Inquadramento neurologico della SLA

DIPARTIMENTO
DI SCIENZE NEUROLOGICHE
Centro SLA – Umberto I Policlinico di Roma

SAPIENZA
UNIVERSITÀ DI ROMA

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Disease names

- Amyotrophic lateral sclerosis (ALS)
- Motor neurone disease (MND)
- Charcot's disease
- Lou Gehrig's disease

- **History of ALS**
- **» 1850** - English scientist Augustus Waller describes the appearance of shriveled nerve fibers
- **» 1869** - French doctor Jean-Marie Charcot first describes ALS in scientific literature
- **» 1881** - "On Amyotrophic Lateral Sclerosis" gets translated into English and published in a three-volume edition of *Lectures on the Diseases of the Nervous System*
- **» 1939** - Lou Gehrig is diagnosed with ALS
- **» 1941** - Lou Gehrig dies at age 38
- **» 1950s** - ALS epidemic occurs among the Chamorro people on Guam
- **» 1991** - Researchers link chromosome 21 to FALS
- **» 1993** - SOD1 gene on chromosome 21 found to play a role in some cases of FALS
- **» 1996** - Rilutek® becomes the first FDA-approved drug for ALS
- **» 1998** - El Escorial is developed as the standard for confirming ALS
- **» 2001** - Alsin gene on chromosome 2 found to cause ALS2
- **You are here:** History

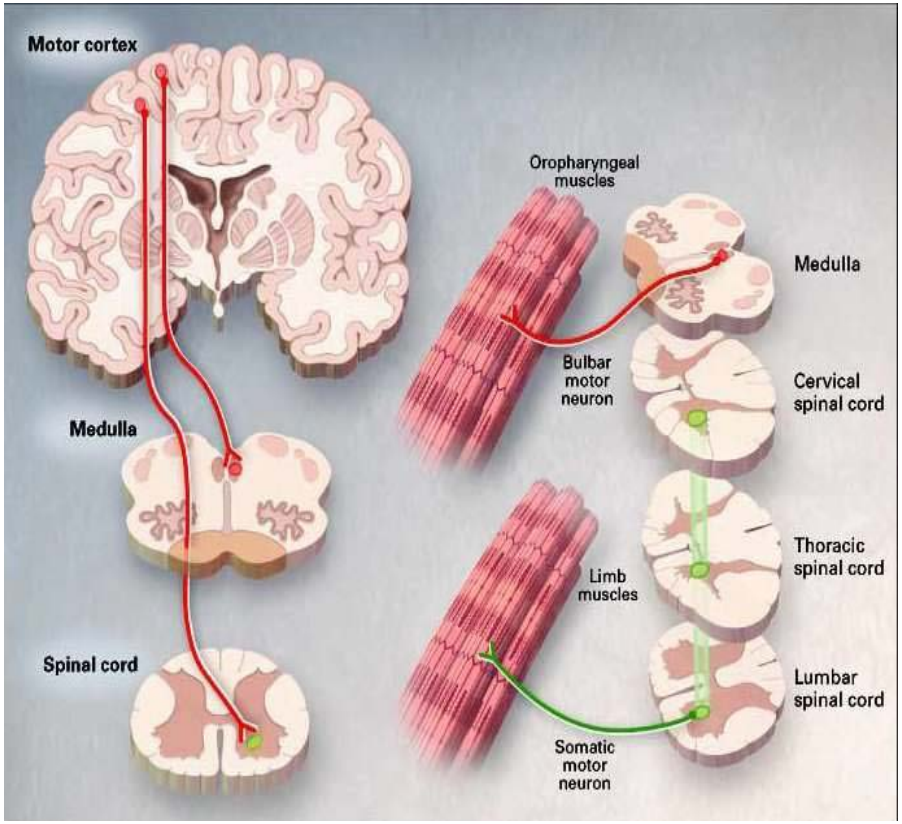
Included diseases

- Amyotrophic lateral sclerosis (ALS)
  - *term used to cover the spectrum of neurodegenerative syndromes characterised by progressive degeneration of motor neurones*

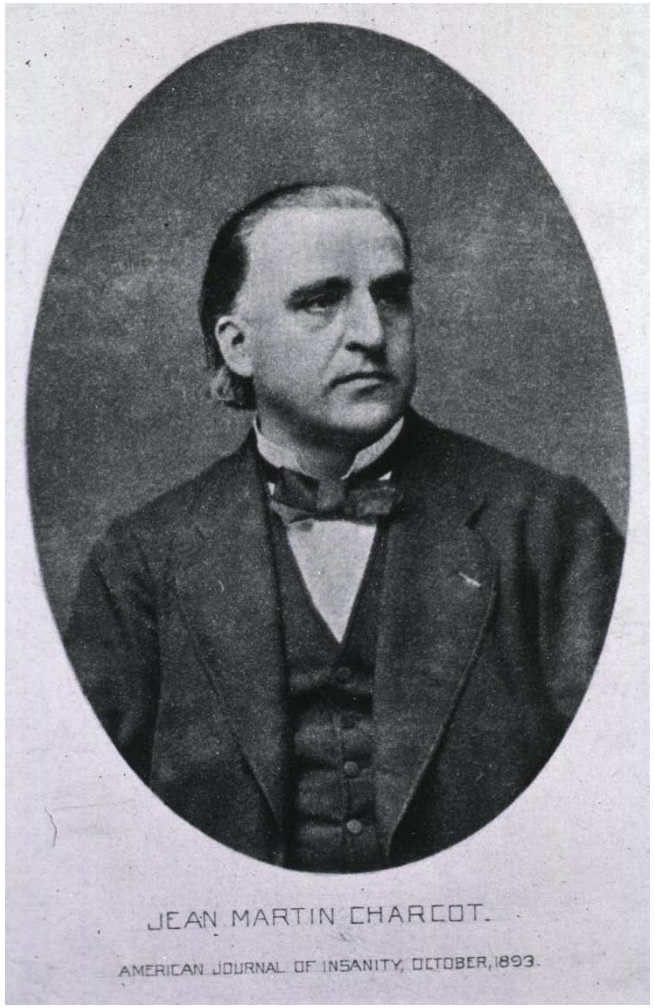
- in modern clinical practice indicate the commonest form of the disease the Classical (Charcot's) ALS or “spinal onset ALS”

Other syndromes related to this spectrum

- Progressive bulbar palsy
  - *Currently “bulbar onset ALS”*
- Progressive muscular atrophy
- Primary lateral sclerosis
- Flail arm syndrome
  - *Brachial amyotrophic diplegia*
  - *Vulpian-Bernhardt syndrome*
- Flail leg syndrome
  - *Pseudopolyneuritic form*
  - *Marie-Patrikios syndrome*
- ALS with multi-system involvement
  - *e.g. ALS-Dementia*

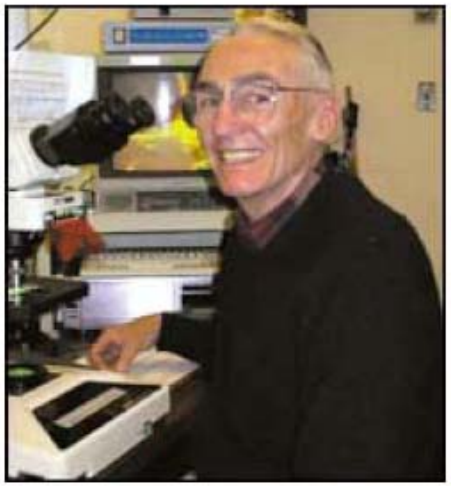


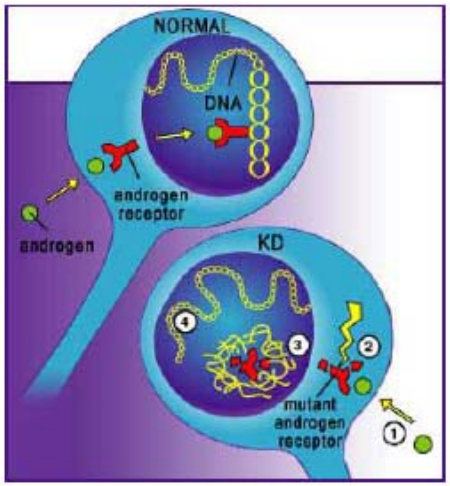
Motor neurone disease (MND)



- syndromes share a common molecular and cellular pathology
  - motor neurone degeneration
  - presence of characteristic intraneuronal inclusions
    - ubiquitin-immunoreactive
    - TDP-43 immunoreactive

Adult-onset spinal muscular atrophies

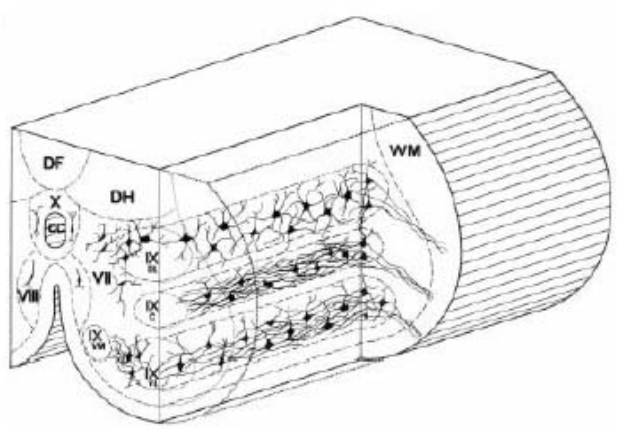




- another group of neurodegenerative motor neurone disorders
- affect anterior horn cells of the spinal cord and/or brainstem
  - have a distinct molecular pathology unrelated to ALS
  - have a more benign disease course

Definition and diagnostic/classification criteria

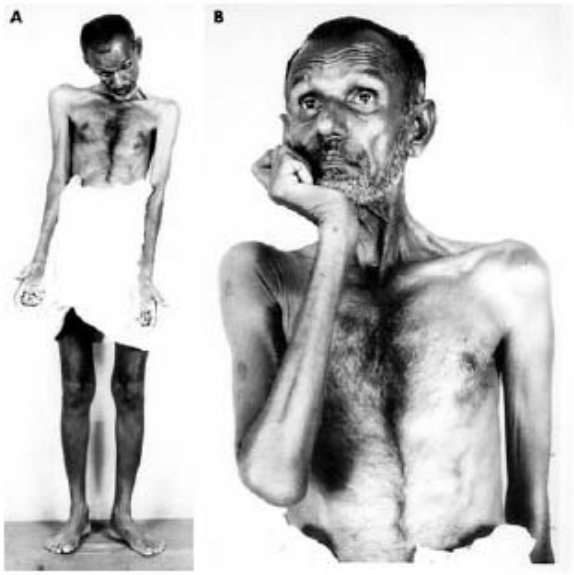
- neurodegenerative disorder
- progressive muscular paralysis
- reflecting degeneration of motor neurones
  - in the primary motor cortex
  - in the brainstem
  - in the spinal cord



“Amyotrophy” and “Lateral sclerosis”

- atrophy of muscle fibres

- hardening of the anterior and lateral corticospinal tracts



Diagnosis of ALS

- based on the presence of very characteristic clinical findings

in conjunction with

- investigations to exclude "ALS-mimic" syndromes
  - lead to diagnostic error in 5–10% of cases

Table 3: Diagnostic errors and most common 'ALS mimic syndromes'. (Modified from Kato et al., with permission)

Final diagnosis	Characteristic features	Distinguishing diagnostic features and investigations
Cerebral lesions	Focal motor cortex lesions very rarely mimic ALS, but frontal lesions with co-existent cervical or lumbo-sacral root damage may cause confusion.	MRI/CT; no EMG evidence of widespread chronic partial denervation (CPD) in limbs
Skull base lesions	Lower cranial nerve signs (bulbar symptoms and signs; wasting of tongue, often asymmetrical); seldom significant long tract signs unless foramen magnum involved in addition	MRI; CT with bone windows; no EMG evidence of CPD in limbs unless wasting of C8/T1 muscles (rare, but present in some lesions at foramen magnum or high cervical level)
Cervical spondylotic myelopathy	Progressive limb weakness. Asymmetrical onset; combined UMN and LMN signs in arm(s); spastic paraparesis; occasionally fasciculations in arms.	Pain in root distribution, but pain may not be severe and may resolve quickly; often progression followed by clinical stabilisation; no bulbar involvement; MRI evidence of spinal cord and root compression; no evidence of CPD on EMG (NB: patients may have co-existent lumbo-sacral motor radiculopathy with lower limb denervation)
Other cervical myelopathies • Foramen magnum lesions • Intrinsic and extrinsic tumours • Syringomyelia	Progressive weakness; foramen magnum lesions and high cervical cord lesions may be associated with focal (C8/T1) wasting; syringomyelia usually associated with LMN signs and dissociated sensory loss	Usually involvement of cerebellar and/or sensory pathways; MRI of head and cervical spine reveal pathology
Conus lesions and lumbo-sacral radiculopathy	Progressive mixed UMN and LMN syndrome	Usually significant sensory symptoms if not signs; bladder involvement; MRI thoracic and lumbo-sacral region; EMG evidence of radiculopathy

