Motor neurone disease Diagnosis and overview

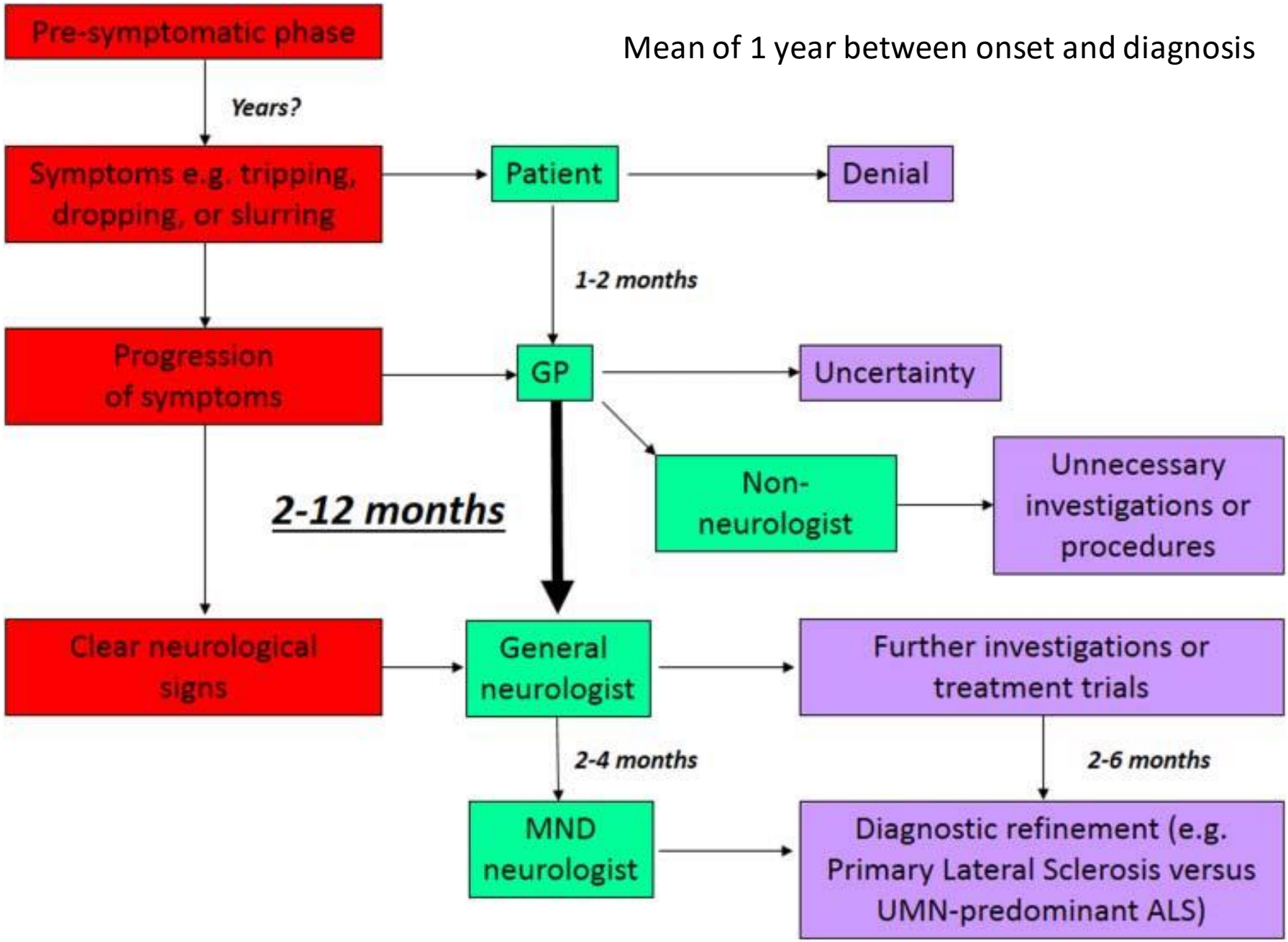
Mark Wardle

The 3 ‘P’s of MND

- Progressive no progression? Not MND
- Painless
- Paralysis

- A clinical syndrome with no “test”
- Investigations are usually to exclude other causes

Mean of 1 year between onset and diagnosis



Epidemiology of MND

- Typical reported figures suggest prevalence 7 per 100,000. Typical GP may see one patient per 10 years.
- Male > Female for younger patients
- Male = Female for older patients
- 95% sporadic, 5% familial

Definitions

- Upper motor neurone vs Lower motor neurone
- Sporadic (95%) vs Familial (5%)

- Primary lateral sclerosis — UMN
- Amyotrophic lateral sclerosis — UMN and LMN
- Progressive muscular atrophy — LMN

- Progressive bulbar palsy — Bulbar

- Flail arm — PMA variant affecting arm(s) only spread 12/12
- Flail leg — PMA variant affecting leg(s) only spread 12/12
- ALS-plus — ALS variant – with other features (e.g. dementia)

Defining diseases

- Phenotypes define:
  - Groups of patients with similar patterns
  - Prognosis
  - Investigations of disorders that can mimic MND
  - Cohorts for future study

