- Anterior horn cell disease

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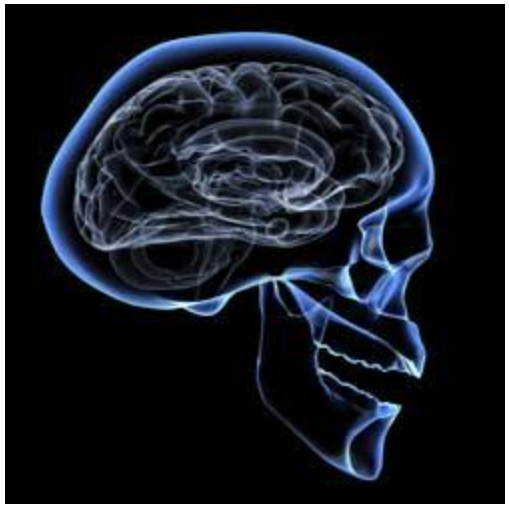
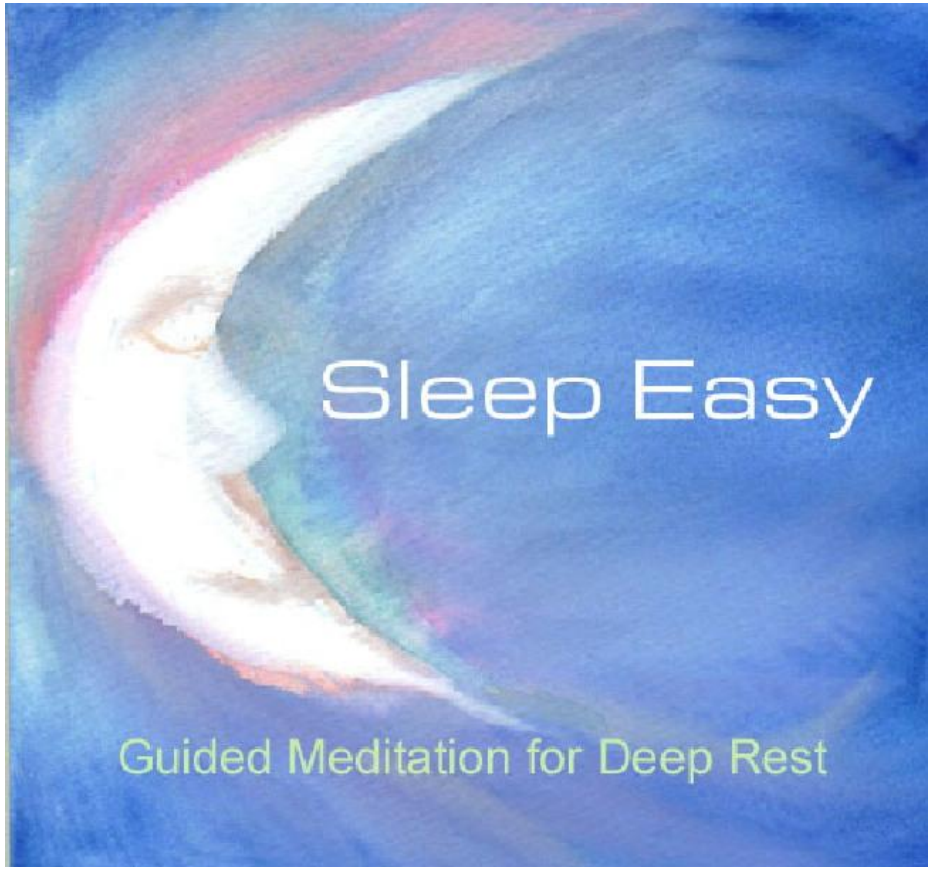
- February 2012




Sleep Easy
Guided Meditation for Deep Rest

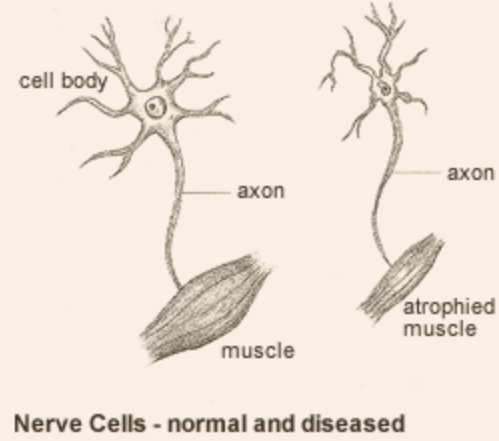
Anterior horn cell disease

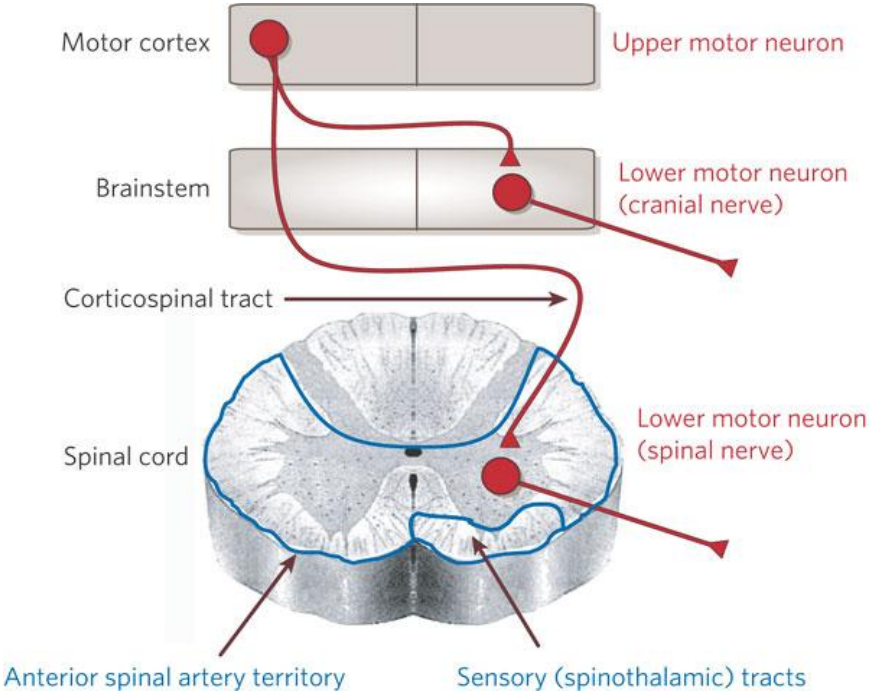
Motor neuron pathology.

- Vulnerable to defects in excitotoxicity, RNA transport and splicing,axonal protein transport, mitochondrial function,protein misfolding and oxidative stress.
- Sporadic, late onset, degenerative - motor neuron disease (MND) = amyotrophic lateral sclerosis (ALS)
- Untreatable and fatal.