ASL mimic syndromes, con't

Inclusion body myositis (IBM)	Progressive weakness; bulbar symptoms; sometimes respiratory muscle weakness	Characteristic wasting and weakness of deep finger flexors and quadriceps femoris; EMG evidence of myopathy; muscle biopsy as definitive test (rimmed vacuoles)
Cramp/fasciculation/myokymia syndromes	Cramps, undulating muscle contractions, +/- weakness, stiffness (Isaac's syndrome; peripheral nerve hyper-excitability syndrome)	EMG evidence of myokymia; ~30% VGKC antibodies; ~20% associated with thymoma or lung cancer; association with other autoimmune diseases
Multifocal motor neuropathy (MFMN)	Focal asymmetrical onset, often upper limb; pure LMN syndrome; may stabilise for months or years; M:F 4:1;	Conduction block on nerve conduction studies (NCS); weakness often out of proportion to wasting; improvement with intravenous immunoglobulin (IVIG) in ~70%
Kennedy's disease (X-linked bulbar and spinal muscular atrophy)	Males symptomatic; slowly progressive bulbar and limb weakness	Family history; fasciculations of facial muscles; gynaecomastia; proximal symmetrical weakness in addition to foot drop; mild sensory neuropathy on NCS; positive DNA test for CAG repeat mutation in exon 1 of androgen receptor gene

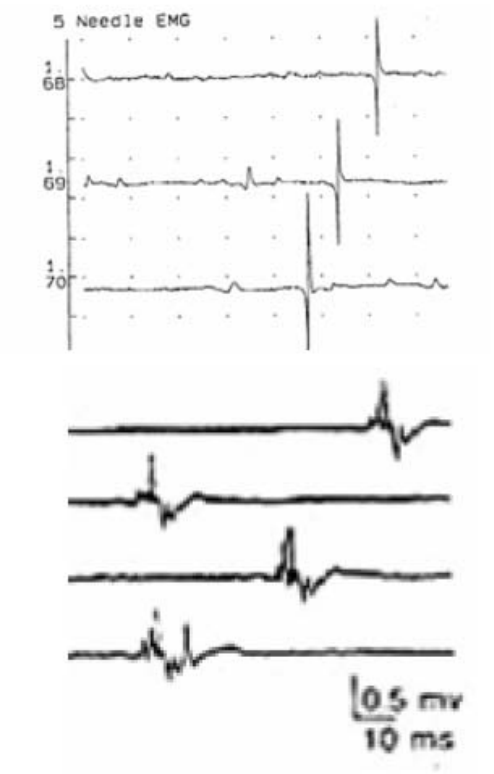
Clinical finding of signs suggestive of

- combined upper motor neurone (UMN) and lower motor neurone (LMN)
- that cannot be explained by any other disease process
  - evident on electrophysiological, imaging, cerebrospinal fluid, or serological studies

- together with progression compatible with a neurodegenerative disorder

Investigation results alone

- evidence of chronic denervation on EMG
  - not adequate for achieving a diagnosis
- must be interpreted in light of the patient's history and clinical findings



Definite ALS
is defined on clinical grounds alone by the presence of UMN as well as LMN signs in the bulbar region and at least two of the other spinal regions or the presence of UMN and LMN signs in three spinal regions. The important determinants of diagnosis of definite ALS in the absence of electrophysiological, neuroimaging and laboratory examinations are the presence of UMN and LMN signs together in multiple regions.

Probable ALS
is defined on clinical grounds alone by UMN and LMN signs in at least two regions. While the regions may be different, some UMN signs must be rostral (above) the LMN signs. Multiple different combinations of UMN and LMN signs may be present in patients with probable ALS.

Possible ALS
is defined on clinical grounds alone when the UMN and LMN signs are in only one region or UMN signs alone are present in 2 or more regions or LMN signs are rostral to UMN signs (the latter distribution of signs needs to be differentiated from multiple non-ALS processes). Monomelic ALS, progressive bulbar palsy without spinal UMN and/or LMN signs and progressive primary lateral sclerosis without spinal LMN signs and progressive primary lateral sclerosis without spinal LMN signs constitute special cases which may develop LMN or UMN signs to meet the criteria for probable ALS with time or be subsequently confirmed at autopsy by specific LMN and UMN neuropathologic findings.

Suspected ALS
will manifest only LMN signs in 2 or more regions, although UMN pathology might be demonstrated at autopsy. However, only clinical signs are considered pertinent to this classification at the time of diagnostic evaluation.

The revised 2000 'Airlie House' criteria

The diagnosis of ALS requires:
1 Evidence of LMN degeneration by clinical, electrophysiological or neuropathological examination;
2 Evidence of UMN degeneration by clinical examination, and
3 Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination,

Together with the absence of:
[1] Electrophysiological and pathological evidence of other disease that might explain the signs of LMN and/or UMN degeneration, and

[2] Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs

Categories of clinical diagnostic certainty on clinical criteria alone

Definite ALS
• UMN signs and LMN signs in 3 regions
Probable ALS
• UMN signs and LMN signs in 2 regions with at least some UMN signs rostral to LMN signs

Probable ALS – Laboratory supported
• UMN signs in 1 or more regions and LMN signs defined by EMG in at least 2 regions

Possible ALS
• UMN signs and LMN signs in 1 region (together), or
• UMN signs in 2 or more regions
• UMN and LMN signs in 2 regions with no UMN signs rostral to LMN signs

UMN signs: clonus, Babinski sign, absent abdominal skin reflexes, hypertonia, loss of dexterity.
LMN signs: atrophy, weakness. If only fasciculation: search with EMG for active denervation.
Regions reflect neuronal pools: bulbar, cervical, thoracic and lumbosacral.

'Clinically suspected' category

- removed from previous 1994 classification
  - contains patients with a pure LMN syndrome
- but..
  - a significant number of patients will not fall into these categories in the revised criteria
- 'Airlie House' criteria probably more useful for research purposes and therapeutic trials
  - rather than day-to-day clinical practice

Further rationalisation of the El Escorial Criteria

Clinical Neurophysiology 119 (2008) 497–503

www.elsevier.com/locate/clinph

Review

Electrodiagnostic criteria for diagnosis of ALS ☆

Mamede de Carvalho [a], Reinhard Dengler [b], Andrew Eisen [c], John D. England [d], Ryuji Kaji [e], Jun Kimura [f], Kerry Mills [g], Hiroshi Mitsumoto [h], Hiroyuki Nodera [i], Jeremy Shefner [j], Michael Swash [k,*]

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The Awaji-shima consensus

Awaji-shima consensus recommendations for the application of electrophysiological tests to the diagnosis of ALS, as applied to the revised El Escorial Criteria (Airlie House 1998)

1. Principles (from the Airlie House criteria)
The diagnosis of amyotrophic lateral sclerosis [ALS] requires
(A) the presence of
(1) evidence of *lower motor neuron (LMN) degeneration* by clinical, electrophysiological or neuropathological examination
(2) evidence of *upper motor neuron (UMN) degeneration* by clinical examination; *and*
(3) *progressive spread of symptoms or signs* within a region or to other regions, as determined by history, physical examination, or electrophysiological tests
(B) the absence of
(1) *electrophysiological or pathological evidence of other disease processes* that might explain the signs of LMN and/or UMN degeneration, and
(2) *neuroimaging evidence of other disease processes* that might explain the observed clinical and electrophysiological signs
2. Diagnostic categories
Clinically definite ALS is defined by *clinical or electrophysiological* evidence by the presence of LMN as well as UMN signs in the bulbar region and at least two spinal regions or the presence of LMN and UMN signs in three spinal regions
Clinically probable ALS is defined on *clinical or electrophysiological* evidence by LMN and UMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs
Clinically possible ALS is defined when *clinical or electrophysiological* signs of UMN and LMN dysfunction are found in only one region; or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs. Neuroimaging and clinical laboratory studies will have been performed and other diagnoses must have been excluded

These recommendations emphasize the equivalence of clinical and electrophysiological tests in establishing neurogenic change in bodily regions. The category of "Clinically Probable Laboratory-Supported ALS" is rendered redundant.

Epidemiology

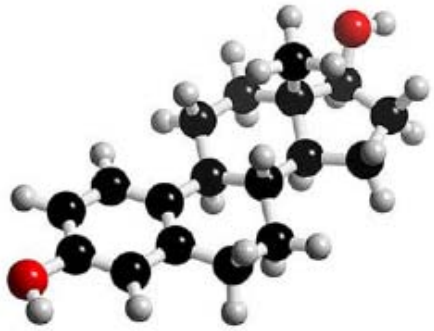
Sporadic ALS in the 1990's

- incidence 1.5-2.7 per 100,000 population/year
  - avg 1.89 per 100,000/year in both Europe and North America

- point prevalence 2.7-7.4 per 100,000
  - avg 5.2 per 100,000 in western countries

- lifetime risk by the age of 70 estimated at 1 in 1,000
  - more accurate estimate is more likely to be1 in 400

Gender



- **Slight excess of males M:F ratio about 1.5:1**
  -underascertainment of elderly women in some population registers?

- **Recent data suggests gender ratio may be approaching equality**

Mortality rates

Original Paper

Neuroepidemiology

Neuroepidemiology 2005;25:144–152
DOI: 10.1159/000086679

Published online: June 29, 2005

Amyotrophic Lateral Sclerosis Mortality in the United States, 1979–2001

James J. Sejvar[a] Robert C. Holman[a] Joseph S. Bresee[a]
Kenneth D. Kochanek[b] Lawrence B. Schonberger[a]

[a]Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Ga., and [b]Division of Vital Statistics, National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Md., USA

- 1.84 per 100,000 persons

Mean age of onset

- **Sporadic ALS (s-ALS)**
  - *varies between 55–65 years*
  - *median age of onset of 64 years*

- **Only 5% of cases onset before 30 years**
  - *juvenile sporadic onset cases are being increasingly recognised*

- **Bulbar onset commoner in women and in older age groups**
  - *43% of patients over-70 present with bulbar symptoms compared to 15% below-30*

Familiarity

- **5 to 10% of cases have a family history of ALS (familial ALS)**
  - *often Mendelian inheritance and high penetrance*
  - *most cases AD pattern of inheritance, AR pedigrees reported*

- **f-ALS affects males and female equally have a shorter survival**

- **age of onset off-ALS is about a decade earlier than for sporadic cases**
  - *normal Gaussian distribution*
  - *sporadic ALS has age dependant incidence*

Familial Aggregation of Amyotrophic Lateral Sclerosis

Fang Fang, MD,[1,2] Freya Kamel, PhD,[2] Paul Lichtenstein, PhD,[1] Rino Bellocco, ScD,[1,3] Pär Sparén, PhD,[1] Dale P. Sandler, PhD,[2] and Weimin Ye, MD, PhD[1]

Objective: To assess the relative risk for amyotrophic lateral sclerosis (ALS) in families of ALS patients.
Methods: We conducted a cohort study based on the Swedish Multi-Generation Register in 1961 to 2005. Among 6,671 probands (first ALS case in the family), 1,909 full siblings, 13,947 children, and 5,405 spouses were identified (exposed group). Other persons in the Multi-Generation Register, who were siblings, children, or spouses to persons without ALS, served as the reference group. Relative risks for ALS among the exposed group, compared with the reference group, were calculated from Poisson regression models. Concurrence of ALS within twins was assessed in 86,441 twin pairs registered in the Swedish Twin Register.
Results: Nine cases of ALS were noted among the siblings and 37 cases among the children of the probands, giving a 17-fold risk among the siblings (95% confidence interval, 8.1–30.4) and a 9-fold risk among the children (95% confidence interval, 6.2–12.0), compared with the reference group. Siblings and children had a greater excess risk if the proband was diagnosed at a younger age, and the excess risks decreased with increasing age at diagnosis of the proband ($p < 0.001$). Spouses had no significantly increased risk ($p = 0.27$). Two cases were identified among the cotwins of ALS probands, giving a relative risk of 32 (95% confidence interval, 5.2–102.6).
Interpretation: The siblings and children of ALS patients have an about 10-fold risk for ALS compared with the reference group. The excess risks vary with both age and kinship, indicating a major genetic role in familial ALS.