- Genotypes define:
  - The molecular underpinning for disease

Amyotrophic lateral sclerosis

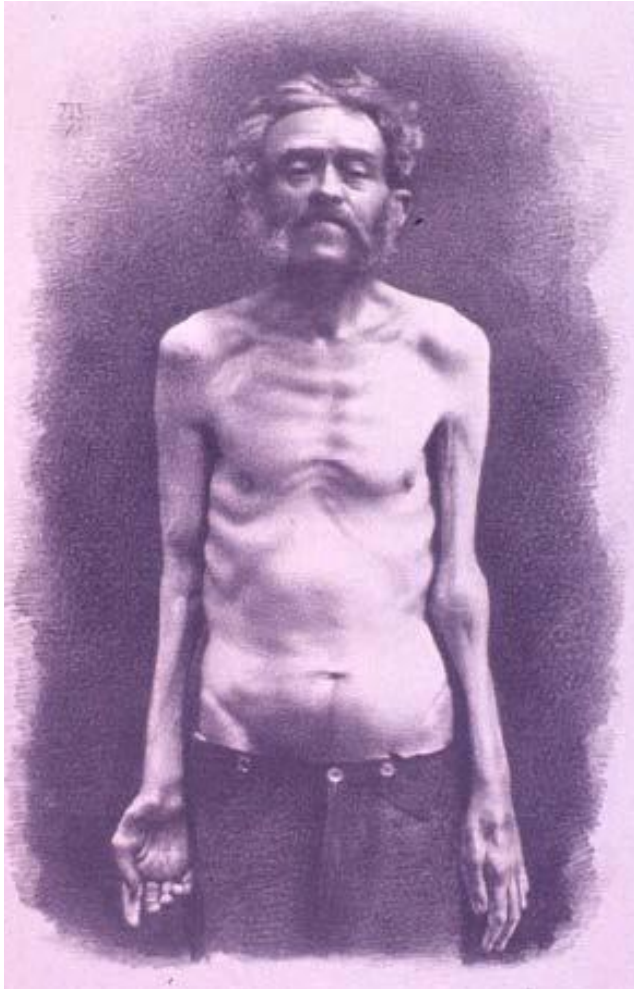
- Combination of upper and lower motor neurone signs and symptoms

- UMN: weakness, slowness, brisk reflexes, spasticity
  at post-mortem: lateral corticospinal tract is gliotic and hardened

- LMN: weakness, atrophy, fasciculations
  degeneration of lower motor neurones

Progressive muscular atrophy

- Progressive lower motor neurone disorder
- Survival prolonged compared to ALS
  (median survival 48 months vs 36 months)
- >1/5 develop upper motor neurone signs within 2 years = “LMN onset ALS”.
- Even if clinically pure LMN, at post-mortem frequently have UMN pathology.



Primary lateral sclerosis

- Progressive isolated upper motor neurone disorder
- Slower progression than ALS, no weight loss and absence of LMN signs.
- Over 1/2, later develop LMN signs (e.g. 77% of those who did, did so within 4 years) “UMN-onset ALS”

Progressive bulbar palsy

- Progressive upper and lower motor neurone disorder of cranial muscles.
- E.g. Tongue – spastic and yet wasted and fasciculating

- Frequently spreads to other regions -> “Bulbar-onset ALS”

Flail arm syndrome

- Brachial amyotrophic diplegia
- Often asymmetric
- Only LMN signs in arm(s) with no other involvement clinically.
- Man-in-a-barrel syndrome
- Progress less quickly, remain ambulant for longer, less respiratory involvement?

- Also: Flail leg syndrome

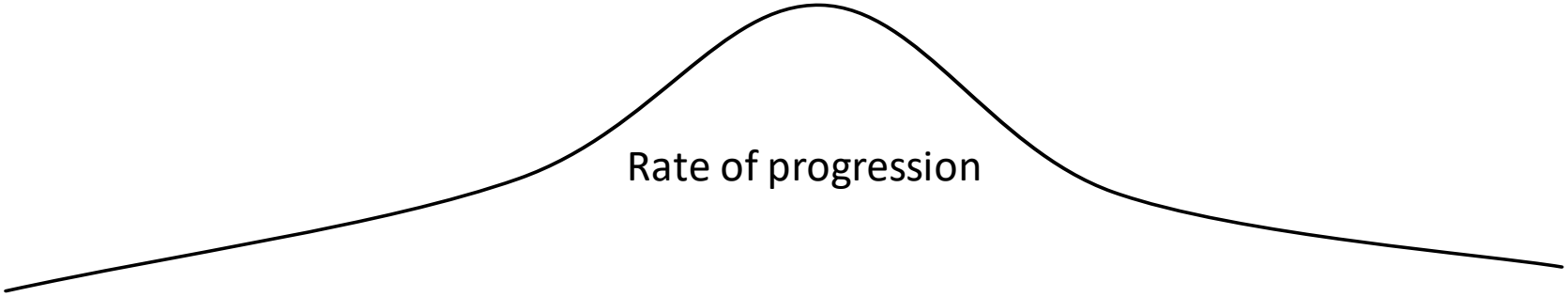
ALS-plus syndromes

- Frontotemporal dementia
- Parkinsonism
- Supranuclear gaze palsies
- Sensory involvement