Neuroanatomy

- Lower motor neurons in brainstem and spinal cord





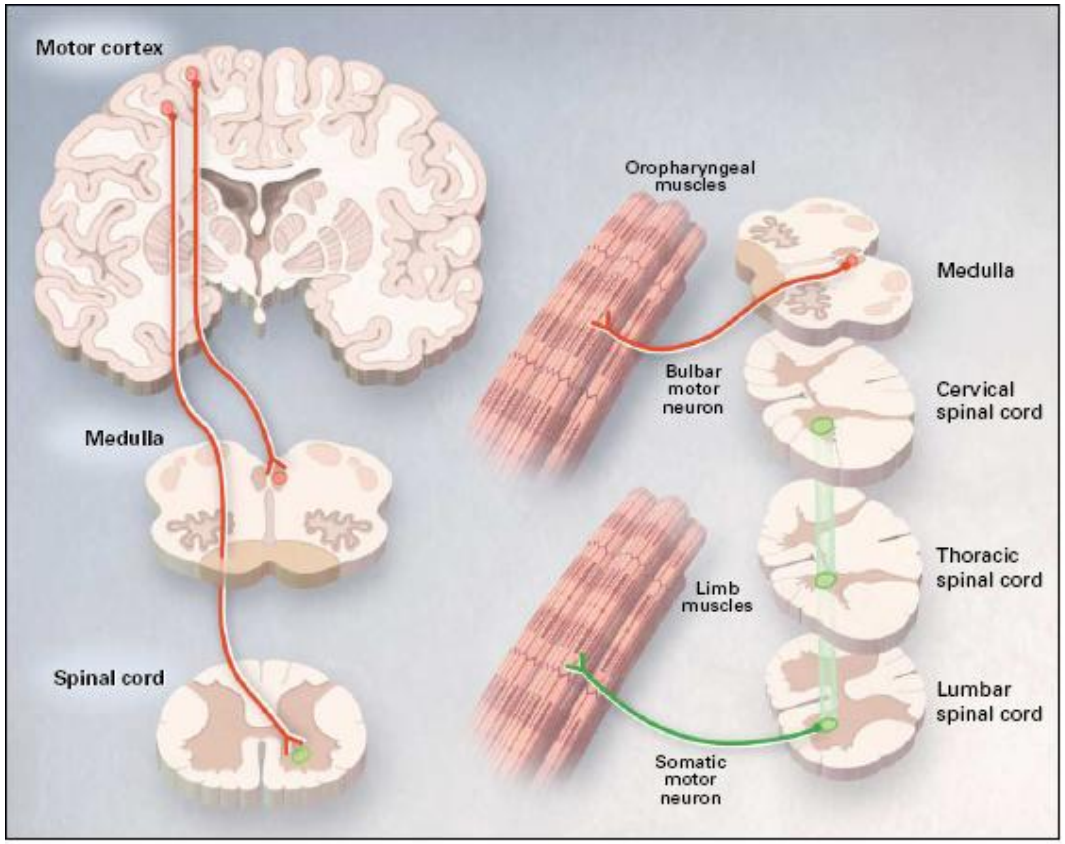


Figure 1. Motor Neurons Selectively Affected in ALS.

Degeneration of motor neurons in the motor cortex leads to clinically apparent signs of upper motor neuron abnormalities: overactive tendon reflexes, Hoffmann signs, Babinski signs, and clonus. Degeneration of motor neurons in the brain stem and spinal cord causes muscle atrophy, weakness, and fasciculation.

AETIOLOGY

- Environmental exposure
- Age, male gender and a family history
- Absence of a family history - sporadic ALS

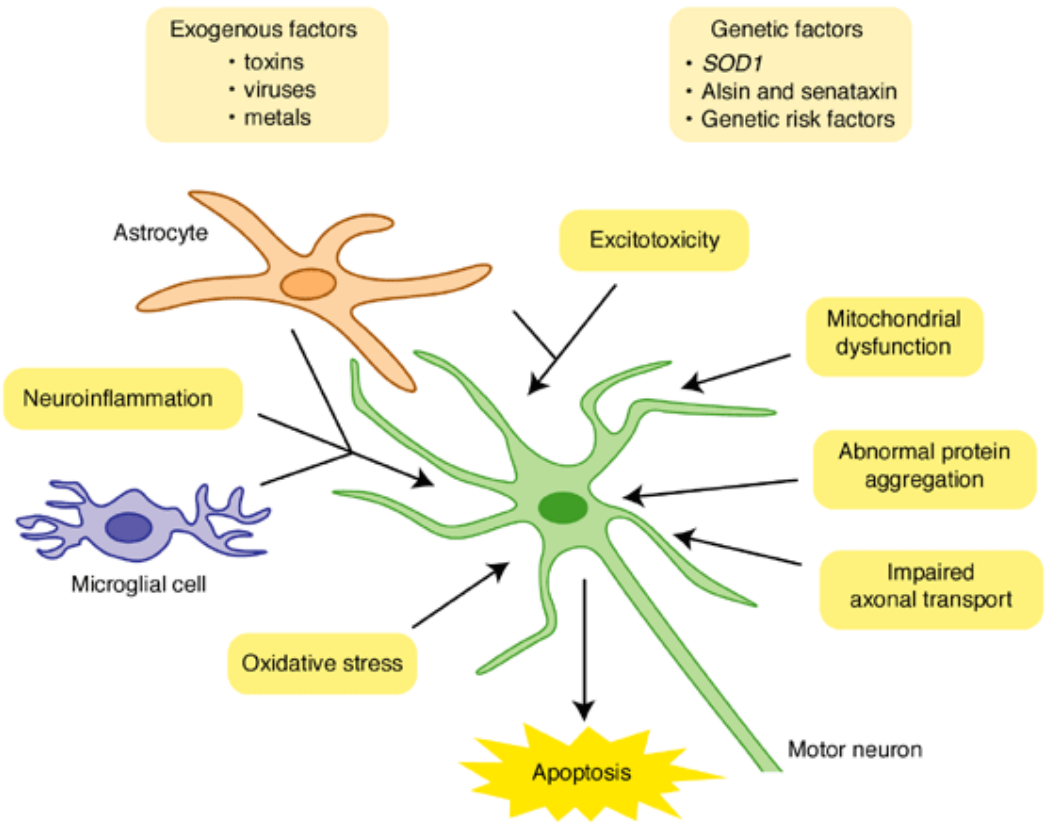
Familial ALS

- Clinically indistinguishable from sporadic disease .
- Onset 10 years younger than sporadic ALS.
- All subtypes of ALS can be found .