Ann Neurol 2009;66:94–99

Juvenile onset ALS (j-ALS)

- Most cases are AR
  - *chr2q33 (ALS2, alsin)*
  - *chr15q12-21*

- Dominant inheritance reported
  - *chr 9q34 (ALS4, senataxin)*

term used when age of onset is less than 25 years

doi:10.1093/brain/awp325 Brain 2010: 133; 591–598 | 591

BRAIN
A JOURNAL OF NEUROLOGY

SPATACSIN mutations cause autosomal recessive juvenile amyotrophic lateral sclerosis

Antonio Orlacchio,[1,2] Carla Babalini,[1] Antonella Borreca,[1,2] Clarice Patrono,[1] Roberto Massa,[1,2] Sarenur Basaran,[3] Renato P. Munhoz,[4] Ekaterina A. Rogaeva,[5,6] Peter H. St George-Hyslop,[5,6,7] Giorgio Bernardi[1,2] and Toshitaka Kawarai[8]

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Genetic disease currently accounts for as much as 18% of all ALS when “sporadic” cases tested for currently known genes are included

Ravits et al, 2009

Geographic loci

Geographic loci

- Chamorro people
  - *Guam and Marianasisland, the Kii peninsula of Honshu Island*
- Auyuand Jakai people
  - *south west New Guinea*
- ALS associated with the Parkinsonism and dementia (ALSPD complex)

Clinical features

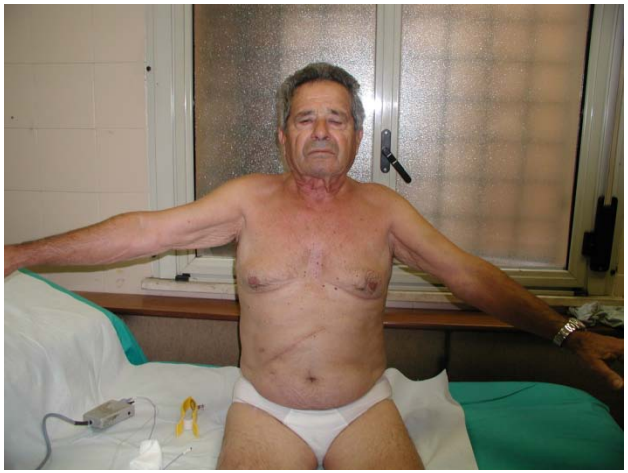
- First clearly described as a clinico pathological entity by Jean Martin Charcot
  - *1869 and 1874 articles*
- Bell (1824)
- Aran (1850)
- Duchenne (1851)
- Cruveilher(1853)

Classical Charcot ALS: usual disease onset

- **Approximately 2/3 pts with typical ALS have a spinal form of the disease**

- **Present with symptoms related to focal muscle weakness**
  - symptoms may start either distally or proximally in the upper limbs and lower limbs

- **Weakness is usually of insidious onset**
  - exacerbated by cold weather



Classical Charcot ALS: unusual disease onset

- **Weakness may be preceded by**

  - *fasciculations or cramps for some months(or years), but rarely presenting symptoms*
  - *focal muscle wasting (very rarely)*

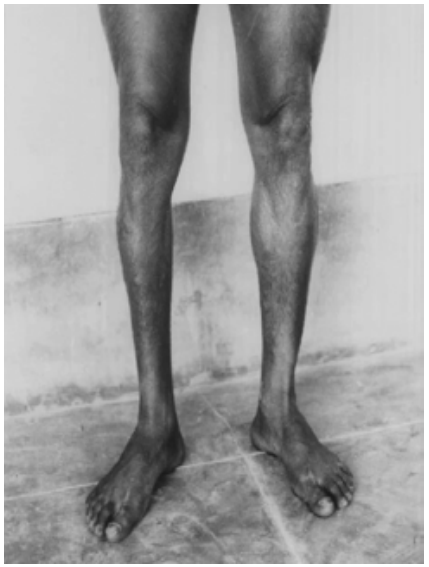
Lou GEHRIG

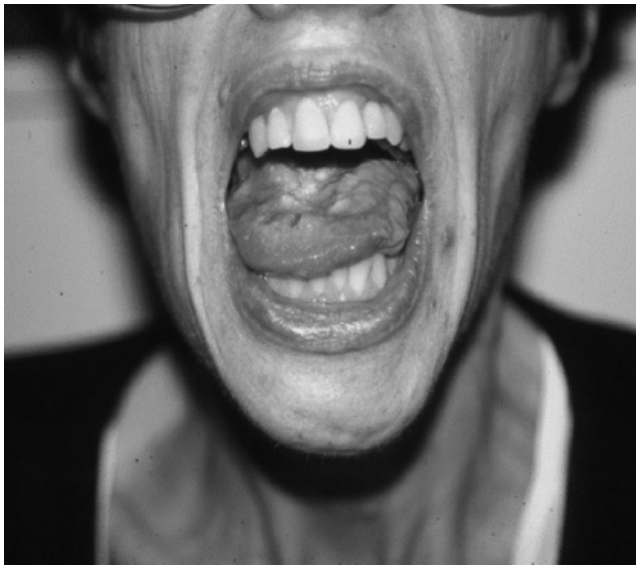
- **Some patients may present with a spastic paraparesis**

Borgonovo

Signorini

Classical Charcot ALS: unusual disease onset



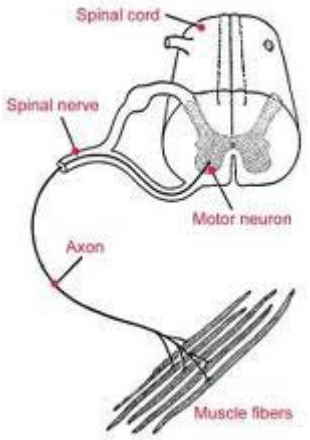


- although usually asymmetrical at onset, other limbs develop weakness and wasting sooner or later
- most patients also develop bulbar symptoms
- eventually respiratory symptoms
  - *not necessarily in that sequence*

Classical Charcot ALS: spasticity

- **gradually develops in the weakened atrophic limbs**
  - affects manual dexterity and gait

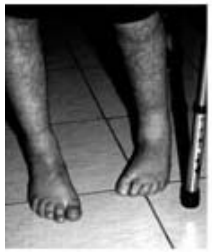
- **flexor spasms in late stages**
  - involuntary spasms occurring due to excess activation of the flexor arc in a spastic limb

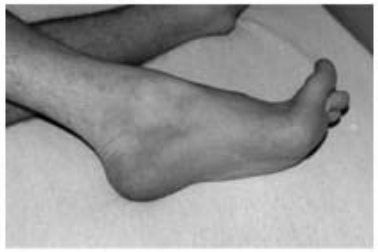


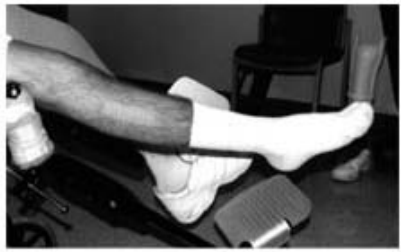

The Adducted/Internally Rotated Shoulder


The Flexed Wrist


The Pronated Forearm

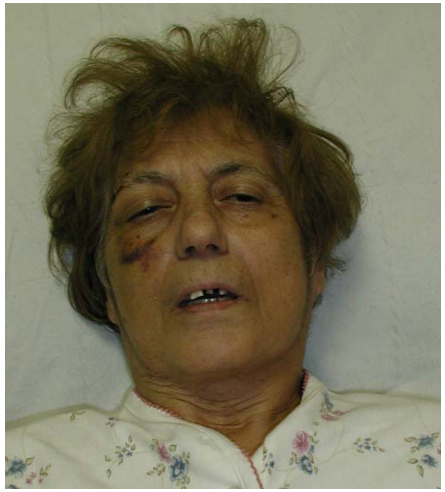

Equinovarus

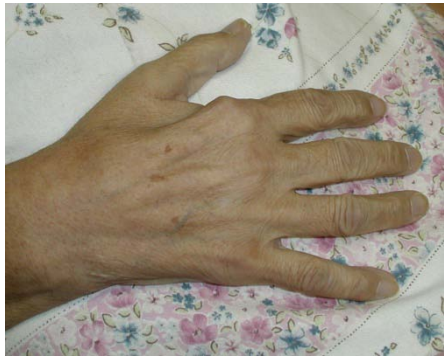

Striatal Toe


Stiff Knee

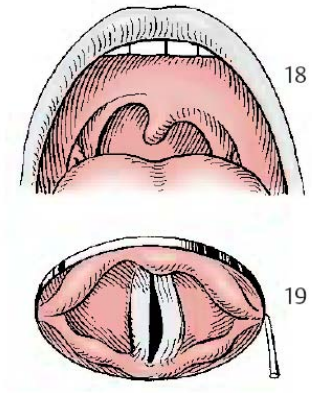
Classical Charcot ALS: rare symtomps

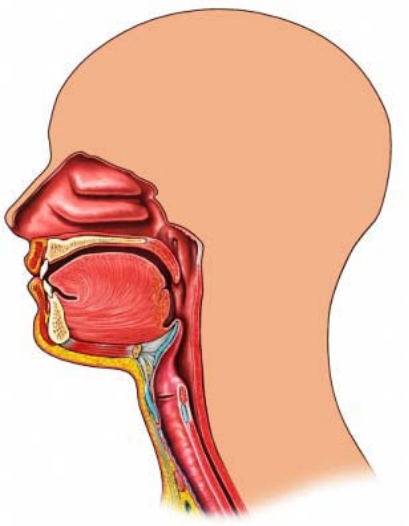
- **sensory symptoms**
- **cognitive symptoms**
- **multi-system involvement**
  - e.g. dementia, parkinsonism





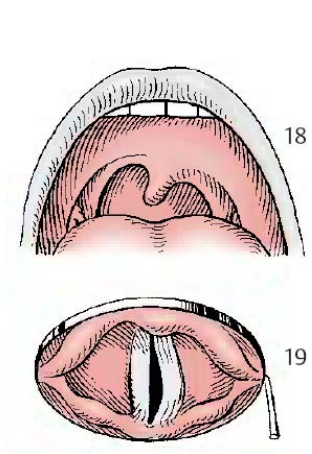
Bulbar onset ALS: dysarthria

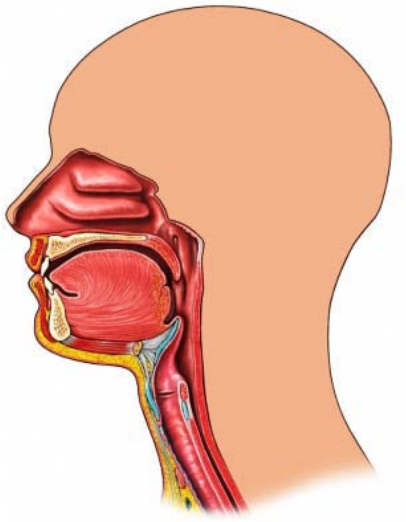




- **usually present with dysarthria of speech**
  - *may initially only be apparent after ingestion of alcohol*