A syndromic continuum

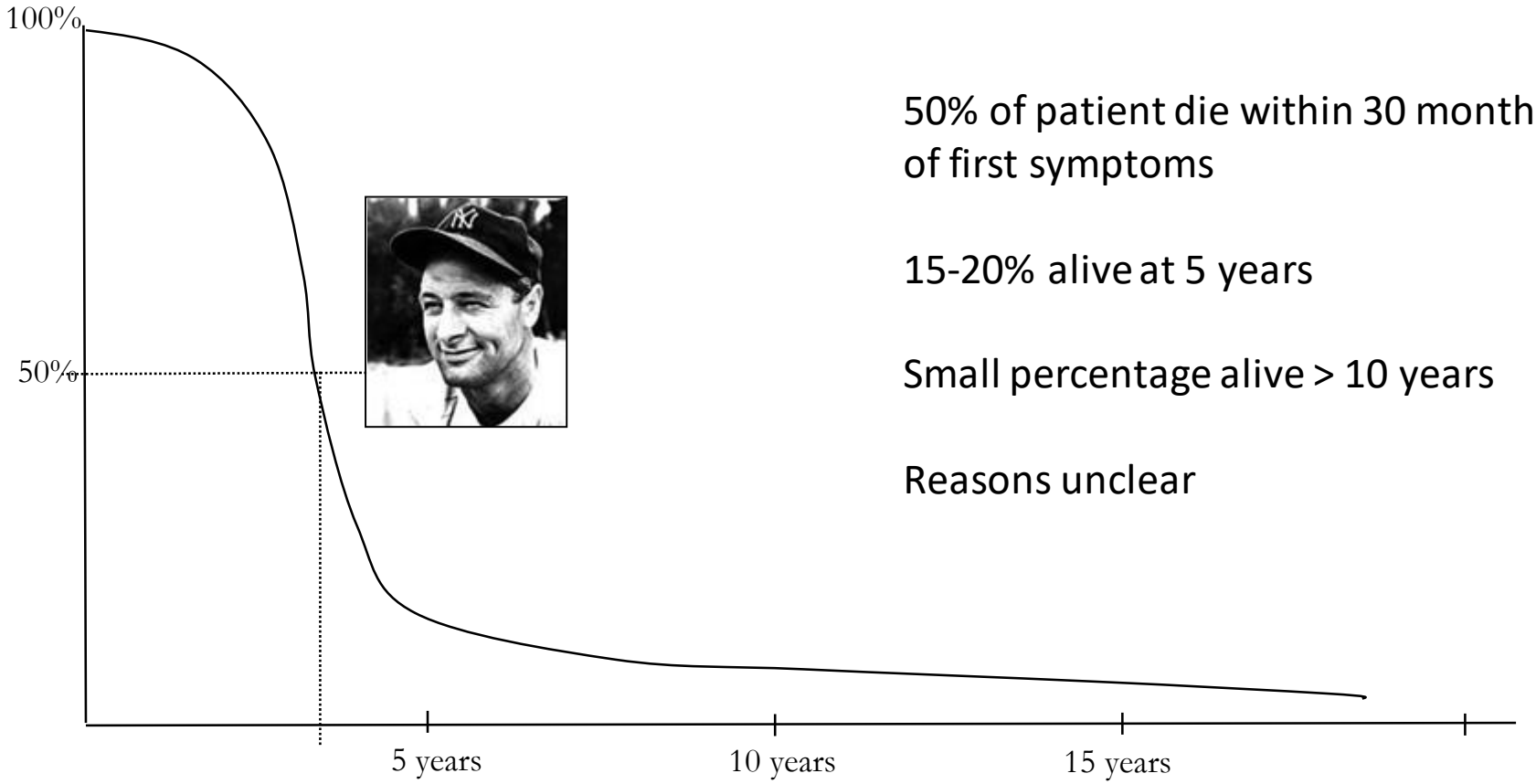
UMN	ALS			LMN
Primary lateral sclerosis without fasciculations	Primary lateral sclerosis with fasciculations	Complete “Charcot” type	Progressive muscular atrophy with fasciculations	Progressive muscular atrophy without fasciculations

NB: Patients change over time



Splitters vs. lumpers… and does it matter?

Heterogeneity in survival



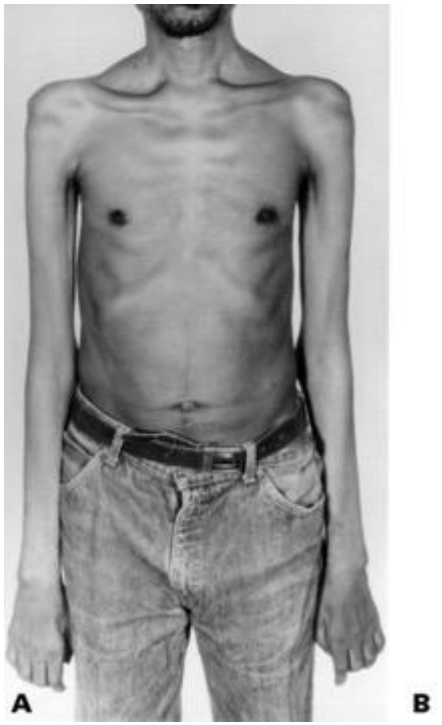
50% of patient die within 30 months of first symptoms

