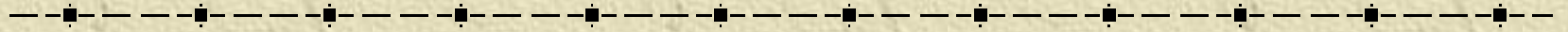


# MOTOR NEURONE DISEASE



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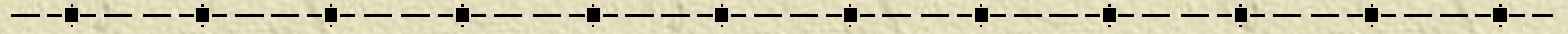
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# Motor Neurone Disease

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- ✧ Umbrella term in UK and Australia (ALS in USA)
- ✧ Neurodegenerative disorder of unknown etiology
  - ◆ Loss of anterior horn cells
  - ◆ Degeneration of UMN and LMN with preservation of cognition
    - Progressive motor weakness +/- bulbar dysfunction
- ✧ Male>female
  - ◆ Disease of middle age – mean onset 58 years

# Prevalance of MND



✧ Incidence of MND 3/100 1000

✧ Prevalence increasing – 5.7/100 1000

- ◆ People with MND are living longer

✧ Decreased mortality

- ◆ Riluzole

- ◆ Attention to management

- Nutrition and PEG

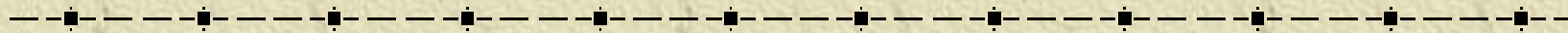
- Non-invasive ventilation



# Motor Neurone Disease

- 
- ✧ Family history in approximately 10% percent
    - ◆ 20% of families have point mutations in the SOD1 gene
  
  - ✧ Prognosis – 50% 3 year survival after diagnosis
    - ◆ 5% alive at 10 years
    - ◆ No real difference in survival between familial and sporadic ALS
    - ◆ Spinal onset disease live longer than bulbar onset

# Prognosis



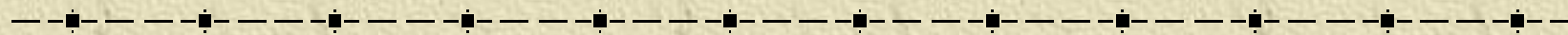
- ✦ Bulbar worse than spinal onset
- ✦ Older age at diagnosis
- ✦ Rate of disease progression within the 1<sup>st</sup> year
  
- ✦ Respiratory dysfunction
- ✦ Nutritional status and weight loss



# Amyotrophic Lateral Sclerosis

- 
- ✧ Accounts for about 85% of all cases of MND
  - ✧ Combination of UMN and LMN dysfunction
    - ◆ Evidence of spinal and cortical involvement
    - ◆ Asymmetrical weakness and wasting of limbs associated with corticospinal tract damage  
(Increased tone, brisk reflexes, extensor plantars)
    - ◆ Cranial nerve involvement with tongue wasting and fasciculation and dysarthria
    - ◆ Cramps

# Spinal Muscular Atrophy



- ✧ Pure lower motor neurone syndrome
- ✧ Minority of patients – 10%
- ✧ More slowly progressive than ALS
  
- ✧ **Progressive bulbar palsy**
  - ◆ dysarthria and dysphagia



# Primary Lateral Sclerosis

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- ✧ 1% of cases
- ✧ Symmetrical progression of a spastic tetraparesis with pseudobulbar palsy
  - ✧ Brisk jaw jerk, stiff slow tongue, spastic dysarthria
- ✧ Longer survival (mean 8.5 years – 5-15 years)
- ✧ Relative preservation of muscle strength
- ✧ Emotional lability
- ✧ Normal NCS and EMG



# El Escorial Criteria for MND

✧ No specific test for MND – clinical diagnosis

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## ✧ Definite

- ✧ UMN and LMN signs in 3 regions
  - Bulbar, cervical, thoracic or lumbar

## ✧ Probable

- ✧ UMN and LMN signs in at least 2 regions
  - UMN signs above LMN signs

## ✧ Possible

- ✧ UMN and LMN signs in at 1 region
- ✧ UMN signs alone in 2 or more regions
- ✧ LMN signs above UMN signs

# Electrophysiology

## ✧ NCS

- ◆ Normal motor conduction velocity in 95%
- ◆ Normal sensory studies in 98%

## ✧ EMG – widespread neurogenic

- ◆ Diffuse active denervation in at least 2 muscles supplied by different roots and nerves in different regions of 3 limbs
  - Fibrillation potentials, fasciculations
- ◆ Chronic partial denervation with reinnervation
  - Large duration and amplitude motor units
  - Reduced recruitment