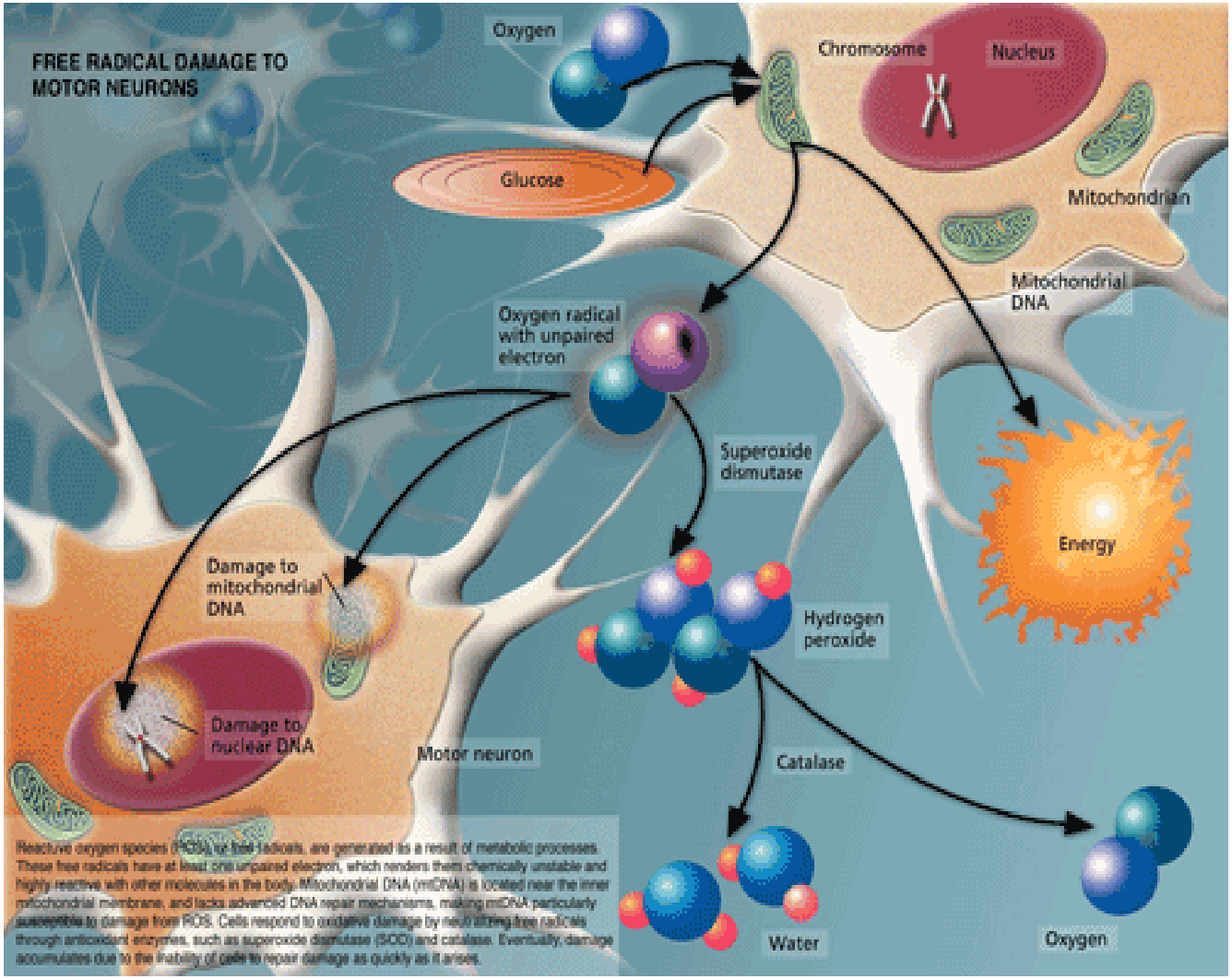
YOU do not need to know this

Table 1 Familial amyotrophic lateral sclerosis

Locus	Gene	Frequency	Phenotype
ALS1 (21q22)*	SOD1	15–20% of familial ALS, 1–2% of total ALS	Typical ALS clinically but no TDP-43 staining at autopsy
ALS2 (2q33)	Alsin	Rare recessive, mostly in inbred populations	Atypical. Juvenile onset upper motor neuron syndrome resembling primary lateral sclerosis
ALS3 (18q21)*	Unknown	One family	Typical ALS
ALS4 (9q34)	Senataxin	Very rare	Atypical. Young onset, slow progression, distal weakness with upper motor neuron features
ALS5 (15q15)	Unknown	Rare recessive	Atypical. Juvenile onset disease with slow progression
ALS6 (16q12)*	FUS	3–5% of familial ALS	Typical ALS
ALS7 (20p13)*	Linkage unconfirmed	One family	Typical ALS
ALS8	VAPB	Very rare, mostly Brazil	Atypical, variable, generally lower motor neuron
ALS9 (14q11)*	Angiogenin	Rare	Typical ALS
ALS10 (1p36)*	TDP-43	1–3% of familial ALS	Typical ALS
ALS-FTD	9q21/9q21, others	Variable	ALS, frontotemporal dementia or both



Overview diagram summarising some of the theories of amyotrophic lateral sclerosis pathogenesis


FREE RADICAL DAMAGE TO MOTOR NEURONS
Oxygen
Chromosome
Nucleus
Glucose
Mitochondrian
Mitochondrial DNA
Oxygen radical with unpaired electron
Superoxide dismutase
Energy
Damage to mitochondrial DNA
Hydrogen peroxide
Damage to nuclear DNA
Motor neuron
Catalase
Water
Oxygen
Reactive oxygen species (ROS), or free radicals, are generated as a result of metabolic processes. These free radicals have at least one unpaired electron, which renders them chemically unstable and highly reactive with other molecules in the body. Mitochondrial DNA (mtDNA) is located near the inner mitochondrial membrane, and lacks advanced DNA repair mechanisms, making mtDNA particularly susceptible to damage from ROS. Cells respond to oxidative damage by neutralizing free radicals through antioxidant enzymes, such as superoxide dismutase (SOD) and catalase. Eventually, damage accumulates due to the inability of cells to repair damage as quickly as it arises.

THE CORE FEATURES OF MND

- Progressive motor syndrome with evidence of UMN + LMN
- Asymmetrical onset and progresses non random pattern .
- Multisystem involvement (cognitive, occasionally sensory or autonomic).

FEATURES OF MND

- Diagnosis clinical
- Imaging to exclude structural pathology mimicking MND.
- Neurophysiology not diagnostic - support denervation and exclude other conditions

Epidemiology

- Incidence 2/100 000 population per year
- 1/1000 death certificates .
- Prevalence 7/100 000.
- age of onset 65 years
- male >

Clinical presentation

- 1/3 upper limb
- 1/3 lower limb
- 1/3 with disorders of speech and swallowing;
- 1–2% isolated respiratory failure.
- Axial weakness- gait or ‘‘dropped head’’.
- Frontotemporal dementia < 5%
- 40–50% executive dysfunction on formal testing.
- 10% frontotemporal dementia develop MND.

Natural history and prognosis

- 2–3 years death.
- Progression linear.
- Slowly progressive in initial phase
- Abrupt changes in functions such as walking, standing and transferring – failure of compensatory muscle power

Natural history and prognosis

- 50% die within 30 months,
- 15–20% alive at 5 years
- Small %> 10 years.

Natural history and prognosis

- Diagnostic delay is marker of survival.
- Bulbar onset, early respiratory muscle weakness and elderly shorter survival.
- Clinical subtypes - prognosis.
- Timing of death predictable
- Terminal phase for long period of time- planning difficult.

- What is the differential diagnosis of a patient with motor neuron disease

- ANSWER
- It depends

Differential diagnosis and investigation

- Weakness in one limb - wide differential diagnosis.
- 8% of patients misdiagnosed with MND.
- Commonest misdiagnosis cervical spine disease - spondylotic myelopathy and radiculopathy

Differential diagnosis

- Inclusion body myositis
- Multiple sclerosis
- Motor neuropathy.

- Progressive wasting and fasciculation of the tongue is almost always due to MND.

Escorial research diagnostic criteria for ALS

- Definite ALS

UMN signs and LMN signs in three regions

- Probable ALS

UMN signs and LMN signs in two 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 two regions.