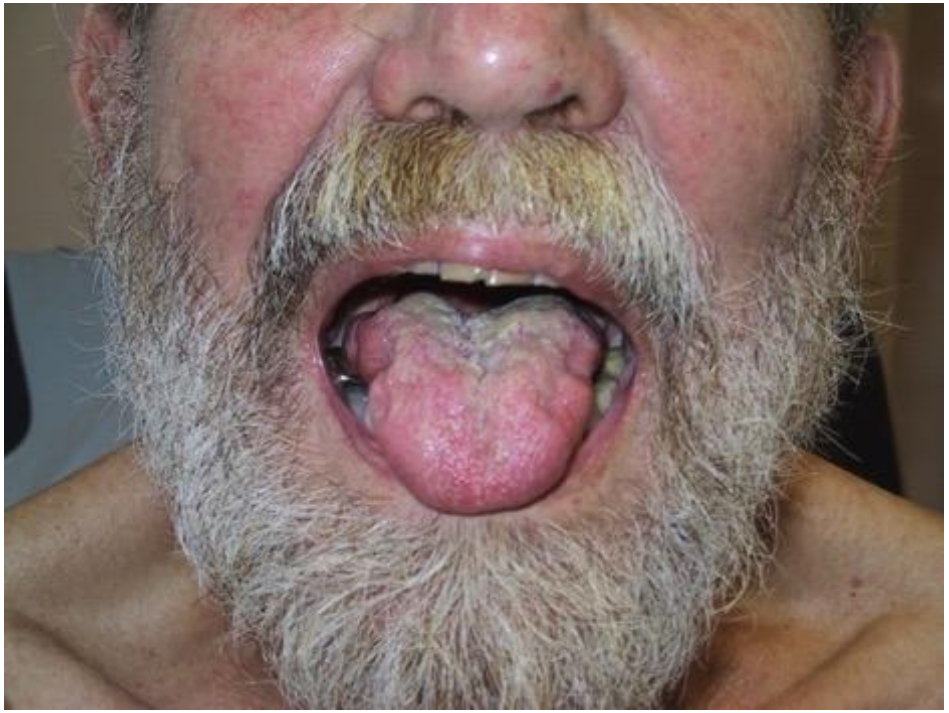
15-20% alive at 5 years

Small percentage alive > 10 years

Reasons unclear

Regional heterogeneity





'Flail arm'

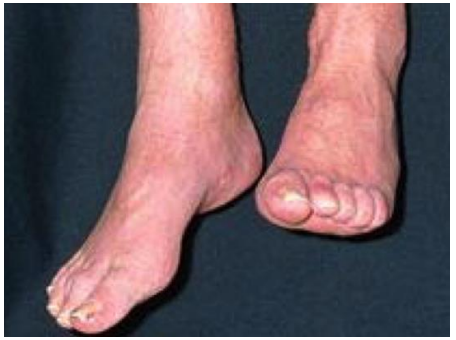
Survival 5-10 years

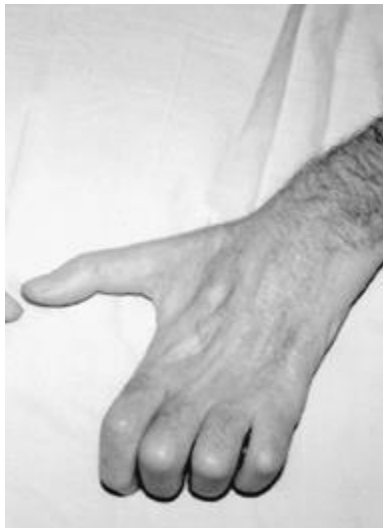
VS.

Bulbar-onset

Survival 1-2 years

Body segments





- Bulbar (20%)
- Arms
- Legs
- 1/3 rule (ish)
- 80% present with asymmetric weakness
  e.g. “foot drop”
  e.g. “split-hand syndrome”
- 1-2% present with respiratory involvement (e.g. we see on ITU for the first time) or other presentations (e.g. dropped head)