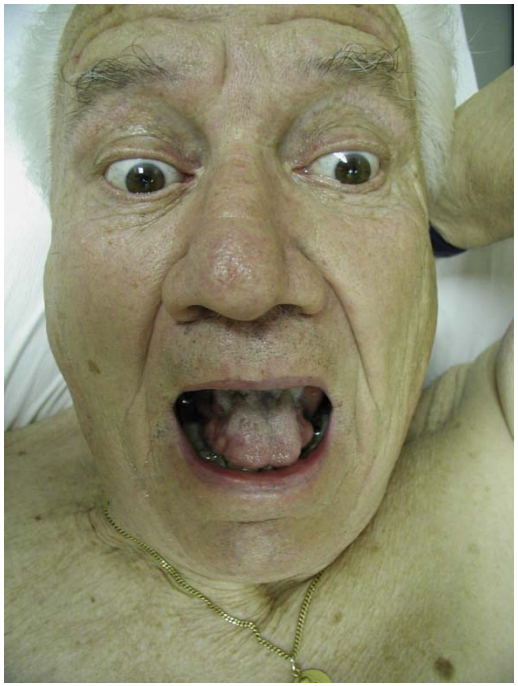
Bulbar onset ALS: dysphagia





Rarely present with dysphagia for solid or liquids

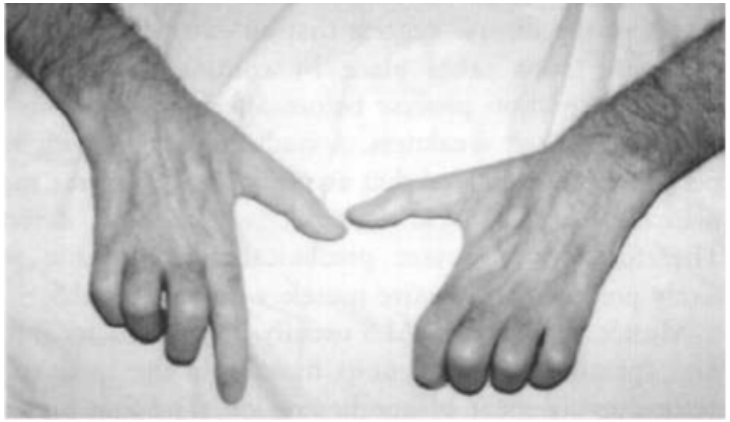
Bulbar onset ALS: other symtomps

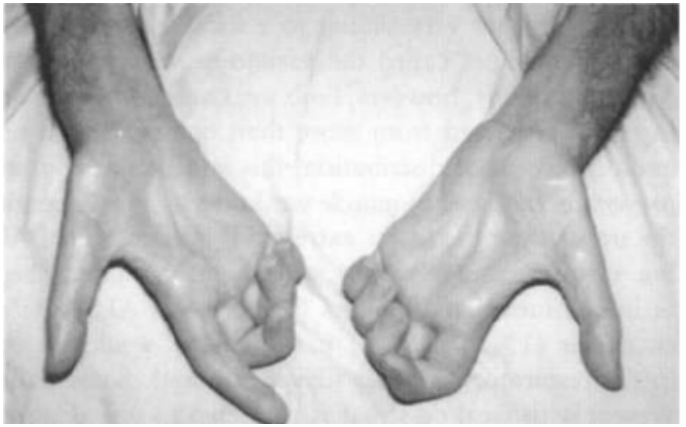


- almost all patients develop sialorrhoea
  - *difficulty swallowing saliva*
  - *mild UMN type bilateral facial weakness*

- ‘pseudobulbar‘ symptoms seen in many cases
  - *emotional lability*
  - *excessive yawning*

Bulbar onset ALS: limb symtomps



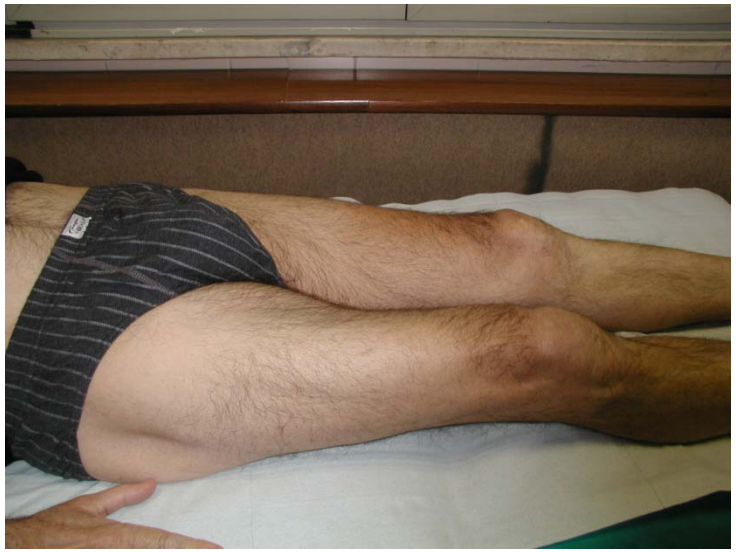


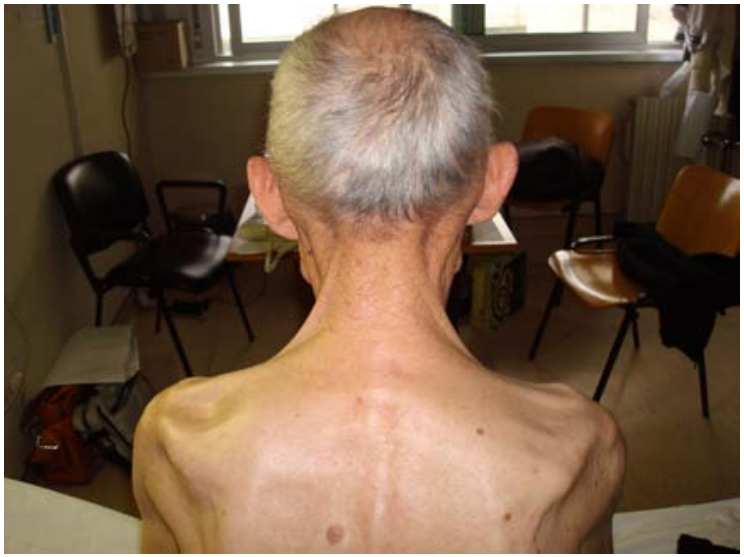
- Can develop almost simultaneously with bulbar symptoms
- in the vast majority of cases within 1–2 years

Onset with respiratory weakness

- **About 5% of cases with ALS present**
  - *without significant limb or bulbar symptoms*
- **Type 2 respiratory failure**
- **Nocturnal hypoventilation**
- **Symptoms**
  - *dyspnoea, orthopnoea*
  - *disturbed sleep, morning headaches, excessive day time somnolence*
  - *anorexia,decreased concentration, irritability or mood changes*

Lower motor neurons signs

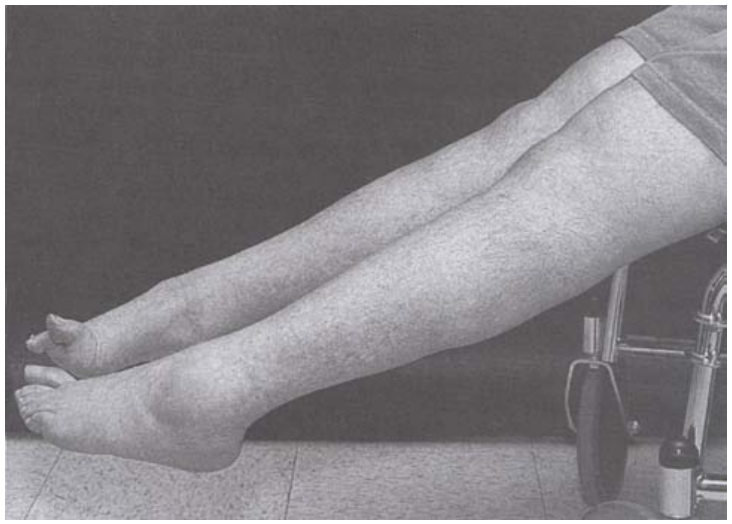


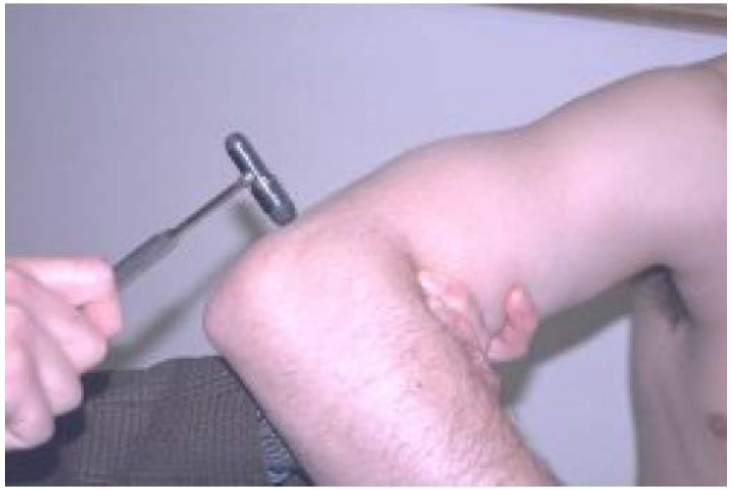


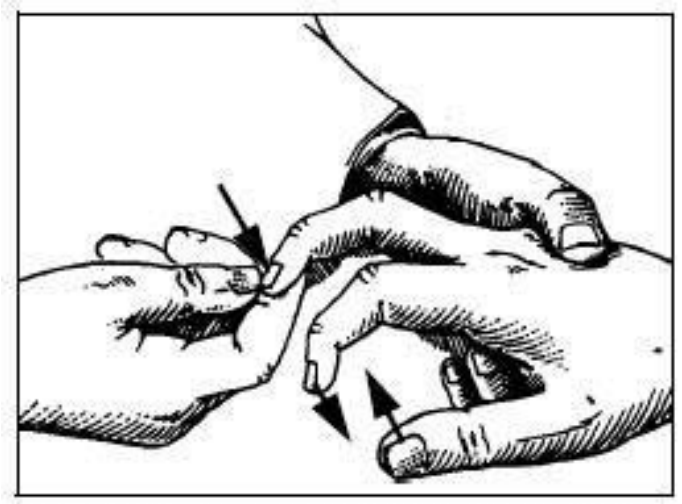
- focal muscle atrophy
  - *especially involving the muscles of the hands, forearms or shoulders in the upper limbs*
  - *proximal thigh or distal foot muscle in the lower limbs*

- fasciculations usually visible in more than one muscle group

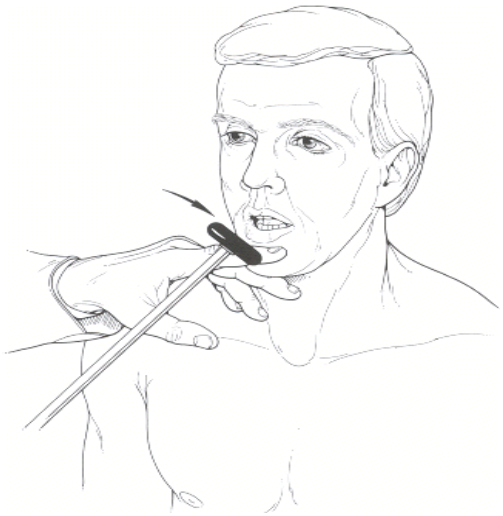
Upper motor neurons signs





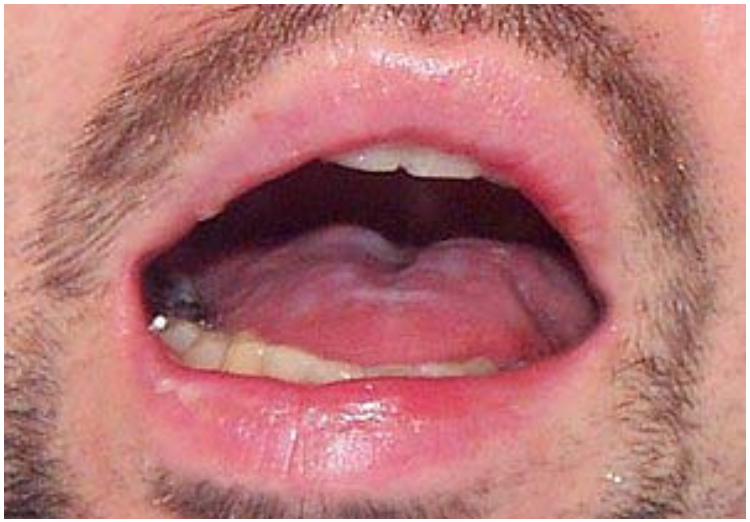


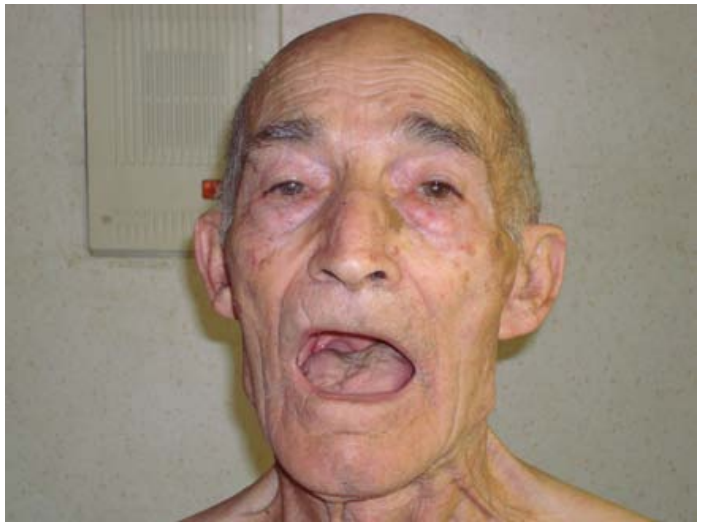
Bulbar dysfunction: dysarthria



- may arise from
  - *either LMN pathology*
  - *or pseudobulbar palsy from UMN disorder*
- slow slurred speech or a nasal quality
- cranial nerves
  - *brisk jaw jerk especially in bulbar-onset disease*