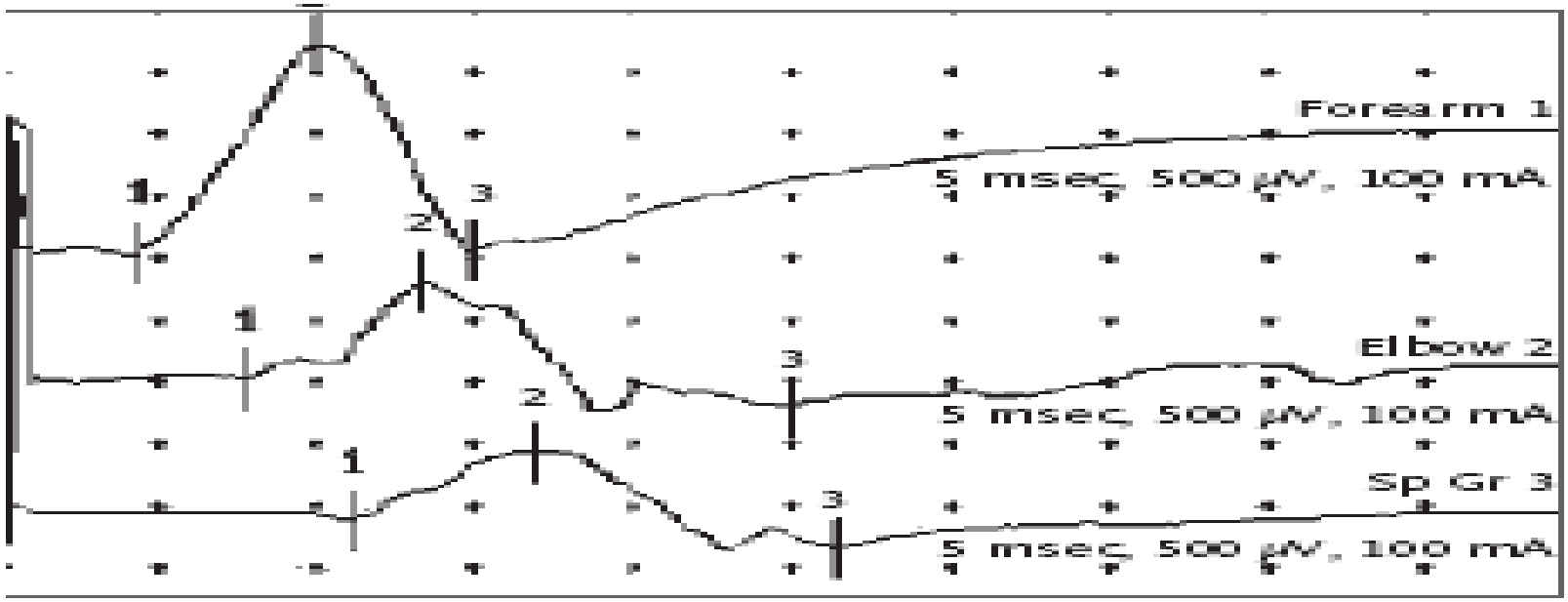
EL ESCORIAL DIAGNOSTIC CRITERIA-2003

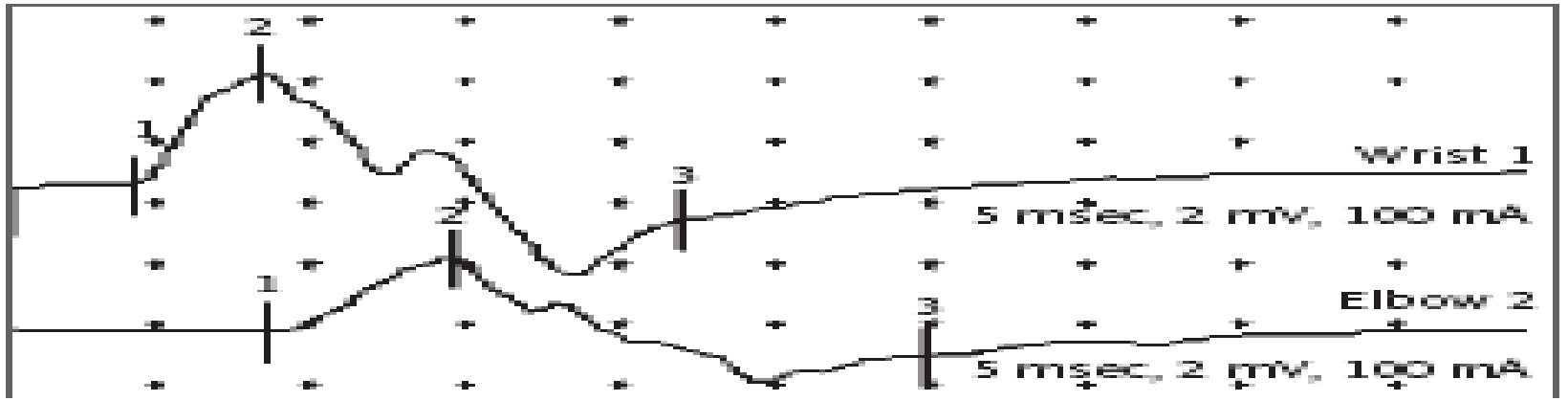
- UMN signs: clonus, Babinski sign, absent abdominal skin reflexes, hypertonia, loss of dexterity.
- LMN signs: atrophy, weakness.
- If only fasciculation: search with EMG for active denervation.
- Regions reflect neuronal pools: bulbar, cervical, thoracic and lumbosacral.

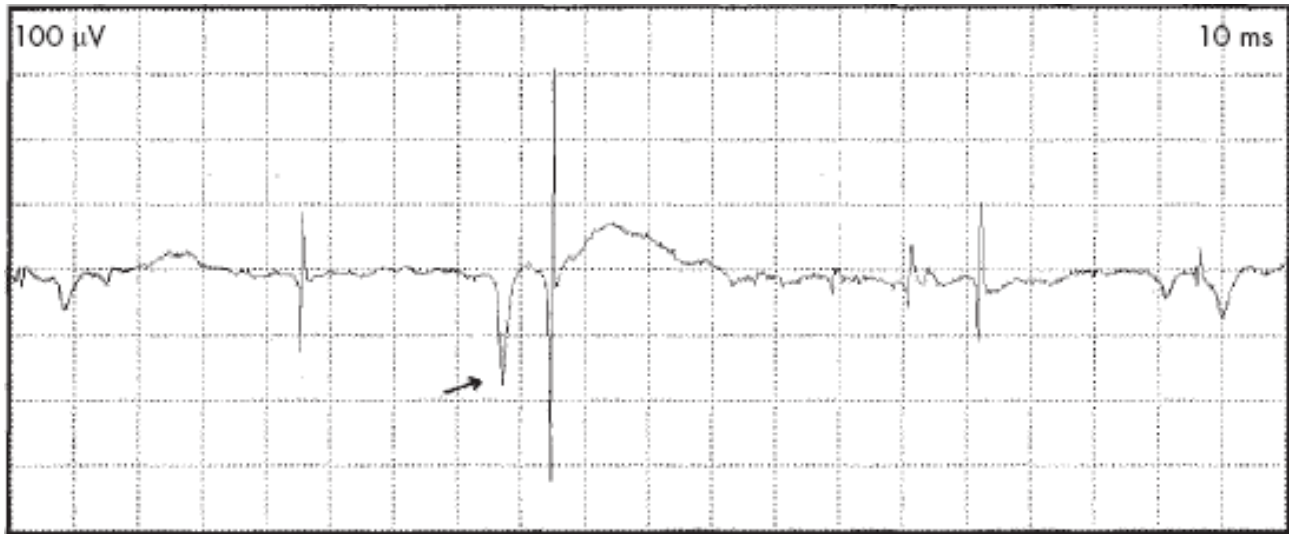
- How would you investigate a patient with motor neuron disease

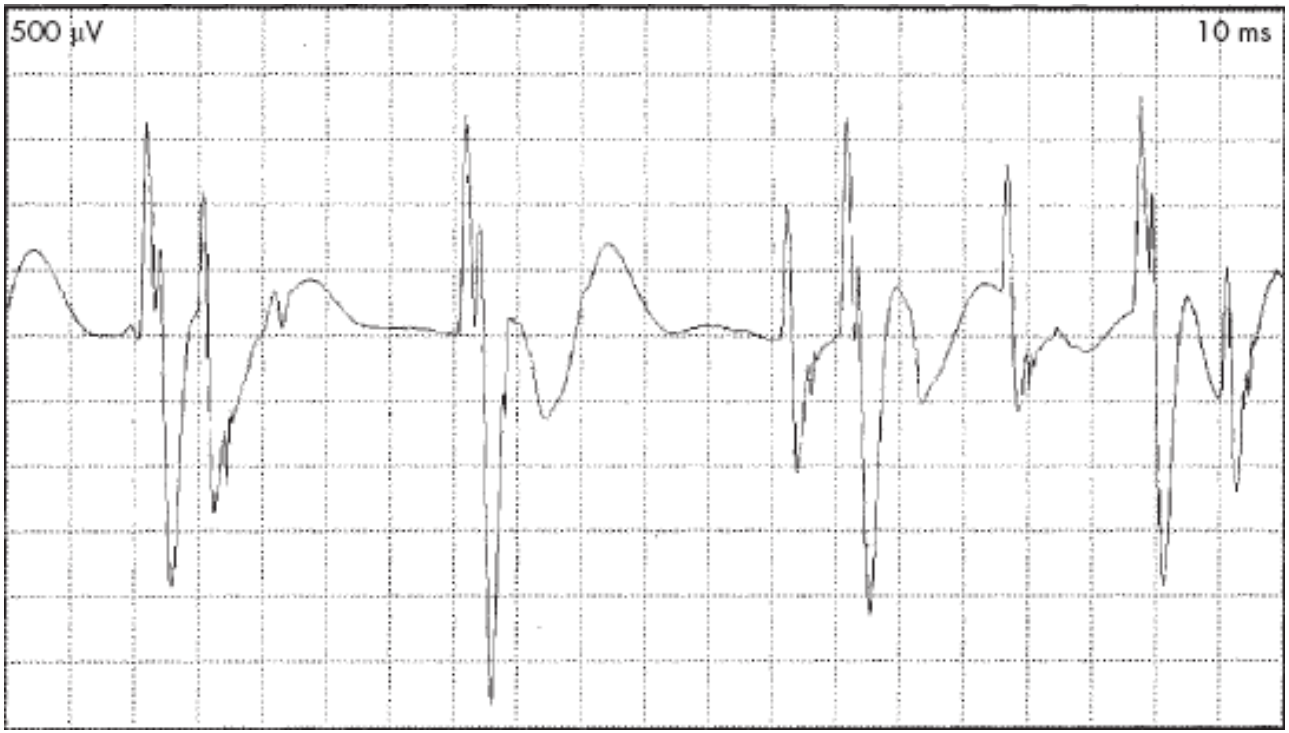
Essential investigations in suspected MND

- Full blood count and erythrocyte sedimentation rate
- Full biochemical profile, including calcium
- Creatine kinase (usually mildly raised or normal, >1000 iu/l is very unusual in MND)
- Serum electrophoresis
- Nerve conduction studies and EMG
- MRI spine/brain as indicated by clinical signs


Forearm 1
5 msec, 500 µV, 100 mA
Elbow 2
5 msec, 500 µV, 100 mA
Sp Gr 3
5 msec, 500 µV, 100 mA