- *Note: no eye movement or sphincter involvement*

secretions
nutrition
communication

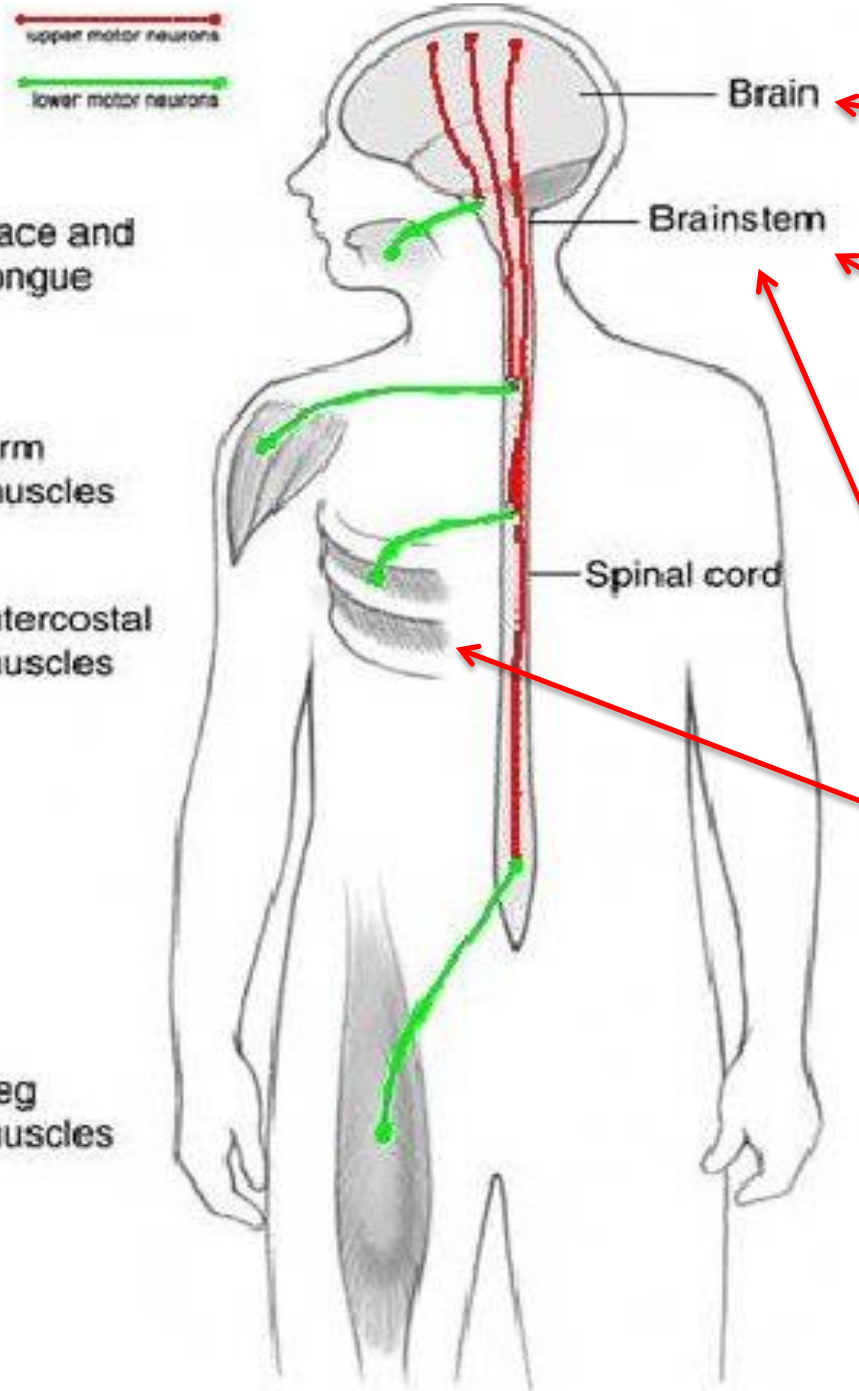
cognition
behaviour

emotionality

disability

loss of
independence

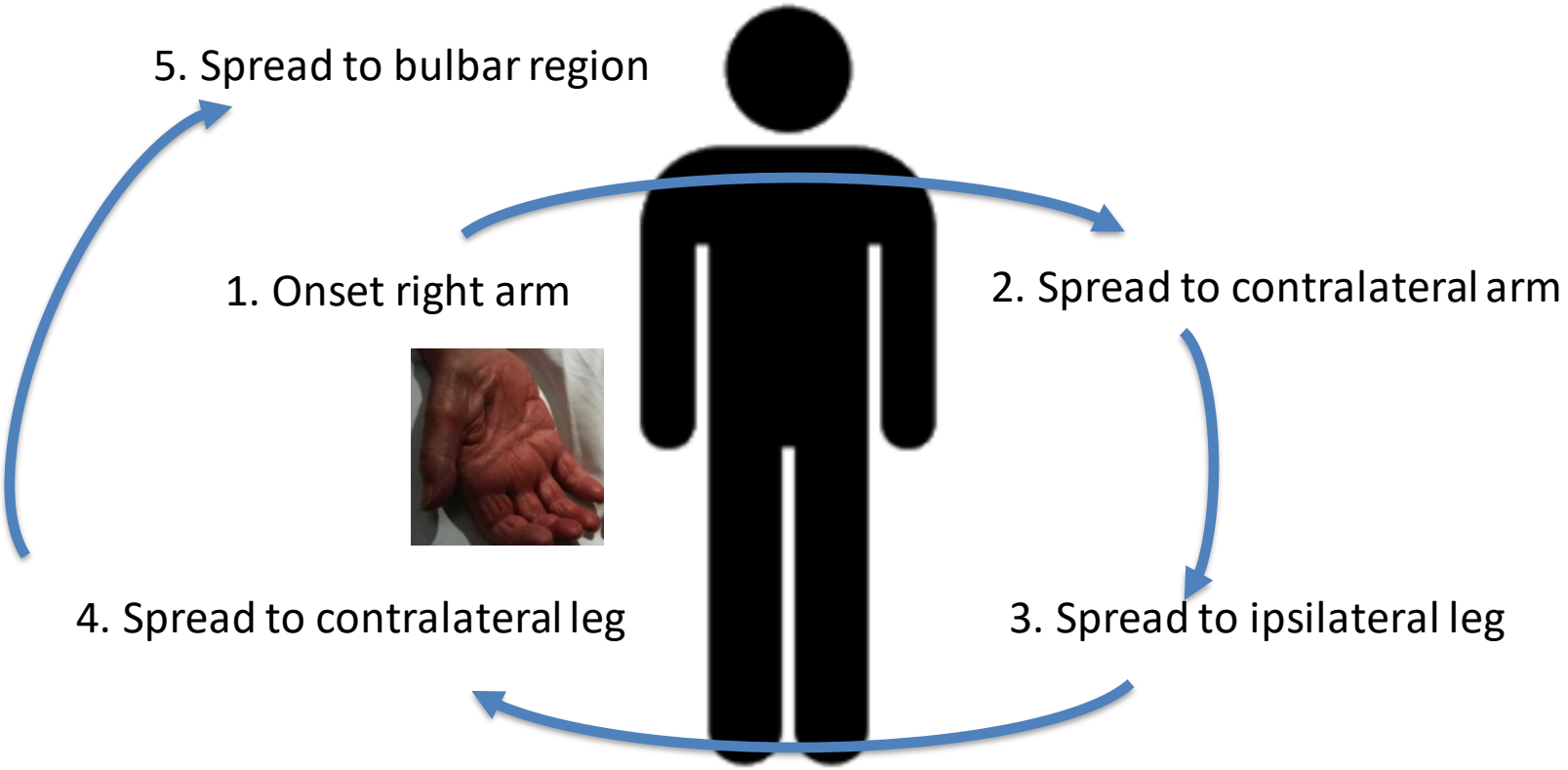
respiratory
insufficiency



From Martin Turner

Progression

- Symptoms spread within segment of onset
- Then to other regions



Motor phenotype summary

- Highly heterogeneous
- 3 primary variables?
  - Body region of onset
  - Relative mix of UMN and LMN involvement
  - Rate of progression

- So where is the disease process?

