UPDATE ON ALS MANAGEMENT & RESEARCH

Orla Hardiman BSc MD FRCPI FAAN
HRB Clinician Scientist
Consultant Neurologist, Beaumont Hospital
Clinical Professor, Neurology, Trinity College Dublin

Motor Neurone Disease
- Motor neuron degeneration of adults
- Commonest neurodegeneration of young and middle aged adults
- Incidence 2.6/100,000
- Unknown aetiology
- 10% familial
- Fatal

Possible causes of MND
- Complex genetic condition
- Selective vulnerability of motor neurones
- ubiquitin-proteasome system: Inclusions
- Neurofilament disruption
- Neurotransmitter system disruption
- Neurotrophic factors
- Heavy metals
- Oxidative stress
- Hypoxia?
- RNA processing

ALS is a Diagnosis of Exclusion: Diagnostic Investigations
Exclude all other causes of symptoms
- blood and CSF analysis
- Electrophysiology (EMG)
- Nerve Conduction studies
- Imaging

NEUROPHYSIOLOGY
- Detailed nerve conduction studies, and search for conduction block (Should not be present)
- Sensory nerve action potentials should be normal

EMG in ALS/MND
- 4 limb EMG and EMG of bulbar muscles:
  - Fibrillations and positive sharp waves
  - Large polyphasic units (partial reinnervation)
  - Reduced interference pattern
**MUNE v MUNIX**

Motor Unit Number Estimation

Needle EMG provides quantitation and tracking of motor unit numbers while simultaneously measuring reinnervation.

Motor Unit Number Index

- Uses CMAP & surface EMG interference pattern to assess number (MUNIX) & size (MUSIX) of motor units (MUs).

---

**Quest for Early Diagnosis**

Diagnostic delay 9-15 months

Development of “red flags” to ensure rapid referral to specialist

Early enrolment into clinical trials

NO RELIABLE BIOMARKER OF ALS

---

**Red Flags: Expert Opinion and Learning From Preliminary Medicare Analysis**

- Unexplained
- Focal
- Pure – ‘without pain’ and ‘without sensory loss’

**Symptoms/Signs**

- **Bulbar**
  - Voice change
  - Speech change
  - Swallowing change
- **Limbs**
  - Muscle weakness
  - Atrophy
  - Falls
  - Gait change
  - Foot drop
  - Shoulder weakness
  - Neck or trunk weakness
  - Muscle cramps
  - Clumsiness
- **Respiratory**
  - Cough
  - Shortness of breath

Require physical examination

- Tongue abnormality
- Atrophy
- Increased or pathological reflexes
- Fasciculations
- Muscle weakness or stiffness

---

**ALS Mimic Syndromes: Common Diagnoses**

- Multifocal Motor Neuropathy
- Non-compressive myelopathy
- Bulbospinal muscle atrophy
- Cervical spondylotic myelopathy
- Hereditary spastic paraparesis
- Post-polio syndrome

---

**Key Points in Recognition of Mimic Syndromes**

- **FAILURE TO PROGRESS**
- Symmetrical Signs
- Pure upper or pure lower motor neurone syndrome
- Upper motor signs caudal to lower motor neurone signs, with no bulbar involvement
- Development of sensory signs
- Development of sphincter disturbances

---

**ALS Classification (2)**

- Spinal Onset
- Bulbar Onset
- Generalized Onset
- “ALS-Plus”
ALS VARIANTS

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical Summary</th>
<th>Other comments</th>
<th>Duration of survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS</td>
<td>Upper and lower motor neuron signs</td>
<td>Mgmt response to treatment</td>
<td>0-2 years</td>
</tr>
<tr>
<td>Primary</td>
<td>Lower motor neuron signs</td>
<td>Motor responses abnormal</td>
<td>3-5 years</td>
</tr>
<tr>
<td>Secondary</td>
<td>Upper motor neuron signs</td>
<td>Motor responses abnormal</td>
<td>6-10 years</td>
</tr>
<tr>
<td>Progressive</td>
<td>Lower motor neuron signs</td>
<td>Motor responses abnormal</td>
<td>0-1 year</td>
</tr>
<tr>
<td>Bulbar</td>
<td>Speech and swallowing difficulties</td>
<td>Motor responses abnormal</td>
<td>0-2 years</td>
</tr>
<tr>
<td>Subclinical</td>
<td>Lower motor neuron signs</td>
<td>Motor responses abnormal</td>
<td>30 years or more</td>
</tr>
</tbody>
</table>

El Escorial Diagnostic Criteria

- **Definite ALS**: UMN and LMN signs in three regions.
- **Probable ALS**: UMN & LMN signs in at least two regions with UMN signs rostral to (above) LMN signs.
- **Possible ALS**: UMN & LMN signs in one region, UMN signs alone in two or more regions, or LMN signs above UMN signs.
- **Suspected ALS**: LMN signs only in two or more regions.