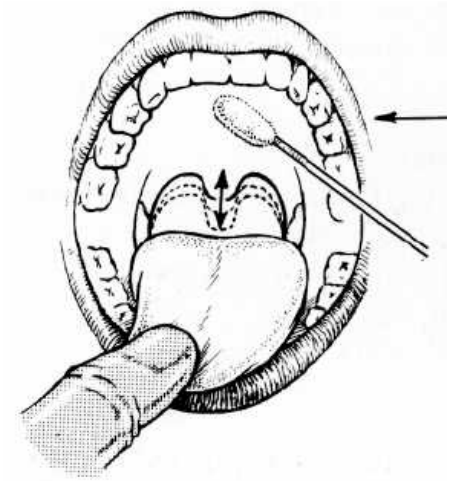
Bulbar dysfunction: facial weakness

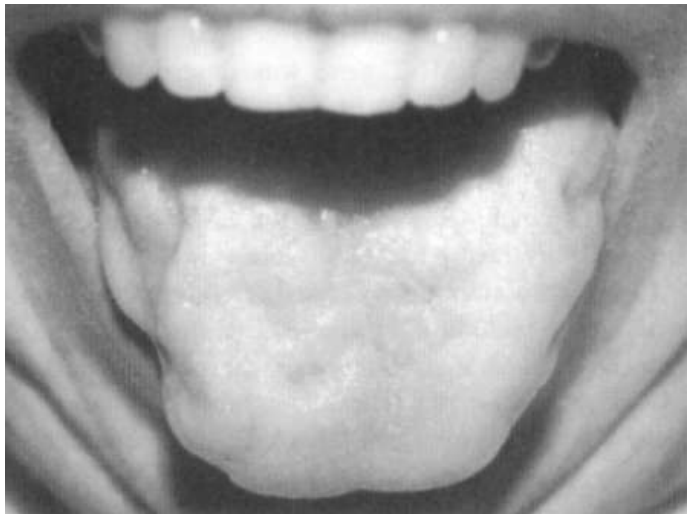




- An UMN type facial weakness affects the lower half of the face causing difficulty with lip seal and blowing cheeks
  - *but often varying degrees of UMN and LMN facial weakness coexist*

Bulbar dysfunction: gag reflex and tongue

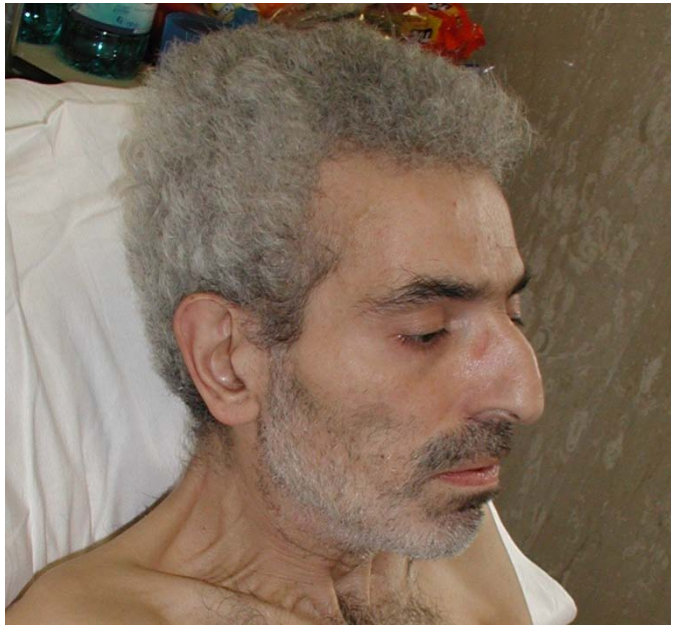


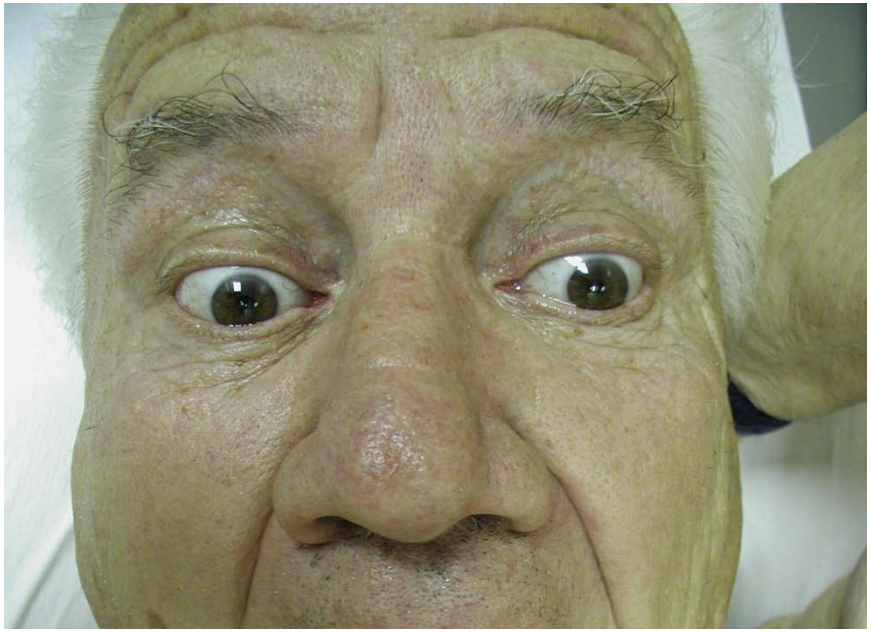


- Gag reflex preserved and often brisk
  - *while the soft palate may be weak*

- Fasciculations and wasting of the tongue
  - *slowed tongue movements due to spasticity*

Bulbar dysfunction: other cranial nerves





- Remain intact
- In late stages patients may very rarely develop a supranuclear gaze palsy
- Sensory examination almost always unremarkable

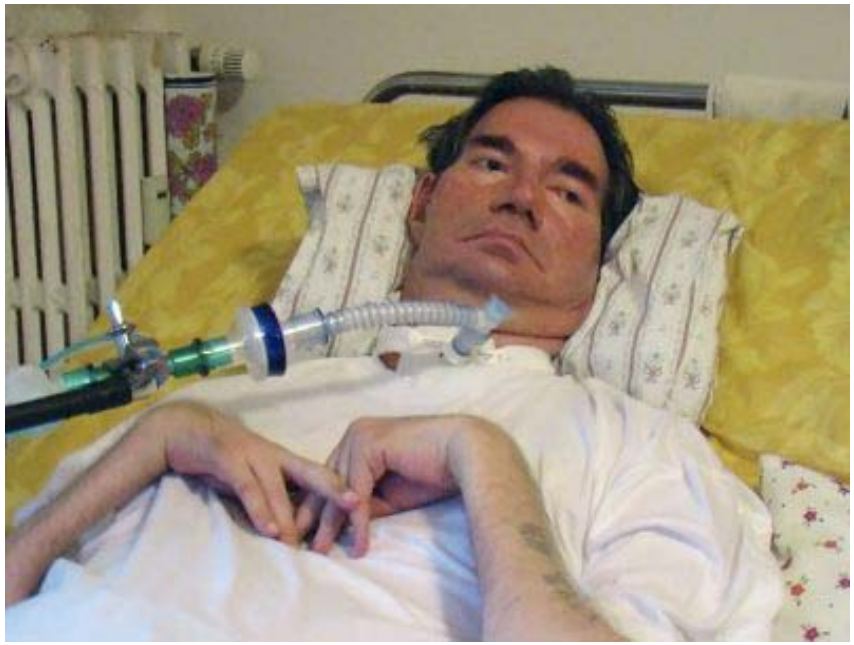
Disease progression

- characteristic combination of UMN and LMN signs coexisting within the same CNS region develops

  - affecting the bulbar, cervical, thoracic and lumbar territories

- respiratory failure and other pulmonary complications are the usual cause of death in ALS

Totally locked-in state



- profound state of motor paralysis eventually developed in patients kept alive by tracheostomy assisted ventilation
- paralysis of all voluntary muscles and varying degrees of oculomotor impairment

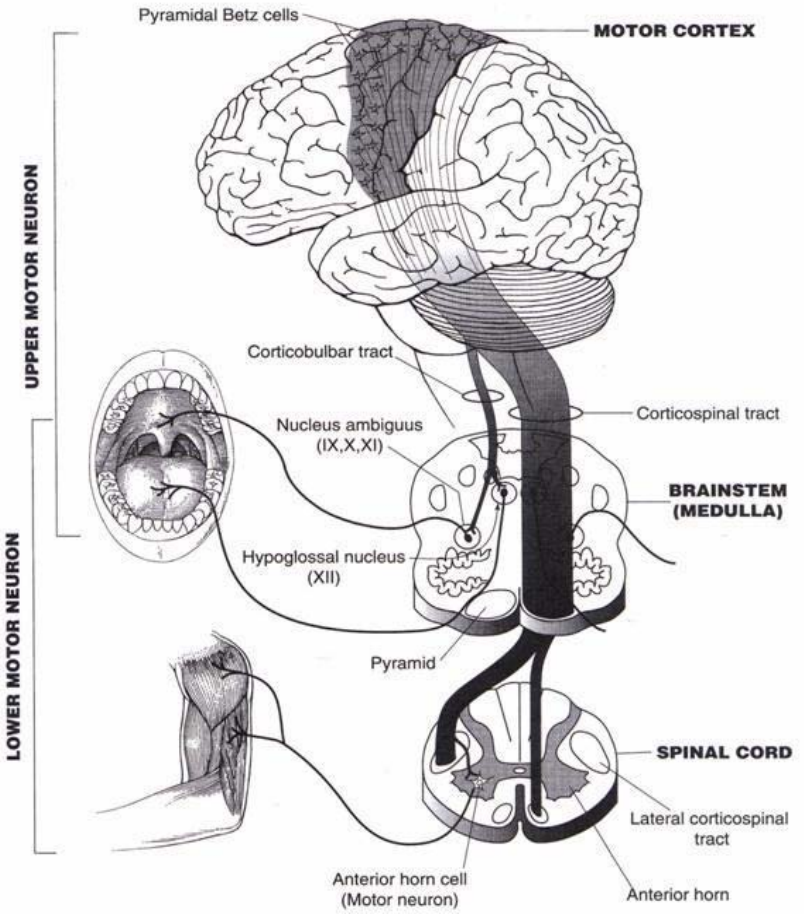
Clinical features of variant disorders

- **Variants of MND**
  - *differing clinical presentation*
  - *differing rate of progression*
  - *differing prognosis*
- **Evidence of a common molecular pathology**
- **Opinion divided**
  - *whether should be classified as separate entities from ALS*

Phenotype heterogeneity, focality, and spread

Phenotype of ALS

- **Highly heterogeneous**
- **Determined by 3 primary independent attributes**
  - *body region of onset*
  - *relative mix of UMN and LMN involvement*
  - *rate of progression*
- **Reflect invivo anatomy of underlying neuropathology**



Contents lists available at ScienceDirect

Neuromuscular Disorders

journal homepage: www.elsevier.com/locate/nmd

Upper motor neuron and extra-motor neuron involvement in amyotrophic lateral sclerosis: A clinical and brain imaging review

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ARTICLE INFO

Article history:
Received 6 March 2008
Received in revised form 25 September 2008
Accepted 5 October 2008

Keywords:
Amyotrophic lateral sclerosis
Motor neuron disease
Imaging of
Neurobiology of
Dementia
TDP-43

ABSTRACT

There is an ongoing discussion whether ALS is primarily a disease of upper motor neurons or lower motor neurons. We undertook a review to assess how new insights have contributed to solve this controversy. For this purpose we selected relevant publications from 1995 onwards focussing on (1) primary targets and disease progression in ALS and variants of ALS, (2) brain imaging markers for upper motor neuron lesion, and (3) evidence for ALS being a multisystem disorder. Clinically, upper motor and lower motor neuron symptoms can occur in any order over time. Brain imaging markers show upper motor neuron involvement in early disease. Overlap syndromes of ALS and dementia, and involvement of autonomic and sensory nerves occur frequently. PET/SPECT scans, functional MRI and voxel based morphometry studies clearly show abnormalities in extra-motor areas of the brain. Pathologically, the 43 kDa TAR DNA-binding protein (TDP-43) provides a clue to these overlapping disorders. In conclusion, evidence accumulates that ALS is a multisystem disorder rather than a pure lower and/or upper motor neuron disorder.