Wrist 1
5 msec, 2 mV, 100 mA
Elbow 2
5 msec, 2 mV, 100 mA


100 µV
10 ms


500 µV
10 ms

diagnosis

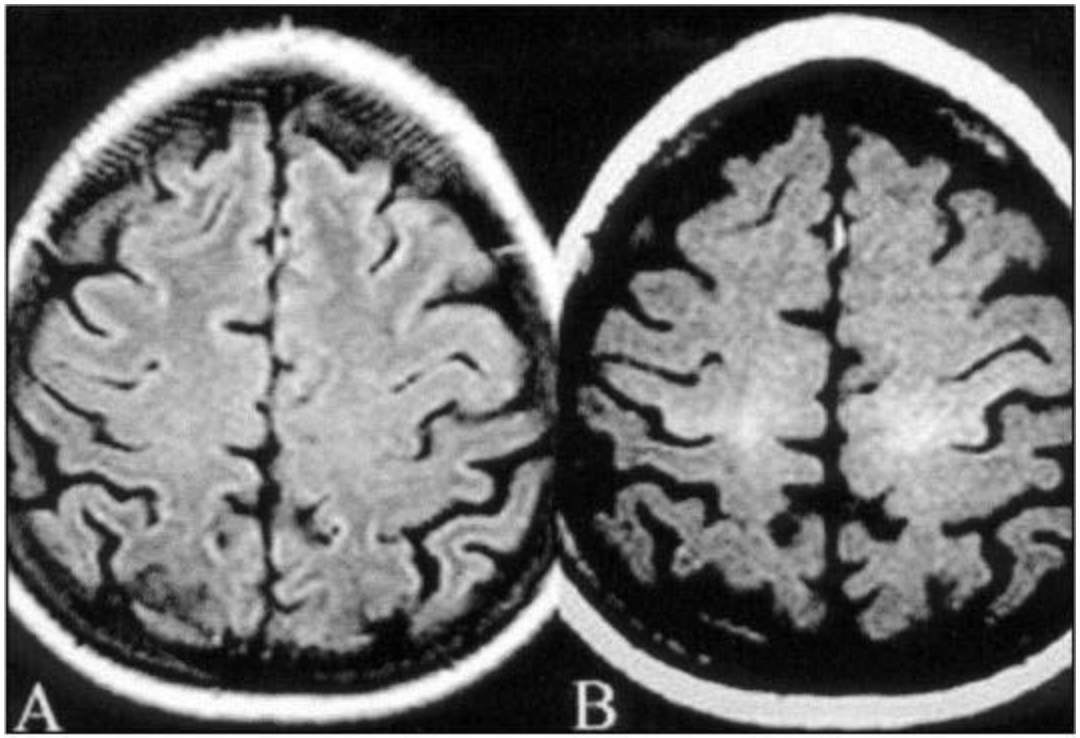


Fig 3. ALS patient. A- Axial FLAIR without abnormal findings. B- Axial T1/SE/MT showing the alterations more conspicuously than on FLAIR.

Additional investigations in selected cases

- Blood B12 level
- Antineuronal antibodies for paraneoplastic syndrome
- Antiacetylcholine receptor antibodies
- HIV serology
- Lyme serology
- Lumbar puncture
- Muscle biopsy

- What are the red flags in a patient with motor neuron disease
- What features would make the disease unlikely or make you consider another diagnosis

Diagnostic "red flags"	Action
▸ Symptoms and signs consistent with a lesion at a single anatomical site ▸ No progression, or major fluctuations in function ▸ Unusual or very prominent sensory symptoms, or objective sensory signs ▸ Dysphagia precedes dysarthria ▸ Major bladder or bowel involvement ▸ Fasciculation without weakness ▸ Symptoms remain confined to one limb ▸ Limb weakness without wasting	▸ MRI of relevant area ▸ Review diagnosis ▸ Repeat neurophysiology ▸ Exclude local structural pathology ▸ Consider other spinal cord diseases ▸ Consider other causes of fasciculation such as cramp fasciculation syndrome or potassium channelopathies ▸ Consider causes of a plexopathy ▸ Consider conduction block neuropathy

- What are the different clinical subtypes of motor neuron disease

- Give a differential diagnosis that you would consider for each subtype.

terminology


dateline: kennel
dogs in the papers of the 50s & 60s

THE SUBTYPES OF MND

- Clinical phenotypes - pattern and progression .
- Justification: (a) pathological features; (b) familial MND (c) initial atypical presentations - progress to generalised
- Clinical patterns - guide management and prognostication.

TERMINOLOGY

- Motor neurone disease (MND) is a synonym for amyotrophic lateral sclerosis (ALS).
- Progressive bulbar palsy
- Progressive muscular atrophy
- Primary lateral sclerosis

Amyotrophic lateral sclerosis

- Progressive weakness with upper and lower motor neuron signs.
- Brisk reflexes + local wasting - clue to the diagnosis.
- Weakness, clumsiness, stiffness or wasting.
- Visible fasciculations (often not noticed by the patient).
- Upper motor neuron predominant as well as lower motor neuron predominant forms.

Amyotrophic lateral sclerosis

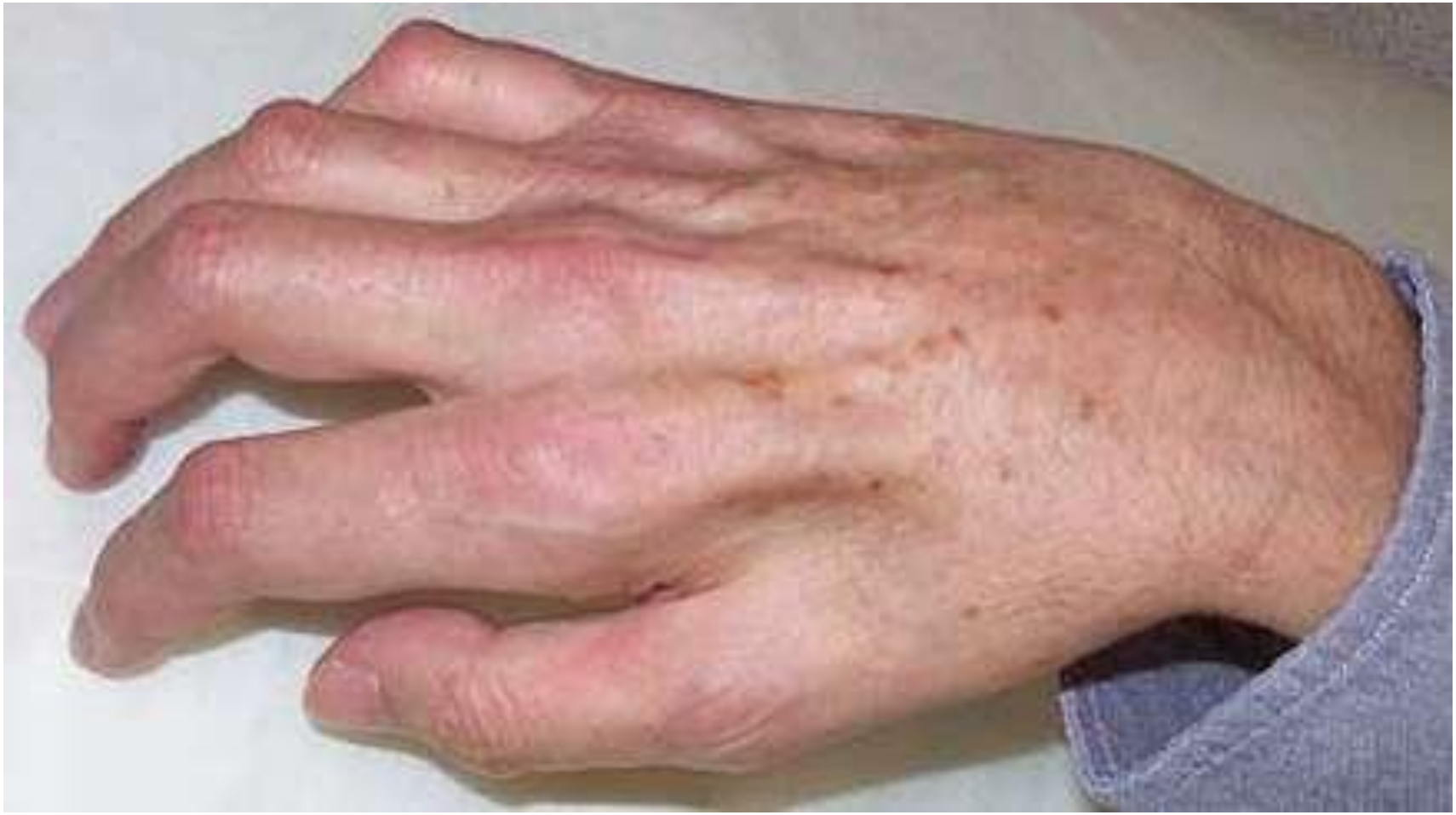
- No sensory, extraocular muscle or sphincter involvement .
- Weakness limbs (60–85%) or bulbar regions (15–40%).
- Asymmetrical distal pattern-claw hand or foot drop.
- Bulbar dysfunction - slow spastic dysarthria, dysphagia or pseudobulbar affect
- Relatively specific for ALS include thoracic paraspinal, posterior neck, tongue , jaw,first dorsal interosseous and tibialis anterior.

