• Anterior horn cell disease

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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.
**Table 1** Familial amyotrophic lateral sclerosis

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

Exogenous factors
- toxins
- viruses
- metals

Genetic factors
- SOD1
- Alsin and senataxin
- Genetic risk factors

Astrocyte

Excitotoxicity

Mitochondrial dysfunction

Abnormal protein aggregation

Impaired axonal transport

Oxidative stress

Motor neuron

Apoptosis

Neuroinflammation

Microglial cell

[Source: Expert Reviews in Molecular Medicine ©2006 Cambridge University Press]
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 DNA 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
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
<table>
<thead>
<tr>
<th>Diagnostic “red flags”</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>► Symptoms and signs consistent with a lesion at a single anatomical site</td>
<td>► MRI of relevant area</td>
</tr>
<tr>
<td>► No progression, or major fluctuations in function</td>
<td>► Review diagnosis</td>
</tr>
<tr>
<td>► Unusual or very prominent sensory symptoms, or objective sensory signs</td>
<td>► Repeat neurophysiology</td>
</tr>
<tr>
<td>► Dysphagia precedes dysarthria</td>
<td>► Exclude local structural pathology</td>
</tr>
<tr>
<td>► Major bladder or bowel involvement</td>
<td>► Consider other spinal cord diseases</td>
</tr>
<tr>
<td>► Fasciculation without weakness</td>
<td>► Consider other causes of fasciculation such as cramp, fasciculation syndrome or potassium channelopathies</td>
</tr>
<tr>
<td>► Symptoms remain confined to one limb</td>
<td>► Consider causes of a plexopathy</td>
</tr>
<tr>
<td>► Limb weakness without wasting</td>
<td>► Consider conduction block neuropathy</td>
</tr>
</tbody>
</table>
• 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 SPONDYLOPHYSIS
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.
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>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersalivation and drooling</td>
<td>Mostly patients with bulbar onset (approx 30%)</td>
<td>Thin secretions: Hyoscine patches, amitriptyline, glycopyrroinum, botulinum toxin.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thick secretions: pineapple or papaya juice, nebulised saline, β blockers</td>
</tr>
<tr>
<td>Spasticity, cramps and fasciculation</td>
<td>Often a transient feature which recedes with disease progression. Not necessary to treat in most.</td>
<td>Exercise and physiotherapy, baclofen or tizanidine, gabapentin, botulinum toxin, especially once the patient can no longer walk</td>
</tr>
<tr>
<td>Nocturnal sleep fragmentation and daytime somnolence</td>
<td>Symptomatic in about 40-50% of ALS patients</td>
<td>Nasal intermittent positive pressure ventilation by mask</td>
</tr>
<tr>
<td>Dyspnoea at the end of life</td>
<td>A minority</td>
<td>Oramorph, with consent of patient, acknowledging secondary respiratory compromise effects of drug treatment</td>
</tr>
<tr>
<td>Emotionality</td>
<td>Approximately 10% of patients, often a transient feature</td>
<td>Amitriptyline, selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>Nutritional insufficiency</td>
<td>Inevitable but affects people at different stages</td>
<td>About 60-70% of patients require enteral feeding (PEG or RIG)</td>
</tr>
<tr>
<td>Neck weakness, head drop</td>
<td>10-20%</td>
<td>Specialist collars such as the “Headmaster”</td>
</tr>
</tbody>
</table>

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