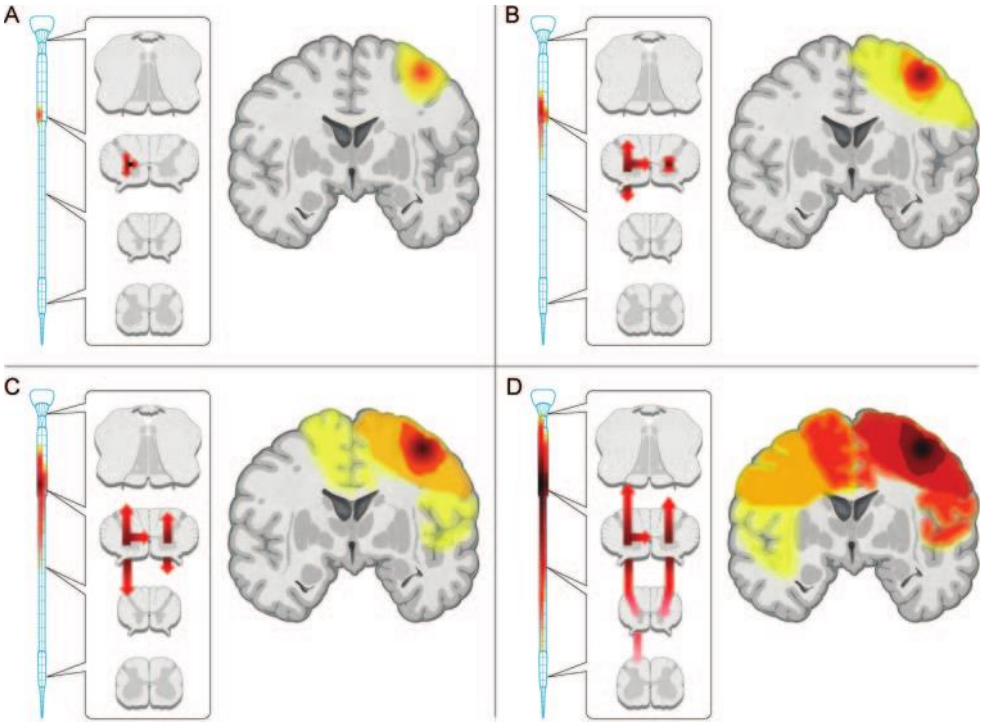
MEDICAL HYPOTHESIS

ALS motor phenotype heterogeneity, focality, and spread

Deconstructing motor neuron degeneration

Neurology® 2009;73:805-811

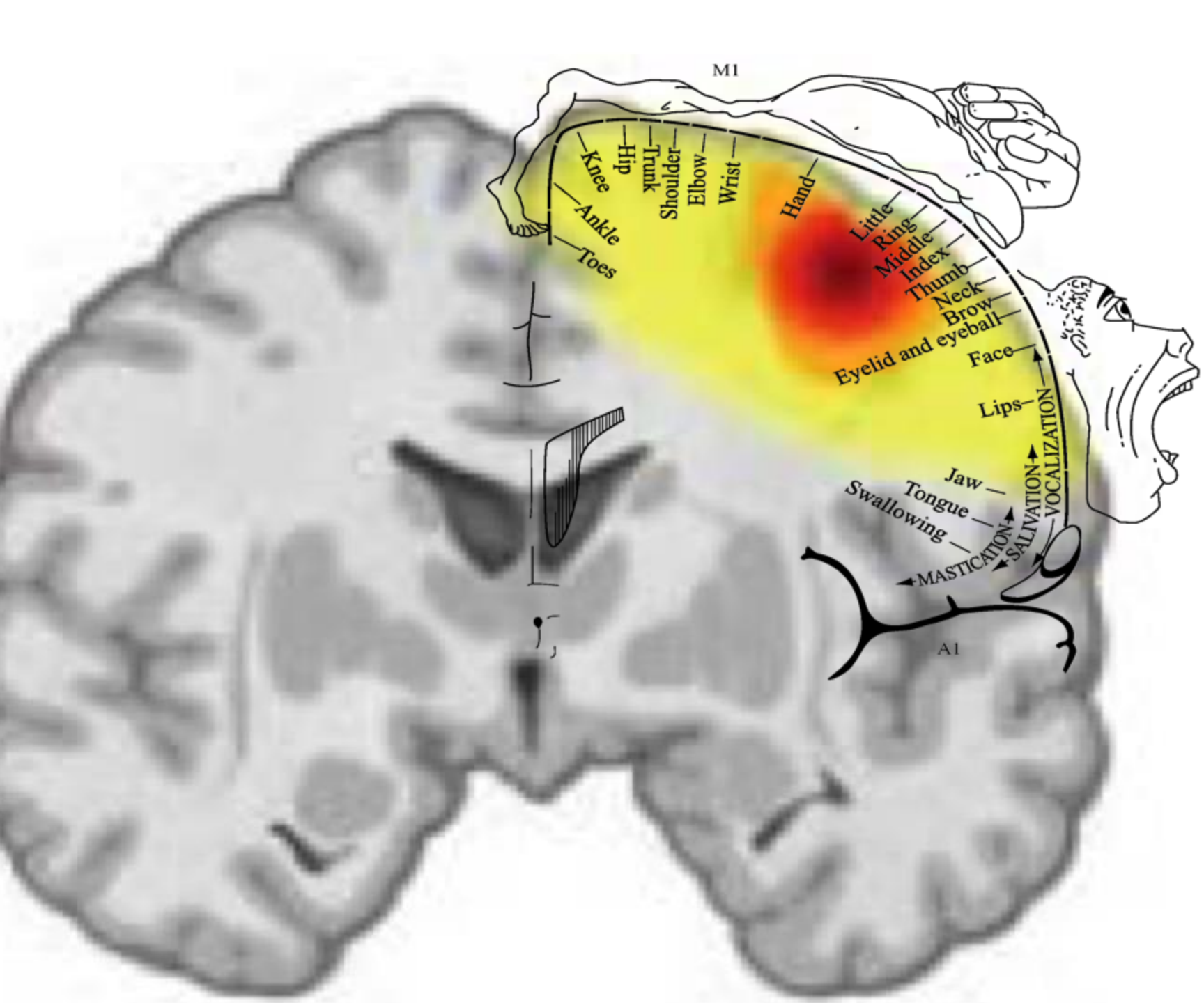
Figure An idealized model of the natural history of amyotrophic lateral sclerosis (ALS) based upon focality and contiguous spread