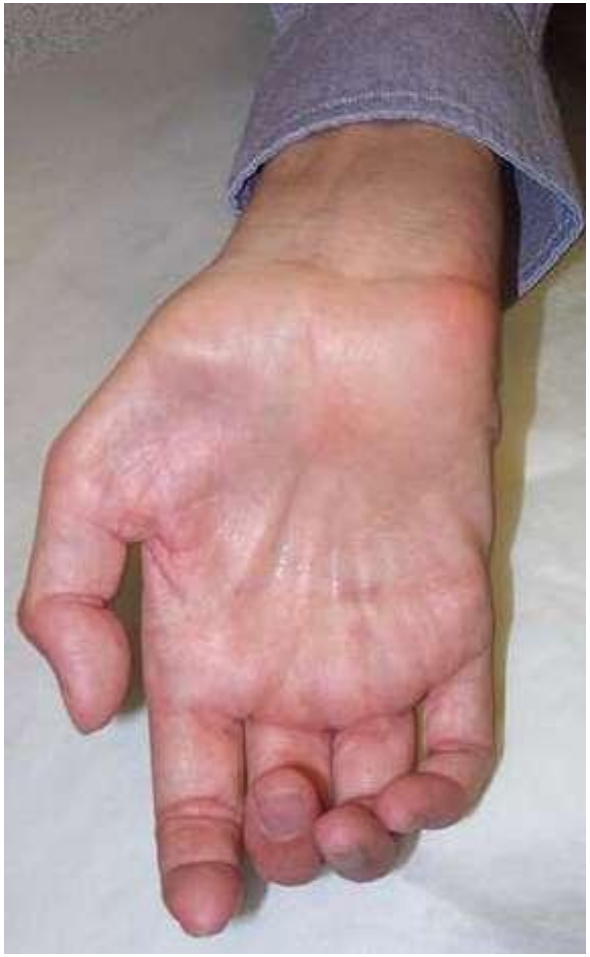
Amyotrophic lateral sclerosis

- Pathological reflexes
- Emotional lability - loss of the normal suppression of reflex laughter and crying;
- Respiratory involvement

Amyotrophic lateral sclerosis

- Bulbar involvement- speech before swallowing
- Bulbar onset - wasting and fasciculation tongue.





ALS –DIFFERENTIAL CHIARI MALFORMATION

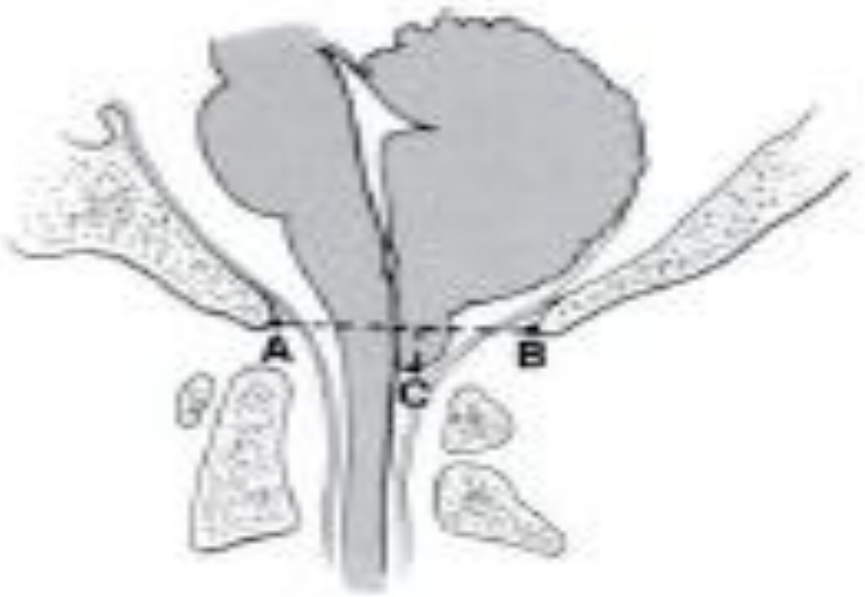
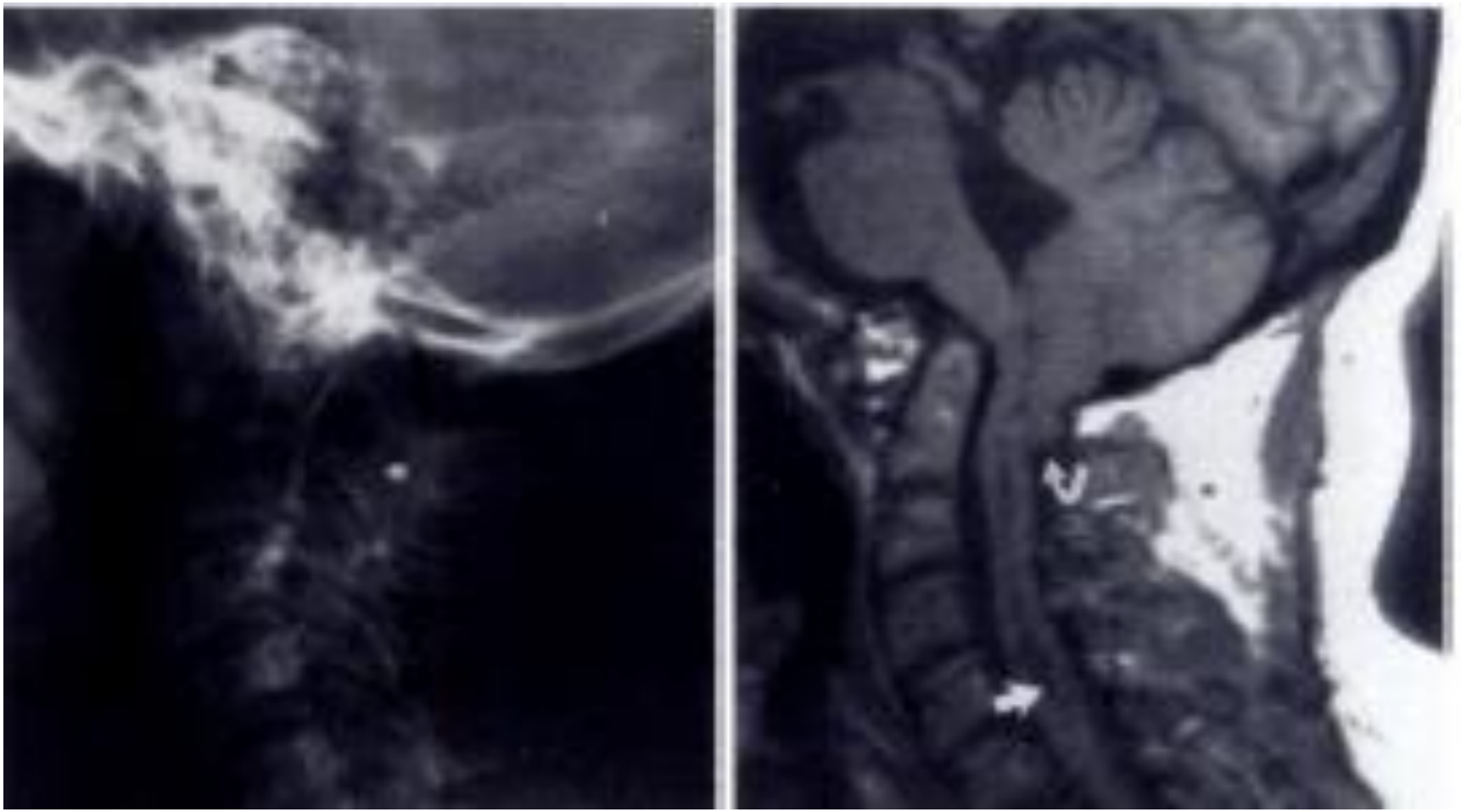
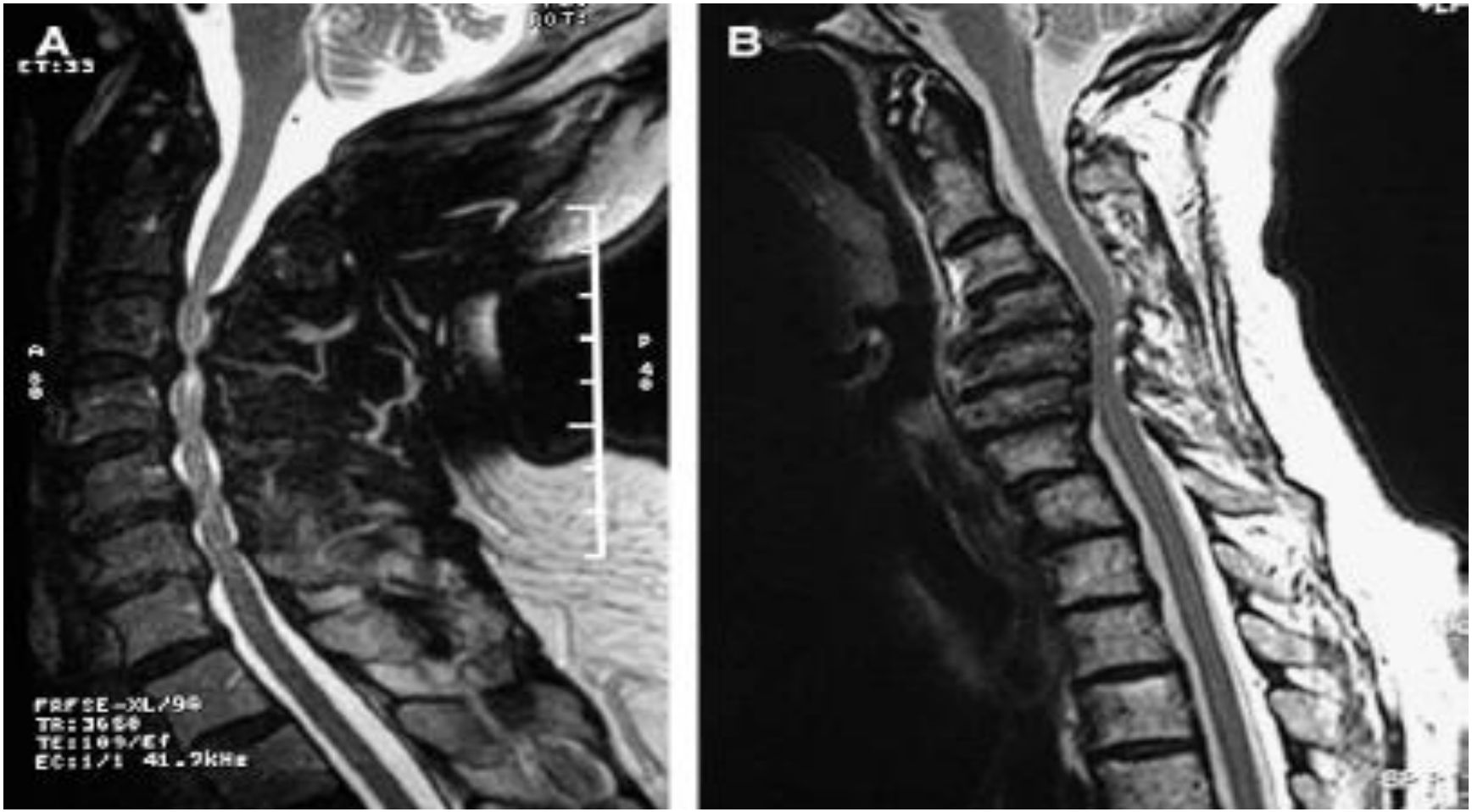