Starting points, the literature

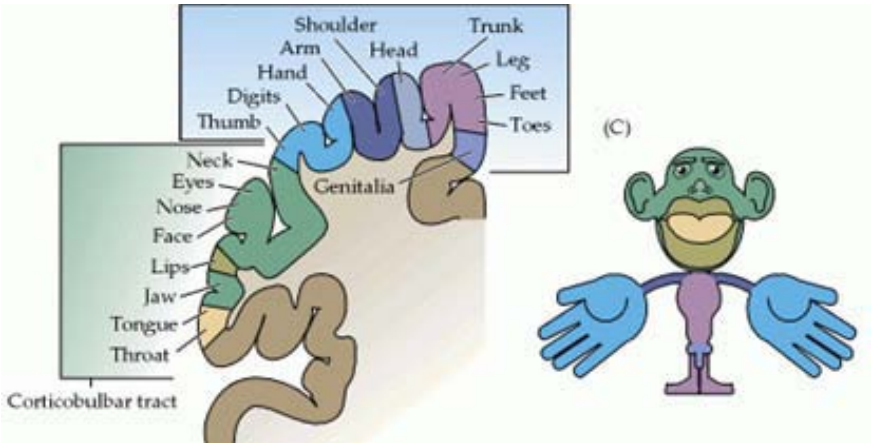
- **Focality of initial symptoms is a common place**
  - *occurs in most patients*

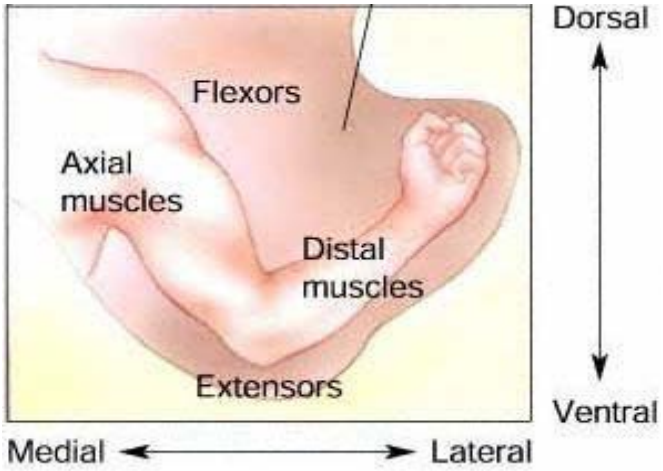
- **Onset site is randomly localized in the neuraxis**

- **Both UMN and LMN deficits**
  - *are maximalin the same peripheral body region*
  - *are highly variable in their severities of involvement*
  - *spread regionally outward along their independent neuroanatomy*

Comparison of UMN and LMN 3-D neuroanatomy

Anatomic feature	UMN	LMN
Location	Cerebral cortex	Brainstem and spinal cord
Motor neurons	Giant cells of Betz	Alpha motor neurons
Nuclei	M1 (~Brodmann area 4)	Motor nuclei and anterior gray horn
Microenvironment	Layer V	Rexed lamina IX
3-D arrangement	Laminar	Columnar
Somatotopic arrangement	Lateral to medial	Rostral to caudal
Anatomic span	12 cm per hemisphere	46 cm midbrain to sacral cord
Origination in neurodevelopment	Anterior (rostral) portion of neural tube in line with LMN progenitors	Posterior (caudal) portion of neural tube in line with UMN progenitors
Functional integrations	Prefrontal networks; convergence and divergence with LMNs	Convergence and divergence from UMNs; motor units





Importance of first clinical manifestations

- Deficits and neuropathology have not undergone temporal-spatial summation
- Are relatively uncomplicated
- Progressive degeneration may have a highly discrete onset

Implications

- **Site of onset may correlate with neuron numbers**
  - *initial triggeris stochastic*
- **Stochastic events at molecular level**
  - *variation in local blood flow triggering molecular pathology mediated by “angion-neurins” such as VEGF*
- **Trigger may occur at any level of the motor network**
- **Trigger is distributed (not caused) by transneuronal signaling or axonal transport**

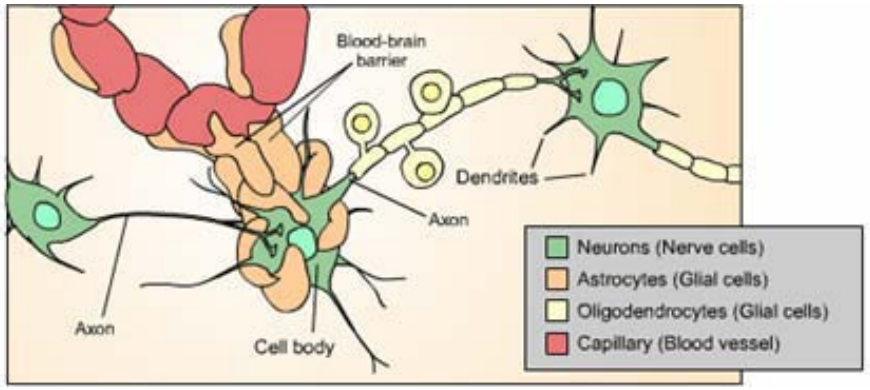
Types of transneuronal signaling

• Synaptic between neurons in series

- *either retrograde or anterograde*

• Relevant to the trigger and initial distribution *between* *U*MNs and LMNs

Types of transneuronal signaling



- Local between neurons in parallel
  - *neurons proximate to each other at same anatomic level*
  - *nonsynaptic, involve the neuron microenvironment*

- Relevant to local progression and contiguous spread at the respective levels once degeneration is triggered

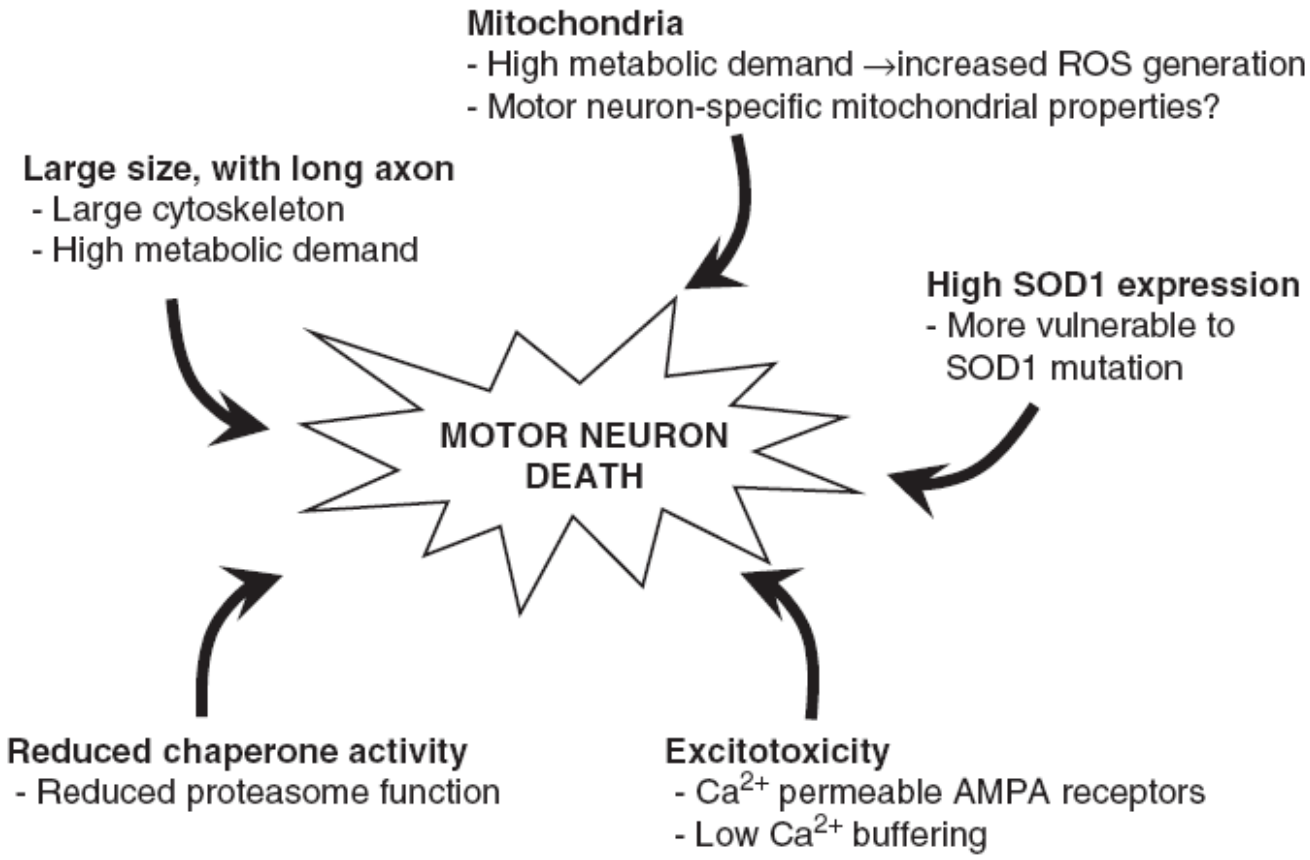
Contiguous spread, the distinctive clinical aspect

- **Underlying degeneration**
  - *spreads along respective UMN andLMN anatomy*
  - *undergoes temporal-spatial summation both within and between the UMN and LMN levels*
  - *has preferential directions of outward spread toward*

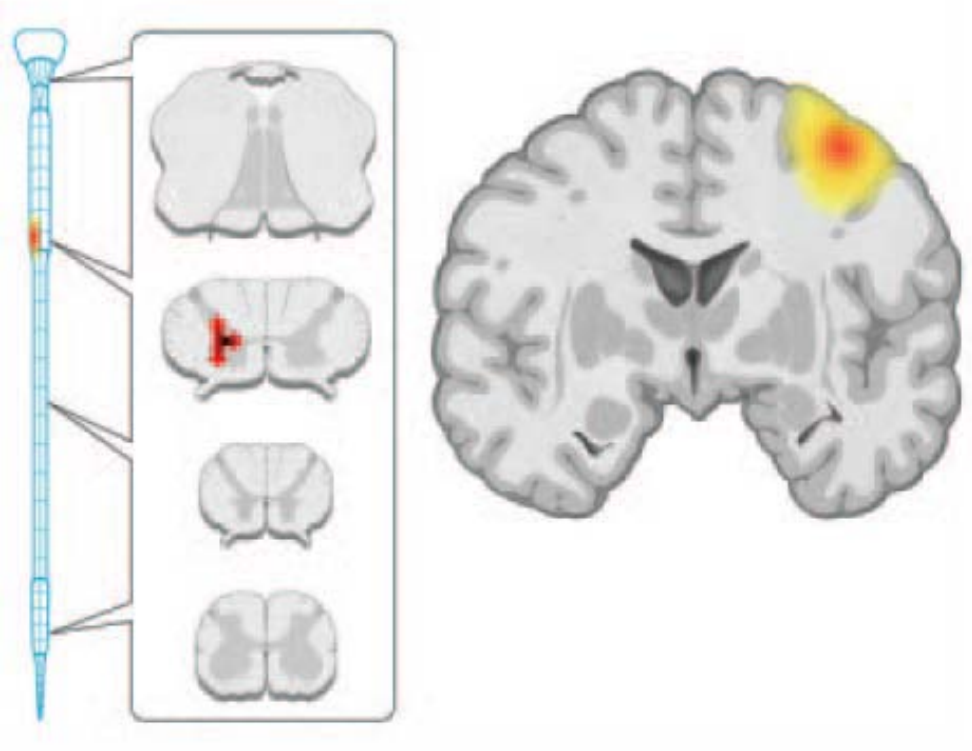
    > *caudal body regions over rostral ones*

