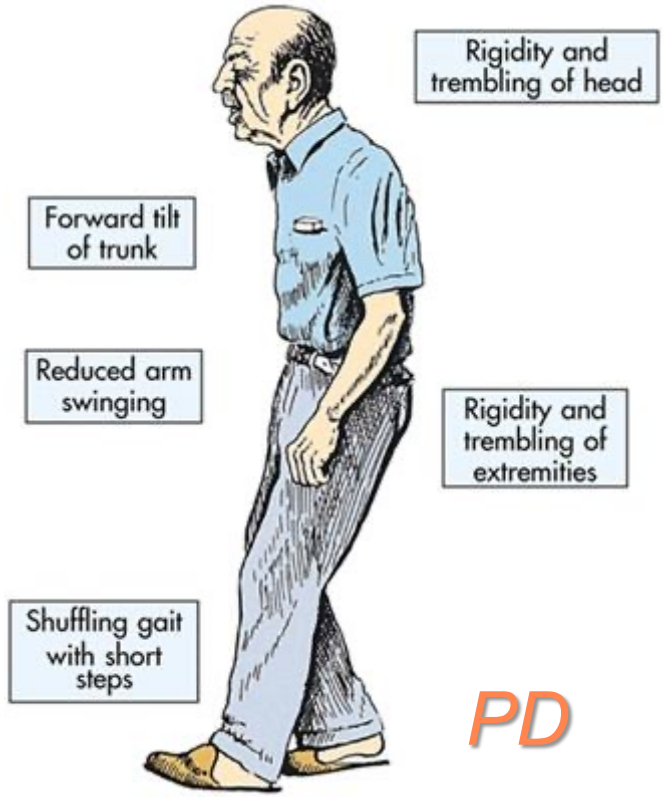
2 Initiate discussions on end-of-life decisions whenever the patient asks – or 'opens the door' – for end-of-life information and/or interventions.

4 Inform the patient of the legal situation regarding advance directives and naming of a health care proxy. Offer assistance in formulating an advance directive.

5 Re-discuss the patient's preferences for life-sustaining treatments every 6 months.

RCT for symptoms management for ALS patients

	RCT target	Number of patients	Study duration	Results
Spasticity (1993)[91]	Effects of L-threonine	33 (all completed)	2 weeks (cross-over)	Effective; p=0·05 with Ashworth scale
Respiratory failure (2003)[92]	Effects of NIV	22 and 15 accepted NIV treatment (10 continued)	26 months	Improved QoL and survival; a prospective cohort study
Pseudobulbar affect (2004[93] and 2010[94])	Dextromethor-phan/ quinidine compound *vs* placebo	140 (129 completed)*	28 days	Palliates PBA and improved overall QoL
Bronchial secretion (2006)[95]	Benefits of HFCWO *vs* no treatment	46 (35 completed)	12 weeks	Less fatigue and breathlessness
Bone fractures (2006)[96]	Etidronate *vs* placebo	82 (all completed)	2 years	Significantly reduced fractures
Muscle weakness (2007)[97]	Resistance exercise *vs* standard stretch exercise	27 (18 completed)	6 months	Better with ALSFRS-R, limb subscales and QoL
Fatigue (2009)[98]	Modafinil *vs* placebo	32 (29 completed)	4 weeks	Indicates promising treatment
Sialorrhoea (2009)[99]	Botox B	20 (18 completed)	12 weeks	Global impression significantly improved
Sialorrhoea (2011)[100]	Botox A *vs* botox B in ALS and Parkinson's disease	27 (14 completed)	4 weeks and until benefits wore off	Botox B has shorter latency and is less expensive than botox A
Physical activity and coping mechanism (2011)[101]	Aerobic exercise with usual care *vs* behavioural therapy with usual care *vs* usual care alone	120 (enrolled)	16 weeks	Results pending
Muscle weakness (2013)[102]	Tirasemtiv *vs* placebo	>300 (ongoing)	12 weeks	Benefits on SVC, but substantial adverse effects
Weight loss (2012)[103]	High calorie and high fat	26 (16 completed)	12 weeks	Weight was stabilised
Weight loss (2014)[104]	Control *vs* hyperalimentation with HC/HC *vs* HF/HC	24 (20 completed)	16 weeks	Slower progression with HC/HC than HF/HC on the basis of ALSFRS-R



Mitsumoto, Brooks, and Silani, Lancet Neurology, 2014

Efficacy of the tertiary ALS Centers in Italy

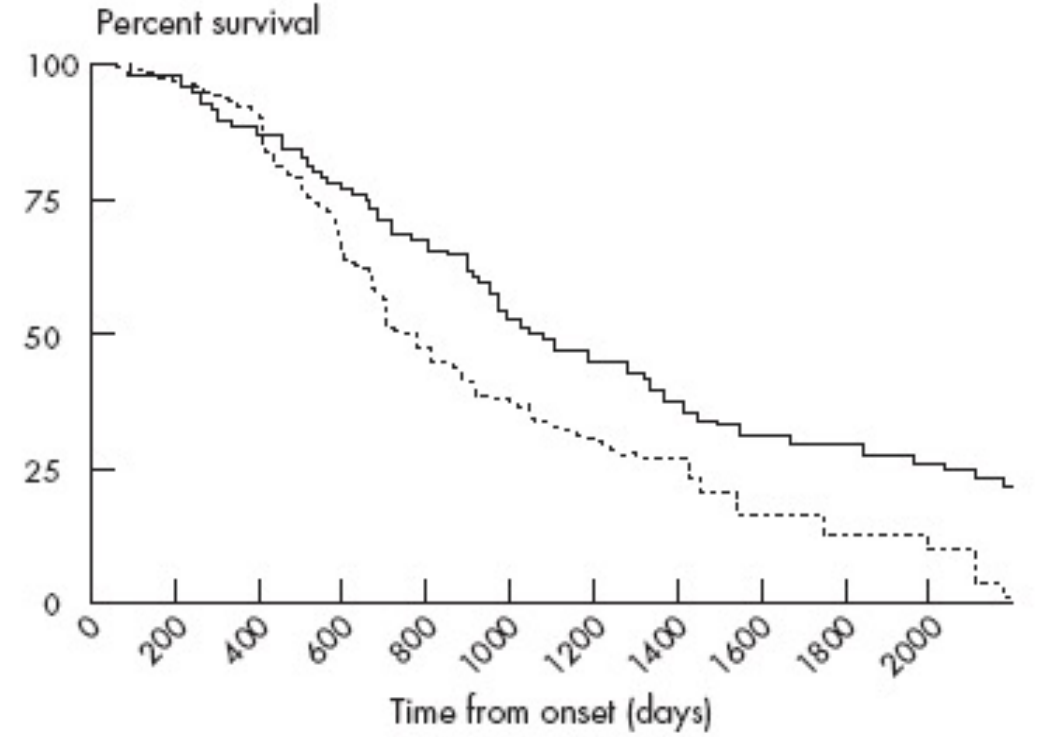


Figure 1 Survival curves of patients with amyotrophic lateral sclerosis (ALS) followed up by tertiary ALS centres (continuous line) and general neurology clinics (dotted line; p=0.0008).

Chiò et al., 2006