Figure 1. Diagram shows system for measuring degree of tonsillar herniation from sagittal MR images. Reference level of the foramen magnum is defined by line *AB* extending from *A* (basion) to *B* (opisthion). Tonsilar tip is denoted by C. Degree of tonsillar herniation is measured as length of perpendicular line from *C* to *AB*. (Adapted from reference 31.)

ALS –DIFFERENTIAL -SYRINX

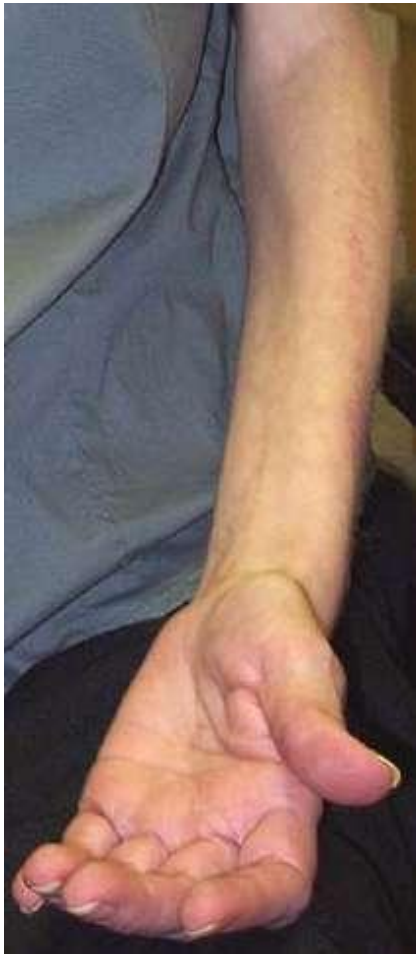


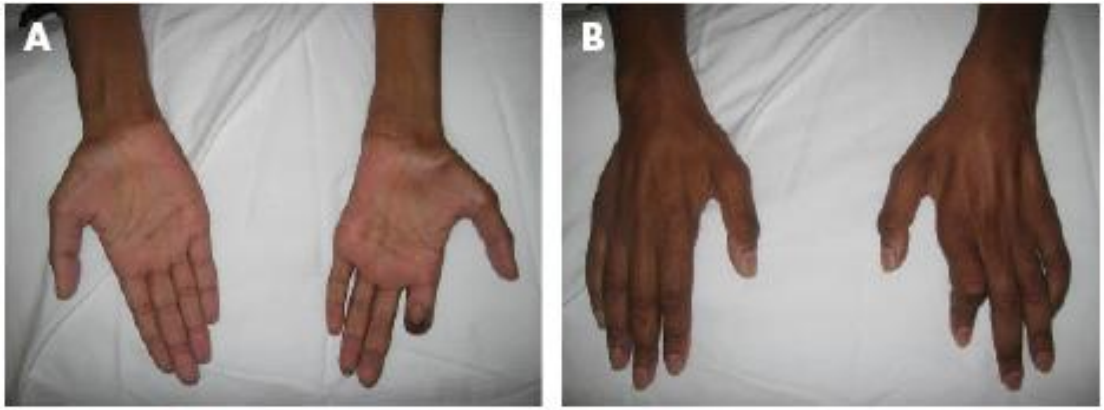
ALS –DIFFERENTIAL CERVICAL SPONDYLOSIS



Progressive muscular atrophy

- Pure lower motor neuron MND
- Asymmetrical weakness and wasting - legs, which spreads.
- wasting often out of proportion to weakness
- long survivors
- Differential diagnosis - conduction block neuropathy, paraneoplastic neuropathy, X linked spinobulbar muscular atrophy (Kennedy's syndrome) and adult onset spinal muscular atrophy.




A
B

Primary lateral sclerosis

- Ascending spastic tetraparesis with involvement of speech
- Develop wasting within 4 years, become reclassified as upper motor neuron predominant ALS .
- Urinary urgency is common.
- Cognitive involvement is the exception.
- Slowly progressive condition - survival for decades- disability high.
- Diff diagnosis – MS,Adrenoleukodystrophy

- Flail arm variant - Bilateral weakness and wasting of the proximal upper limb.