- **Increasingly complex phenotypes of motor deficits**
  - *ultimately diffuse and symmetric*

Preferential directionality, preferential vulnerability

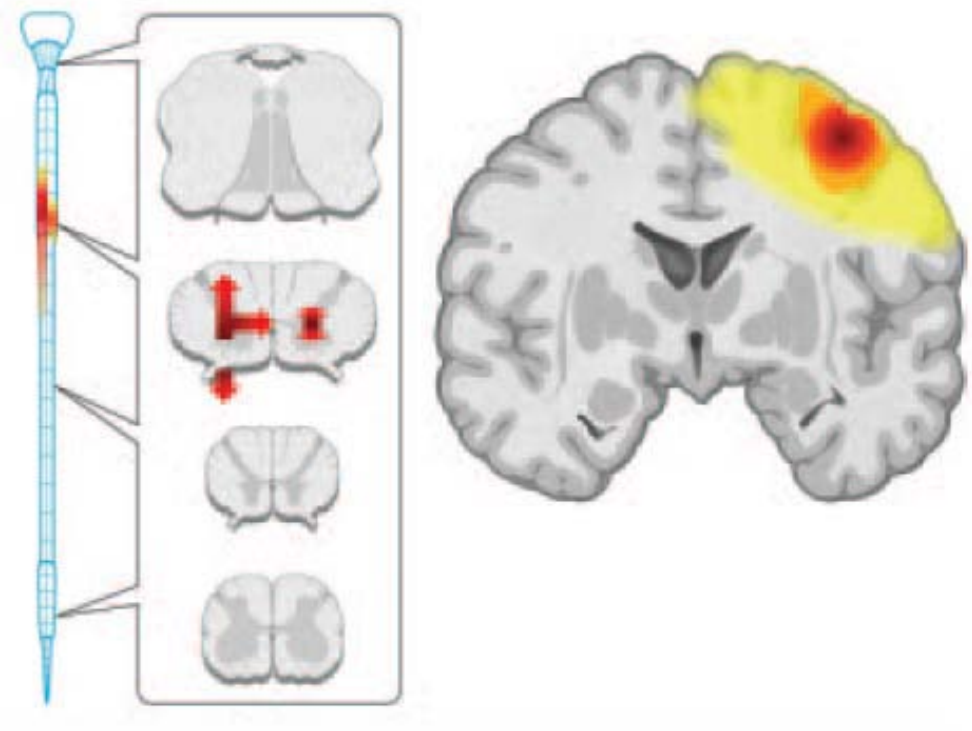


Focal onset and spread, the phenotype complexity



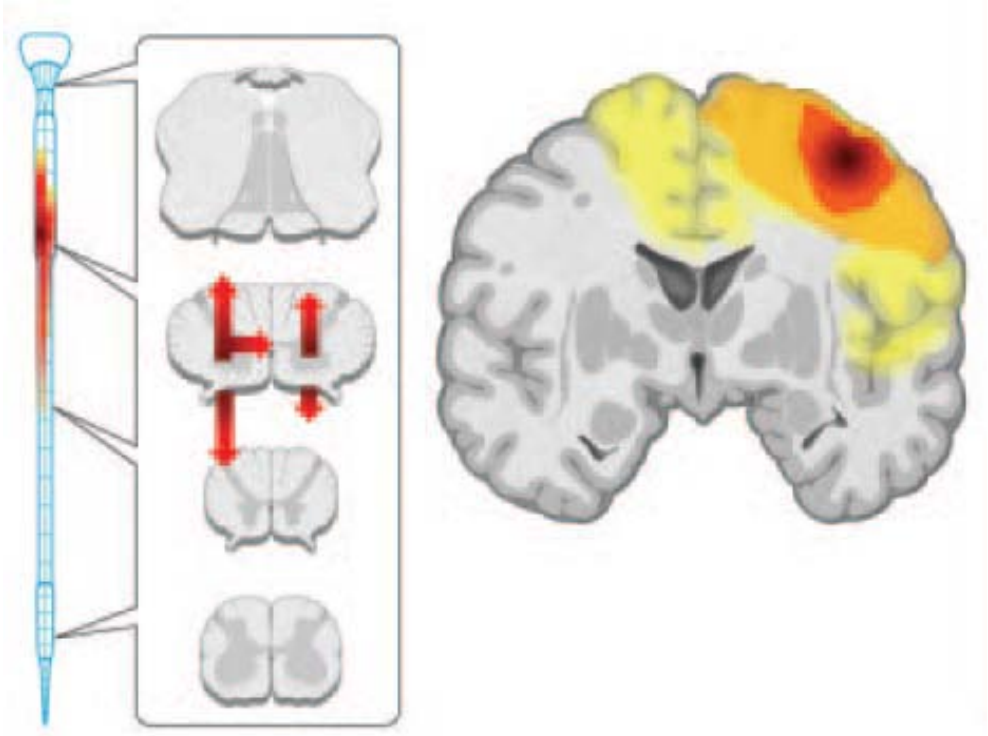
At site of onset, ratio of UMN to LMN involvement, and rate of progression are each highly variable but independent of each other

Early spread from the hand



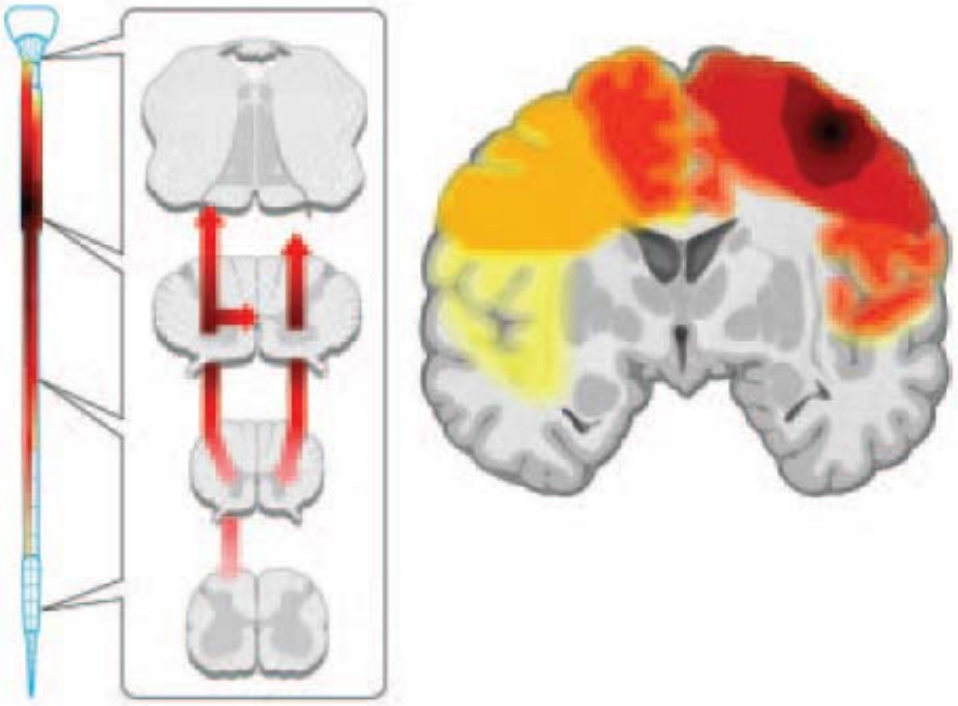
process spreads neuroanatomically through UMN and LMN levels, clinical manifestations become complex due to differences (“incongruity”) between somatotopic anatomy and anatomic distances of the 2 levels

Continued outward spread



• For LMN, spread is rostral-caudal (severity ipsilateral-contralateral) and must pass through the long thoracic region and thus appears to be mostly at one level
• For UMN, however, the ALS disease process continues to spread medial-lateral and more quickly begins to appear as diffuse

Advanced spread



Diffuse and symmetric degeneration through temporal-spatial summation within and between UMN and LMN levels

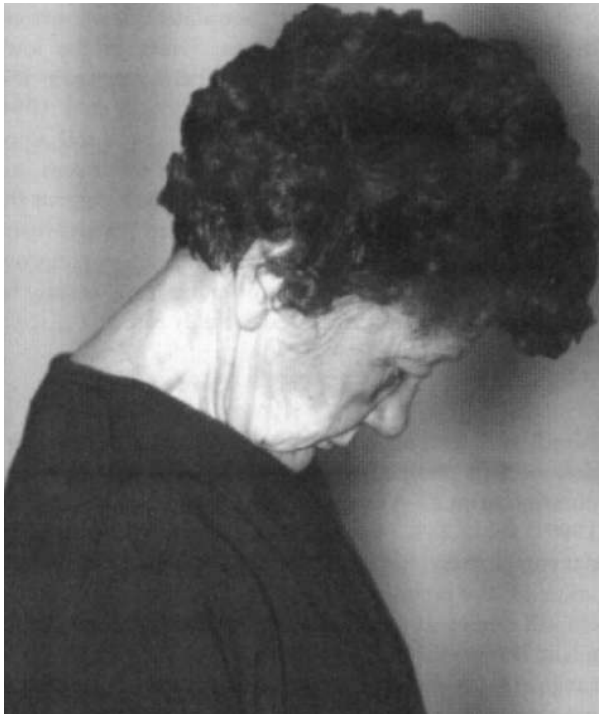
Possible molecular mechanisms

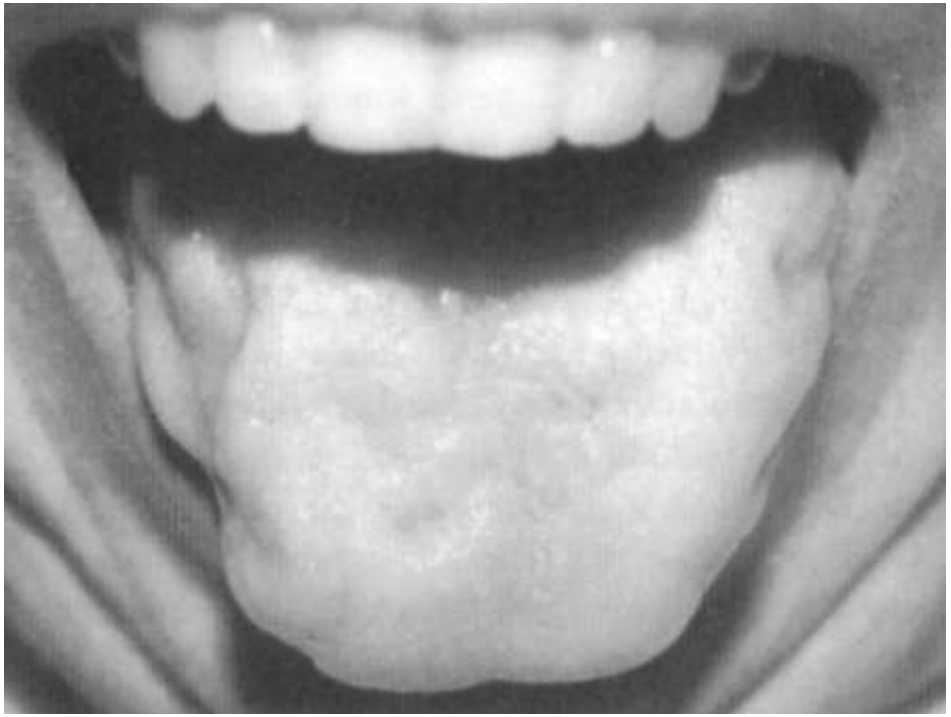
- **Signaling factors**
  - *cytokines, chemokines,or other paracrine signals*
- **Aberrant transmembrane signaling pathways**
- **Diffusion of a toxic fraction through the neuron micro environment**
- **Role of non-neuronal cells, especially glia**
- **Protein folding**