# MIMIC Syndromes

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## False positive diagnoses

- ◆ **Failure to progress**
- ◆ Family history with no affected females
  - (Male to male)
- ◆ Symmetrical signs
- ◆ Development of sensory signs
- ◆ Development of sphincter dysfunction



# Treatable Conditions

- 
- ◆ Multifocal motor neuropathy with conduction block
  - ◆ Compressive cervical spondylotic myelopathy
  - ◆ Pure motor CIDP
  - ◆ Kennedy's disease - X-linked bulbospinal neuronopathy
  
  - ◆ Toxic neuropathies – lead, mercury, arsenic
  - ◆ Myasthenia gravis
  - ◆ Cord compression
  - ◆ B12 deficiency
  - ◆ HIV
  - ◆ Post-polio syndrome
  - ◆ Lymphoma

# Clinical Presentation

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• Site of onset	Male	Female	Total
<b>Limb</b>	62%	48%	56%
<b>Bulbar</b>	27%	45%	35%
<b>Generalised</b>	11%	7%	9%

# Other Presentations of MND

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## ✧ **Respiratory**

- ✧ Progressive respiratory failure

## ✧ **ENT**

- ✧ Dysphagia

## ✧ **Rehabilitation / Orthopaedics**

- ✧ Foot drop
- ✧ Radiculopathy

## ✧ **Rehabilitation / geriatrics**

- ✧ Difficulty walking



# Management

✧ Complex needs – patients and carers

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✧ Multi-disciplinary team

- ◆ Physiotherapy

- Mobility, postural support and prevention of contractures

- ◆ Speech therapy

- Swallowing assessment (PEG) and communication aids

- ◆ Occupational therapy

- Aids to maintain function – wheelchair, splints

- ◆ Dietician

- Nutrition advise on maintaining weight

✧ Support groups

✧ Palliative care – end of life decisions

# Multi-disciplinary Clinics

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## ✧ Median survival of ALS clinic patients

- ✧ 677 days compared to 448 for general neurology clinics
- ✧ 1 year and 2 year mortality decreased by 30% and 11% in riluzole treated group

## ✧ Median survival of bulbar onset

- ✧ 657 days compared to 363 for general neurology clinics
- ✧ 1 year and 2 year mortality decreased by 39% and 18% in riluzole treated group



# Multi-disciplinary Clinics - Bulbar

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- ✧ Emphasis on nutrition and bulbar function
- ✧ Early recognition of bulbar dysfunction
- ✧ Closely monitored weight
- ✧ Access to dietician and speech therapist
- ✧ Early insertion of PEG tube
  
- ✧ Riluzole
- ✧ Early recognition of respiratory dysfunction



# Riluzole

- 
- ✧ Only licenced drug
  - ✧ Specific glutamate antagonist
  - ✧ 2 randomised trials lasting 18 months
  - ✧ Prolong tracheostomy free survival by 3-6 months
    - ◆ Median survival 4.2 months longer
    - ◆ Mortality rate reduced by 23% and 15% at 6 and 12 months
  - ✧ Does not improve symptoms

# Riluzole

- ✦ Improves survival with early stages and less effective in advanced disease (benefit lost at 18 months)
  - ◆ Effect in “suspected” and “possible” ALS not established
  - ◆ Inclusion criteria required FVC>60% and definite/probable ALS by El Escorial criteria
  - ◆ Most effective in elderly females with bulbar onset disease
- ✦ **Others drugs trialled** – no evidence of benefit
  - ◆ Vit E, Gabapentin, Creatinine, Celebrex, Toparimate
  - ◆ Nerve growth factors – BDNF, ILGF-1
  - ◆ Minocycline



# Complications

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## ✧ Fronto-temporal dementia

- ✧ 3-10% of cases
- ✧ Language, memory, praxia and frontal
- ✧ Correlates with widespread neuronal degeneration

## ✧ Respiratory failure

- ✧ FVC inefficient in identifying early changes
- ✧ Maximum inspiratory (MIP's) and MEP's
- ✧ Sniff nasal inspiratory pressures (SNIP's) more sensitive

# Non-invasive PPV

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## ✧ Management of progressive respiratory failure

- ✧ VC <50% predicted
- ✧ MIP's and SNIP's <40% predicted
- ✧ Daytime PCO<sub>2</sub> >45mmHg
- ✧ Nocturnal desaturation PO<sub>2</sub><90% for >5% of night