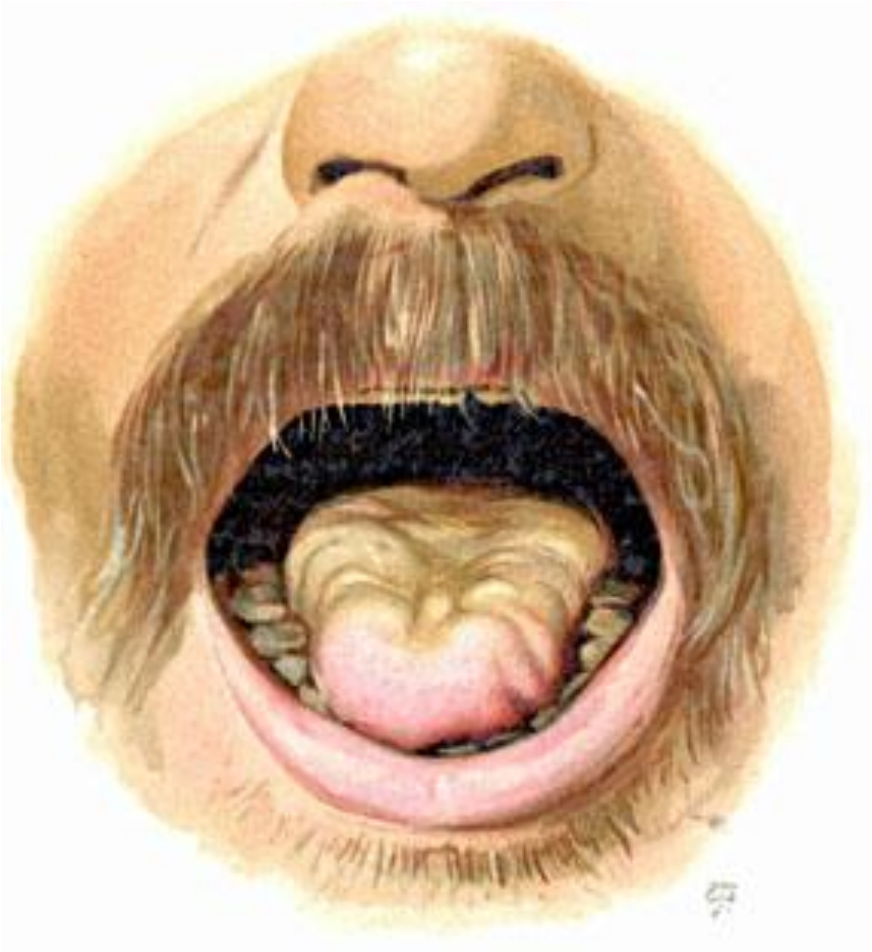
- Lower limb onset
- ‘‘the creeping paralysis’’ or the pseudopolyneuritic variant of MND.

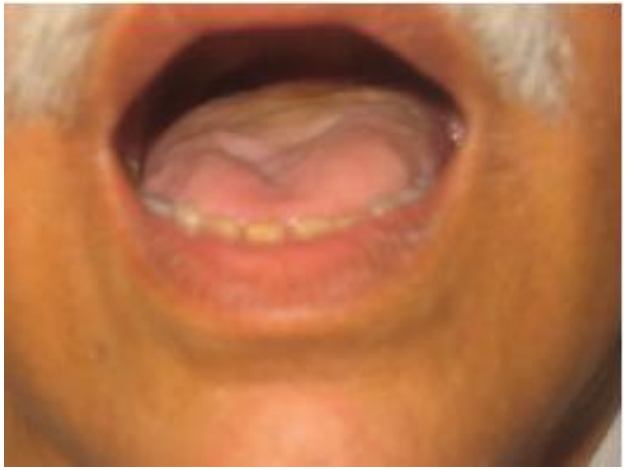
Progressive bulbar palsy (PBP)

- Onset with dysarthria followed by progressive speech and swallowing difficulties;
- Limb involvement usually follows within months but may be delayed for several years;
- M:F ratio 1:1 (PBP relatively more common in older women)
- About 20% of all cases at presentation.
- Median survival 2–3 years

Progressive bulbar palsy

- distinction from ‘‘bulbar onset ALS’’
- complete anarthria in 6–12 months -normal limb
- Upper motor neuron features (slow spastic tongue with a jaw jerk) usually predominate.
- The EMG is frequently normal.
- Diff diagnosis –brainstem stroke,myaesthenia





- How would you manage a patient with a diagnosis of MND

MANAGEMENT

- Regular individualised follow-up to assess the rate of change of the disease and facilitate planning and patient choice and, where possible, to maintain well-being.
- Neurologist, Physiotherapist,Occupational therapist

Table 2 Symptomatic management in patients with motor neuron disease

Symptom	Frequency	Management
Hypersalivation and drooling	Mostly patients with bulbar onset (approx 30%)	*Thin secretions:* Hyoscine patches, amitriptyline, glycopyrronium, botulinum toxin. *Thick secretions:* pineapple or papaya juice, nebulised saline, β blockers
Spasticity, cramps and fasciculation	Often a transient feature which recedes with disease progression. Not necessary to treat in most.	Exercise and physiotherapy, baclofen or tizanidine, gabapentin, botulinum toxin, especially once the patient can no longer walk
Nocturnal sleep fragmentation and daytime somnolence	Symptomatic in about 40-50% of ALS patients	Nasal intermittent positive pressure ventilation by mask
Dyspnoea at the end of life	A minority	Oramorph, with consent of patient, acknowledging secondary respiratory compromise effects of drug treatment
Emotionality	Approximately 10% of patients, often a transient feature	Amitriptyline, selective serotonin reuptake inhibitors
Nutritional insufficiency	Inevitable but affects people at different stages	About 60-70% of patients require enteral feeding (PEG or RIG)
Neck weakness, head drop	10-20%	Specialist collars such as the "Headmaster"

ALS, amyotrophic lateral sclerosis; PEG, percutaneous endoscopic gastrostomy; RIG, radiologically inserted gastrostomy.

- Riluzole
- 900 patients, oral riluzole 50 mg twice daily.
- Survival at 1 year is 9% greater than placebo - 2–3 months greater life expectancy.
- No effect on quality of life, or symptoms

NUTRITION IN MND

- Nutrition and weight loss predict survival.
- Malnutrition related to decreased calorie intake
- Swallowing safety and efficiency

Some common symptoms

Cramps- Changes in motor function?

- Quinine sulfate 200 mg twice daily
- Carbamazepine Phenytoin Magnesium
- Verapamil

Spasticity Corticospinal tract damage

- Baclofen 10–80 mg daily
- Tizanidine 6–24 mg daily
- Dantrolene 25–100 mg daily
- Memantine 10–60 mg daily

Sialorrhoea - Bulbar weakness

- Home suction device
- Atropine 0.25–0.75 mg three times daily (tabs/liquid) Atropine eye drops sublingual
- Hyoscine (tabs/transdermal patches)
- Amitriptyline oral (tabs/liquid)
- Glycopyrrolate (liquid: sc/im/via PEG)
- Salivary gland irradiation)

Tenacious secretions

- Carbocisteine (syrup: 250–750 mg three times daily orally or via gastrostomy)

Emotional lability -Pseudobulbar syndrome

- Amitriptyline

- SSRIs (e.g. citalopram, fluvoxamine)

- Anxiety -Many factors
- Lorazepam (sublingual, oral: 0.5–4 mg)
- Diazepam suppositories
- Midazolam (e.g. 2.5 mg stat, 10 mg/24 hours via gastrostomy or syringe driver)

- Respiratory distress –Positive pressure ventilation

Constipation -Immobility; opiates

Hydration; dietary measures; laxatives

Pain Immobility, stiffness

- Comfort (seating, sleeping, night and day care); simple analgesics; NSAIDS; opiates; antidepressants; gabapentin

Insomnia -Discomfort, pain,depression; (consider respiratory insufficiency)

- antidepressants; hypnotics; adequate analgesia

Depression - Hopelessness; inability to communicate; frustration

- Psychological support and counselling; SSRIs; other antidepressants

CONCLUSIONS

- MND is an Aetiologically complex disease
- No environmental triggers
- Increased knowledge of the genetics
- Advances - enteral feeding and non-invasive ventilation
- Need for early diagnosis - genetic typing .
- Restoring neurological function