(A) Onset: At clinical onset, degeneration involves upper motor neurons (UMNs) and lower motor neurons (LMNs) that in

Motor phenotypes are determined by the anatomy of the underlying neuropathology.

Disease is a focal brain process spreading through the 3-d anatomy of UMN and LMN levels


M1
Knee
Hip
Trunk
Shoulder
Elbow
Wrist
Hand
Ankle
Toes
Little
Ring
Middle
Index
Thumb
Neck
Brow
Eyelid and eyeball
Face
Lips
Jaw
Tongue
Swallowing
MASTICATION
SALIVATION
VOCALIZATION
A1

Defining phenotype

- So it is important from a prognostic point of view….
- Reasons to understand phenotype:
  - (Prognosis)
  - Considering other potential causes and investigations to perform

Diagnosis

- Considering the diagnosis in the first place
- Excluding other causes of
  - UMN syndromes
  - LMN syndromes
  - Mixed UMN/LMN syndromes

Considering the diagnosis

- Progressive weakness AND :
  - Fasciculations
  - Wasting of the tongue
  - The split-hand
  - Head-drop
  - Emotionality (Pseudo-bulbar affect)

Diagnostic red flags

- Symptoms and signs consistent with a lesion at a single anatomical side
  - MRI of relevant area
- No progression or fluctuations
- Unusual or prominent sensory symptoms
- Dysphagia preceding dysarthria
- Sphincter involvement
- Fasciculations without weakness
- Symptoms remain confined to one limb
- Limb weakness but no wasting

Common and less common gotchas

- Cervical myelopathy (LMN signs in upper limbs, UMN signs in lower limbs)
- Multifocal motor neuropathy (MMN)
- Brainstem lesions

- Hereditary spastic paraparesis
- Polymyositis or inclusion body myositis
- Primary progressive multiple sclerosis

	Mimicking disease	Key clues
LMN-predominant signs		
	Benign fasciculations	No weakness
	Multifocal motor neuropathy	Weakness, but no wasting Predilection for finger extensors Conduction block on NCS
	Neuralgic amyotrophy	Pain at onset. Single region.
	Kennedy's syndrome	Very slow. Gynaecomastia. Chin fasciculations. X-linked
	Motor-predominant CIDP	Symmetrical, slow conduction velocities on NCS
	Inclusion body myositis	Raised CK > 1000. Quadriceps
UMN-predominant signs		
	Hereditary spastic paraplegia	Younger-onset, minimal arm involvement. Family history
	Primary progressive multiple sclerosis	Abnormal MRI brain / spine / CSF examination
Mixed UMN and LMN signs		
	Cervical myelo-radiculopathy	Neck pain, sphincter involvement. MRI

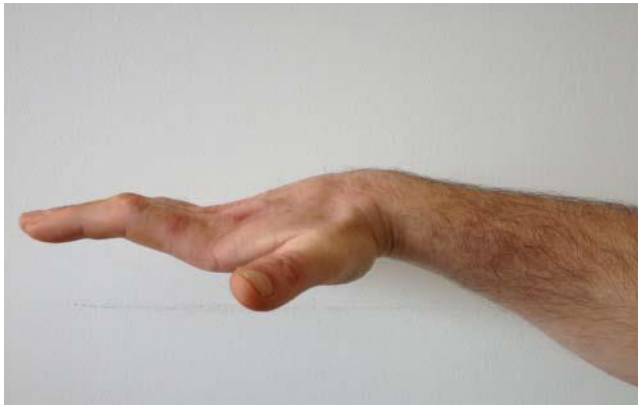
Benign fasciculations

- Exercise, anxiety, caffeine, alcohol
- < 40 years old, medical students and clinicians!
- If no weakness, and age < 40, re-assurance!

- Most patients with MND unaware of fasciculations.

Multifocal motor neuropathy

- Rarer than MND
- Pure motor neuropathy
- Slowly progressive asymmetric weakness
- 3M:1F
- Wrist / finger drop common.
  [but 1/3 LL]