## ✧ Improves survival

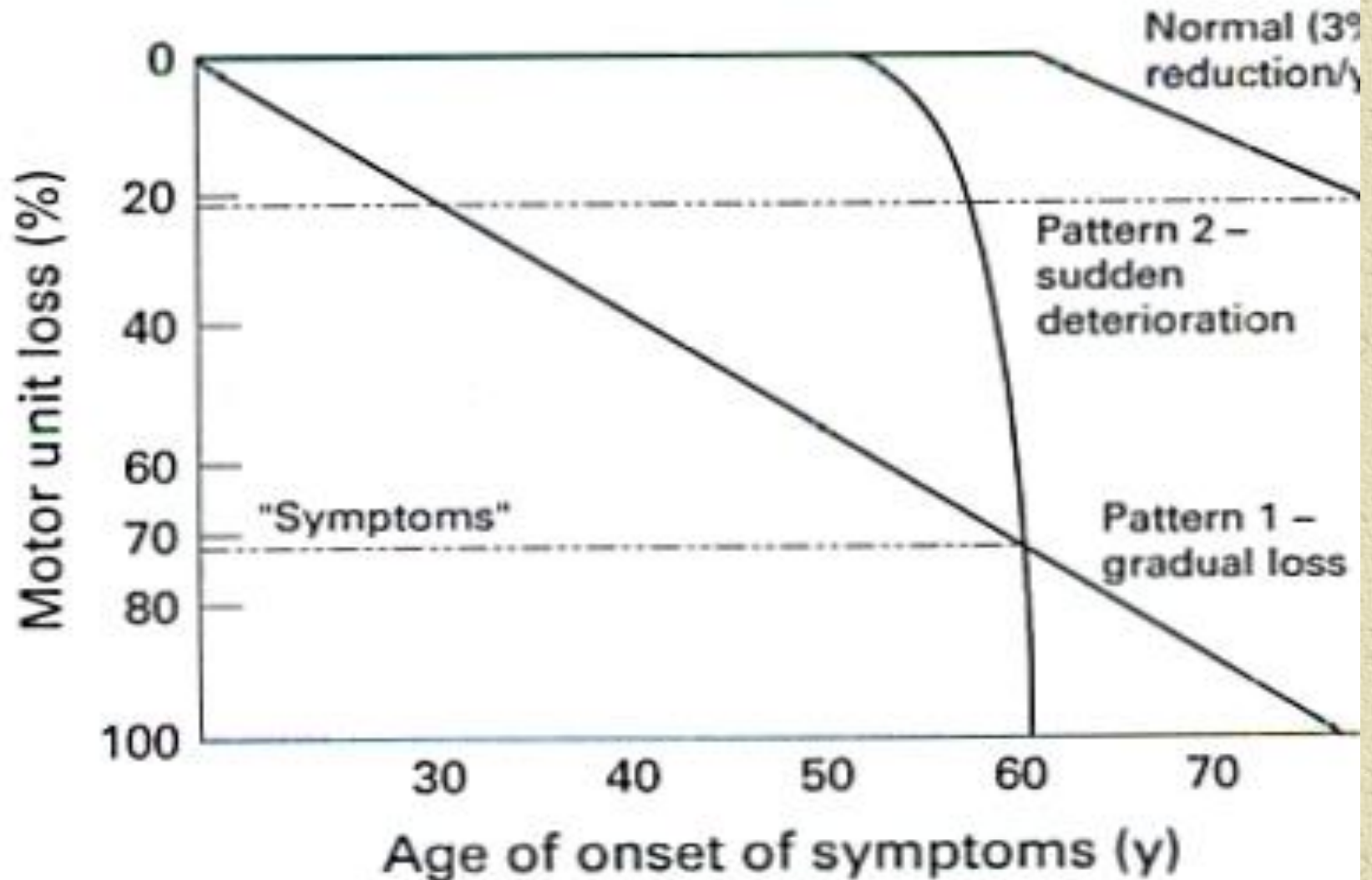
- ✧ May be up to 5 years (av. 512 days)

## ✧ Improves QoL

- ✧ Sleep related symptoms
- ✧ Fatigue
- ✧ Mental health



# Introduction



# Conclusion

- ✦ This is the first study to detect loss of motor neurons in the presymptomatic stage of ALS in humans
  - ◆ Significant fall in MN 33% - 68%
  - ◆ 3-9 months prior to the onset of weakness
- ✦ All SOD 1 mutation carriers had a full complement of motor neurones during the asymptomatic phase, indicating normal survival of motor neurones
- ✦ This implies sudden, catastrophic loss of motor neurons occurs immediately prior to the onset of symptoms rather than gradual attrition over time



# Conclusion

- ✧ Therapy aimed at preserving motor neurones more feasible than trying to replace lost motor neurones.
  - ✧ Measures to diminish SOD1 aggregation to specifically reduce apoptosis in motor neurones.
- ✧ This study demonstrates that if it is possible to identify the biological trigger initiating motor neurone death, it may be possible to develop effective preventions for familial ALS and treatments for sporadic ALS.