Survival According to El Escorial Category at Diagnosis

![Graph showing survival probability over follow-up duration for definite, probable, possible, and suspected ALS categories.]

Awaji Criteria (de Carvalho et al, Clin Neurophysiol 2008)

- Single diagnostic algorithm integrates EMG & clinical neurophysiologic data (including complex unstable units & fascic potential)
- Increases sensitivity of dx in bulbar disease from 38% to 87% (de Carvalho & Swash, Amyotroph Lat Scler 2009)

Cognitive Impairment

- 13% of incident case have FTD
- >30% have cognitive impairment
  - Executive impairment most common
  - Impaired verbal fluency is an early sign

Behavioural Symptoms

- Over-eating and food fads
- Blunted emotions
- Swearing
- Lack of judgement
- Utilisation behaviour
- Impulsive buying
- New onset criminal behaviour
- Ignoring social etiquette
- Change in personal hygiene
- Lack of empathy
- Disinterest, withdrawal
- Increased interest in sex
- Hoarding
- Repetitive behaviour
Clinical Prognostic factors (1)

- Site of onset ➔ bulbar and respiratory worse
- Diagnostic delay ➔ short delay worse
- Family history of ALS ➔ depends on SOD1 mutations (A4V worst)
- Rate of disease progression
- Psychosocial factors ➔ presence of distress worse

Clinical Prognostic Factors (2)

- Cognitive function ➔ Executive dysfunction
- Nutritional status ➔ BMI? Weight loss?
- Respiratory status ➔ FVC<70 worse
- El Escorial diagnostic categories ➔ definite worse than other categories

Symptoms of ALS

Direct
- weakness and atrophy
- fasciculations and muscle cramps
- spasticity
- dysarthria
- dysphagia
- dyspnoea
- laughing/crying

Indirect
- psychological problems
- sleep disorders
- constipation
- drooling
- thick mucous secretions
- symptoms of chronic hypoventilation
- pain

Symptom Management: Pharmacological

- Spasticity
  Baclofen, Tizanidine
- Cramping & fasciculation
  Quinine sulphate
- Salivation & drooling
  Amitriptyline, Scopolamine, irradiation, Botulinum toxin
- Pseudobulbar affect
  Amitriptyline, SSRI

RILUZOLE

- Median survival of riluzole group was 4.2 months longer
- Mortality rate decreased 23% and 15% at 6 and 12 months respectively
- effect is comparable to RCT
- Beneficial effect lost in prolonged follow-up
  - 5.1% lower at 18 months
- ?decreasing pool of neurons
- Curves statistically different with peto test only (p = 0.015), not the logrank test
Multidisciplinary Management of ALS

Multidisciplinary Care Team:
- Social Worker
- SLT (Speech Language Therapist)
- Psychologist
- Respiratory Physiotherapist
- MND Association
- PT (Physical Therapist)
- OT (Occupational Therapist)
- Dietitian
- MND Nurse
- Neurologist
- Patient/Carer

Evidence Based Care in ALS/MND

Symptom Management

- Nutritional Decline
  - Recognition
  - Supplementation
- Respiratory Decline
  - Recognition, early intervention
  - Management
    - Secretion management
    - End of life decisions
    - Non invasive ventilation
    - Invasive mechanical ventilation

Nutritional Status and Survival
(Desport et al. Neurology 1999:53:1059)

Nutritional Supplementation in ALS

- Early intervention
- Dietary alteration: Thickening of fluids
- Adjustment of nutritional content
- Monitoring of length of time to feed
- Monitoring of weight
- Strategies to reduce risks of aspiration

Gastrostomy: Who, Why and When?