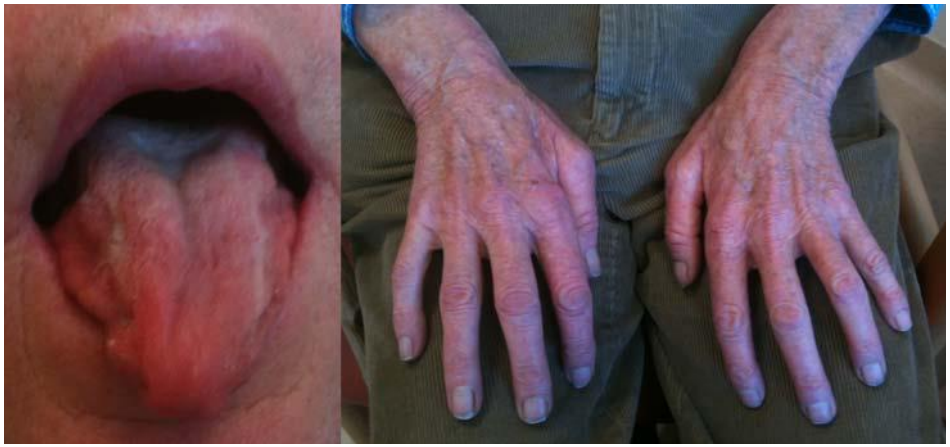
- *Weakness with little wasting*

Neuralgic amyotrophy

- “Brachial neuritis”
  “Parsonage-Turner syndrome”
- Single region with wasting and weakness
- Usually pain at onset but up to 5% can be painless.

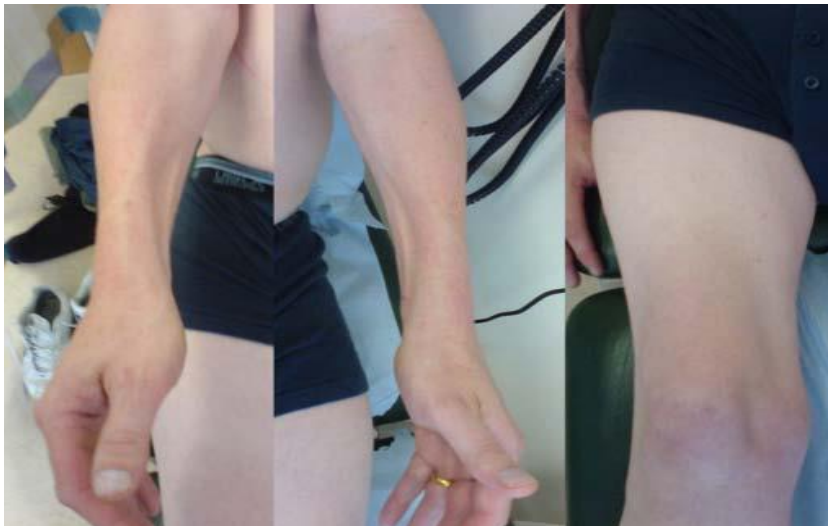
Kennedy's syndrome

- X-linked so men affected
- LMN syndrome. Fasciculations common, particularly in chin
- Reduced fertility and gynaecomastia due to androgen insensitivity.
- Lifespan normal.
- Genetic test



Inclusion body myositis

- Slowly progressive painless myopathy
- Predilection for quadriceps and medial forearm
- CPK > 1000
- Muscle biopsy



Cervical myelo-radiculopathy

- Combination of UMN and LMN signs
- Can have sphincter involvement, but not always
- NB: we see large numbers of patients with incidental spinal degenerative disease (especially given age group!)
- Carefully look for signs above neck to avoid over-interpretation of neck pathology

Investigations

- Creatine kinase : consider alternatives when >1000
- CSF : if inflammatory neuropathy or malignant infiltration considered
- Nerve conduction studies : to look for neuropathy
- Electromyography : to look for evidence of denervation in areas deemed unaffected clinically
- MRI brain : if dysphagia or hemiparesis
- MRI c/spine : lack of signs above neck
- MRI l/spine : LMN-only syndrome in legs
- Muscle biopsy : if myositis suspected

Formal diagnostic criteria

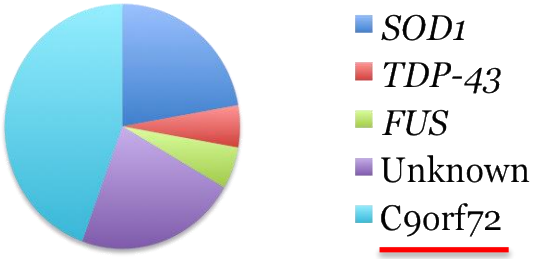
- El-Escorial
- Awaji : earlier diagnosis using neurophysiology
- Evidence of LMN loss and re-innervation with fibrillation and sharp waves
- An affected region:
  - 2 muscles in cervical and lumbosacral
  - 1 muscle in bulbar and thoracic
- Clinically definite ALS:
  - LMN and UMN signs in 3 regions
- Clinically probable ALS:
  - LMN and UMN signs in 2 regions and UMN signs rostral to LMN
- Clinically possible ALS:
  - LMN and UMN signs in 1 region and UMN signs rostral to LMN

But what about genetics?

- Fortunately, genetic panels are now available.
- Unfortunately, such panels can be difficult to interpret and cause difficulties when counselling unaffected relatives.

Family history 5%

MUST CONSIDER FTD



Apparently sporadic 95%

Incomplete penetrance

Death before symptoms

De novo mutations

Non-paternity

Hidden illness, especially FTD

Turner MR *et al.* Lancet Neurology 2013

C9ORF72

- Hexanucleotide repeat expansion
- Phenotypes: classical ALS, FTD and ALS+FTD
- 24-47% of familial MND

Other genetic causes

- SOD1 (ALS1) : 12-20% of familial MND
- FUS : 5%
- ANG : 2%
- TARDBP : 5%
- FIG4 : 3%

- Panels can screen multiple genes in one go, but beware difficulties in interpretation and complications relating to genetic counselling

Conclusions

- Consider MND in painless, progressive paralysis
- Defining the clinical phenotype important in giving prognosis, determining alternative diagnoses and investigations
- Genetic causes – particularly in familial disease