Dynamic determinant of phenotype: progression rate

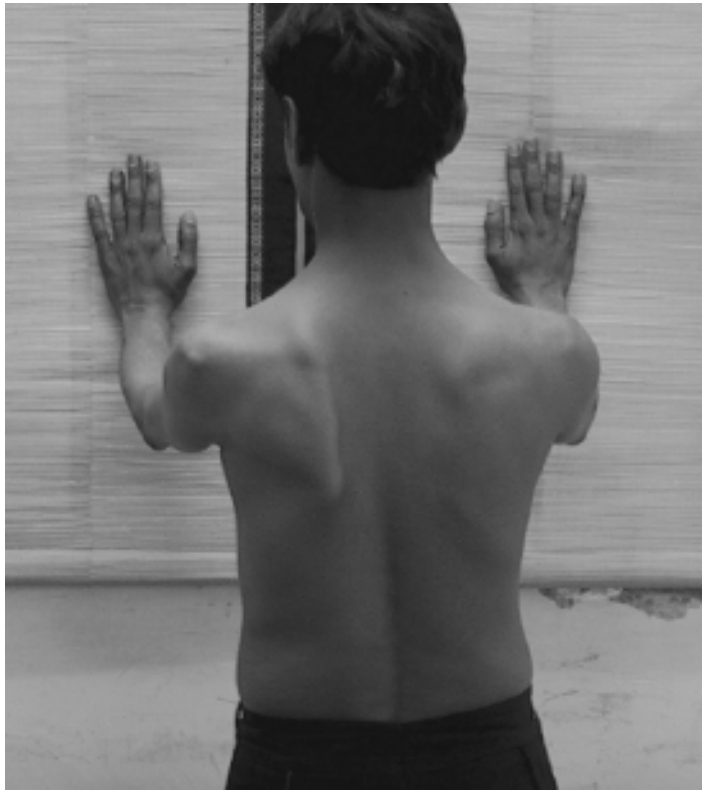
- Usually linear for any one individual patient
- Highly variable among different patients
  - from rapid (1 year) to slow(10 years) progression rate
- Reflects rate of spread and kinetics of underlying motor neuron degeneration

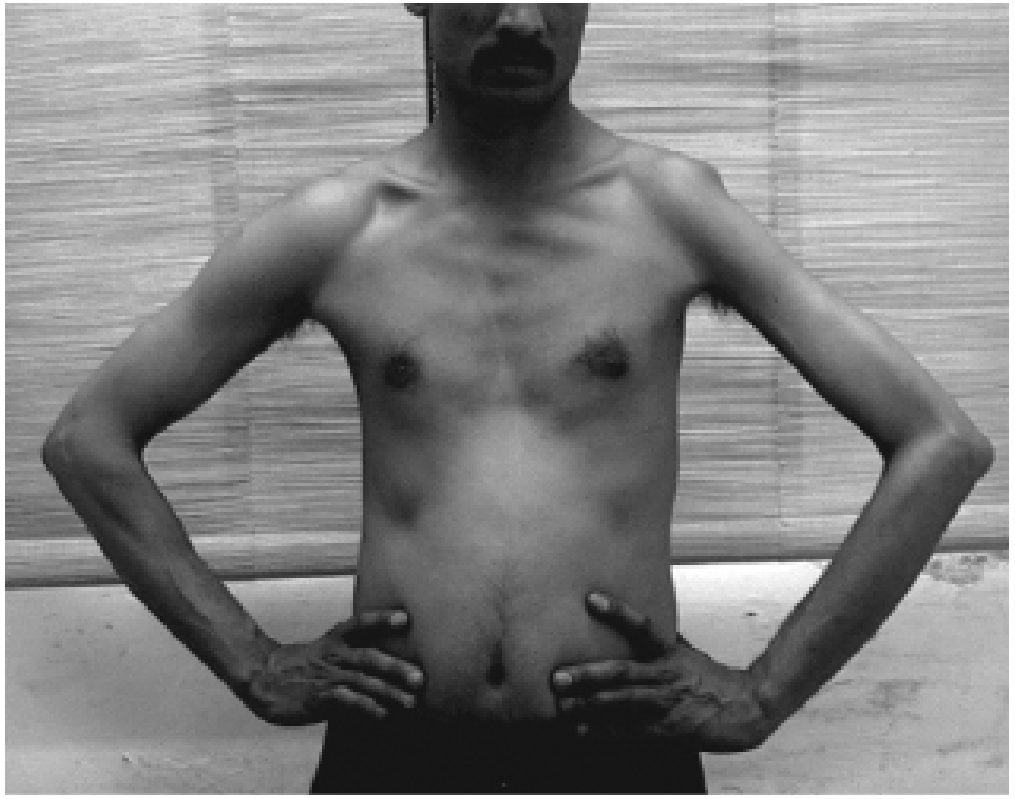
Heterogeneity of phenotype



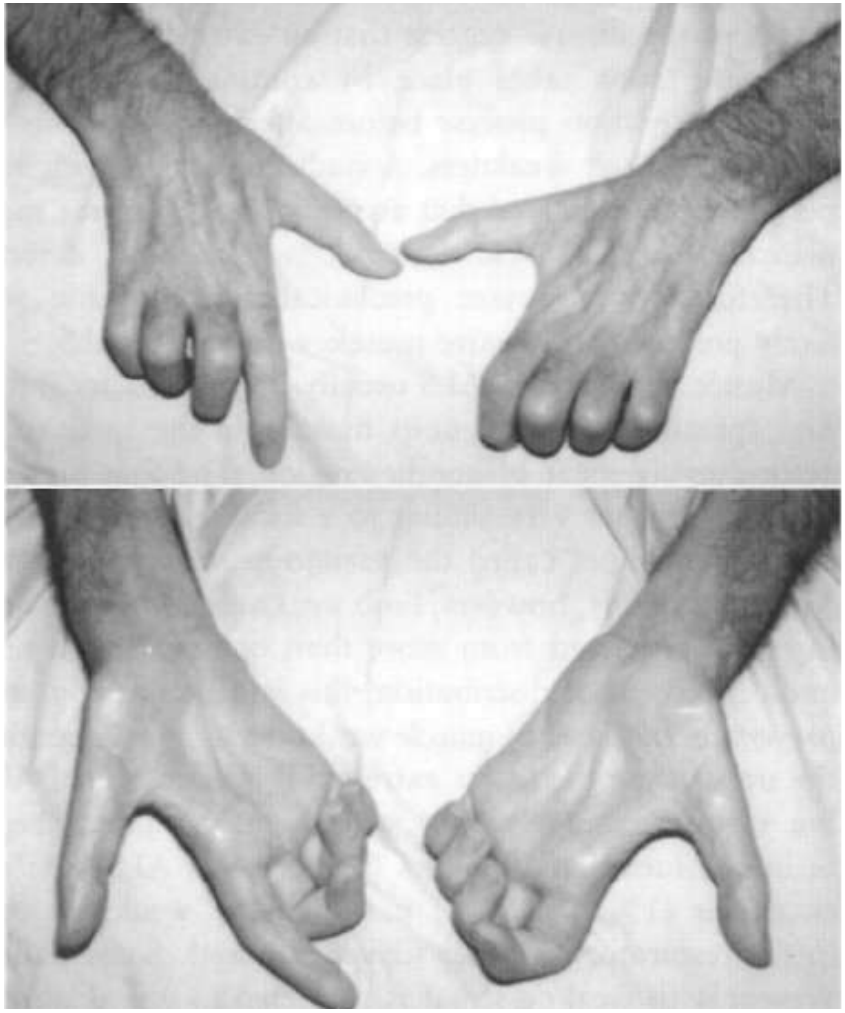


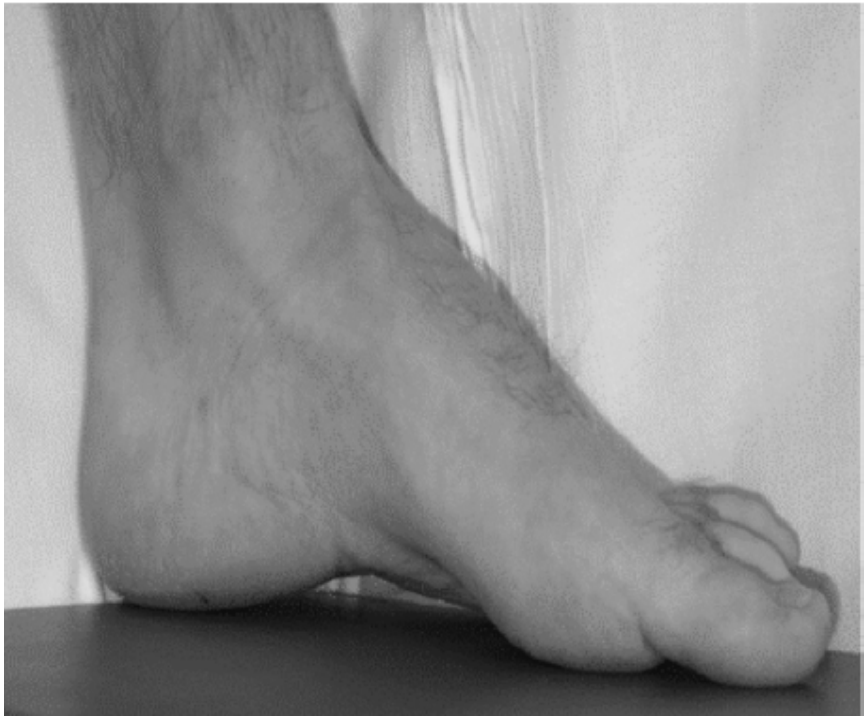
Heterogeneity of phenotype





Heterogeneity of phenotype



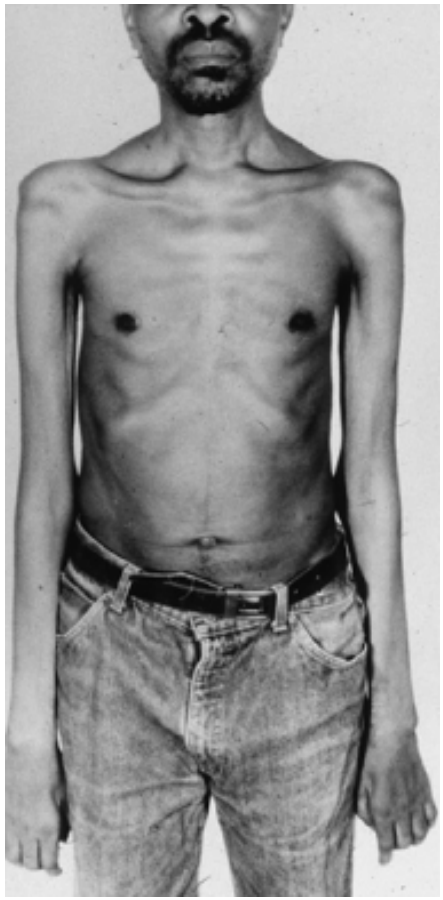


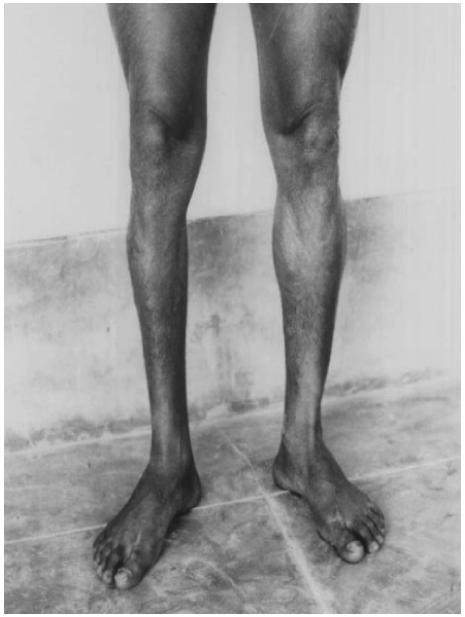
Progressive muscular atrophy

- **Accounts for 5–10% of patients with MND**
- **Indicates a pure LMN syndrome without accompanying UMN signs**
- **Almost alwayslimb onset**
  - *swallowing difficulties may eventually develop*
- **Up to 50% ofpatients may develop UMN signs and go on to develop typical ALS picture**

Predominantly lower motor neurons

- "flail arm" and "flail leg" variants
  - *initially localised forms with predominantly LMN presentation*
- Vulpian-Bernhardt syndrome
- Marie-Patrikios form





- symmetrical weakness and wasting in the distal muscle limbs
- hypotonia anddepressed tendon reflexesusually absent pyramidal signs
- not unusual focal brisk reflexes in the unaffected limb

Heterogeneity of phenotype

- Anatomical determinants
  - *site of onset*
    - *> randomeness, vulnerability*
- Mix of UMN and LMN involvement
  - *contiguos spread in anatomically distincts territories*
- Dynamic determinant progression rate
  - *disease-modifying factors*