- Declining weight
  (>10% loss of body wgt)
- Increased time spent at meals
- Increasing dysphagia
- Quality of life
- Respiratory function
  - FVC>50%
  - SNIP >40cm water
  OR
  TOLERATES NIV
Respiratory Dysfunction
- Cause of death in majority of ALS
- Hypoxic/hypercapnic symptoms can be missed
  - Dyspnoea on exertion, orthopnoea, PND
  - Early morning headaches
  - Daytime sleepiness, nocturnal agitation
  - Nightmares
  - Altered mental status

Symptom Management
- Nutritional Decline
  - Recognition
  - Supplementation
- Respiratory Decline
  - Recognition, early intervention
  - Management
    - Secretion management
    - End of life decisions
    - Non invasive ventilation
    - Invasive mechanical ventilation

Sniff Nasal Inspiratory Pressure
- More accurate predictor that FVC of respiratory dysfunction
- More accurate predictor of survival

SNIP is Superior to FVC as a Predictor of Nocturnal Hypoxia (% time spent below 90% O_2 Sat)

SNIP as a Predictor of Survival

Secretion Management
- Medication
  - Scopolamine
  - Amtriptyline
  - Botulinum toxin
- Parotid Gland Irradiation
- Cough assist
Non-Invasive Ventilation (NIV)

- Criteria for initiation of NIV in ALS not well established
  - Symptoms of hypoxemia
  - FVC, SNP
  - Oximetry
  - Arterial Blood Gases

NIV poorly tolerated by some patients at time of initiation
NI may not be well tolerated in those with cognitive impairment

Survival Effect of NIV: Importance of Compliance

Quality of life in ALS

- ALS patients prefer individual QoL scales
- Family is much more important than health
- NO correlation between individual QoL and functional disabilities or general health status

The term health-related QoL is irrelevant in ALS

End of Life & Advance Directives

- Provide autonomy regarding end of life management
- Legal validity of advance directives varies from country to country.
  - Considered useful in 78% of European centres, but only 30% of patients complete them

RESEARCH

AIMS of the IRISH MND RESEARCH GROUP

- To engage in best practice in the MND clinic & develop innovations in clinical management that improve the patient journey
- To identify subgroups of MND that help to understand the condition, and that are important for clinical trials
- To develop novel technologies that can be utilized as markers of disease onset, subtype and progression
Irish Register of Motor Neurone Disease

- Commenced in 1993
- Ascertainment complete by 1995
- 2 large studies to analyse the entire database now underway
- Data collection ongoing: >1700 incident patients enrolled to date

PROGRAMMES

- Epidemiology
- Genetics
- Neuropsychology
- Biomarkers
- Health Services

European Collaborations

Epidemiology

- Case Control study (2011-2016)
  - Identifying environmental risk factors
- Family Aggregation
  - Finding conditions that are associated with MND
- Clustering

Case Control Study (EUROMOTOR : 2011-16)

- European funded study of people with MND and matched controls
- Questionnaires & samples of DNA, blood & urine analysed to identify differences between those with the condition & those without

Family Aggregation Studies
Family Aggregation of Other Conditions with MND

Is there Evidence of Clustering of MND in Ireland?

Spatial Clustering: Correcting for Population Density

Republic of Ireland v Northern Ireland

Prevalence (31st December 2010)

<table>
<thead>
<tr>
<th></th>
<th>Republic of Ireland</th>
<th>Northern Ireland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>237 cases</td>
<td>93 cases</td>
</tr>
<tr>
<td>Population &gt; 15 years old</td>
<td>3,311,500</td>
<td>1,444,325</td>
</tr>
<tr>
<td>Population &gt; 15 years old</td>
<td>6.8 per 100,000 (95% CI 5.9-7.6)</td>
<td>6.4 per 100,000 (95% CI 5.1-7.7)</td>
</tr>
</tbody>
</table>

Interventions 2006-2010

<table>
<thead>
<tr>
<th></th>
<th>Republic of Ireland</th>
<th>Northern Ireland</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIV</td>
<td>30%</td>
<td>15%</td>
</tr>
<tr>
<td>Gastrostomy</td>
<td>27%</td>
<td>25%</td>
</tr>
</tbody>
</table>
Interventions 2006-2010

<table>
<thead>
<tr>
<th>Republic of Ireland</th>
<th>Northern Ireland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrostomy and NIV 14%</td>
<td>Gastrostomy and NIV 3%</td>
</tr>
</tbody>
</table>

Survival

Is there a clinic effect?

Clinic effect

Neuropsychology

Testing since 2006
Home-visits nation-wide
MND Patients and Controls

Cognitive Function:
 Thinking speed
 Memory
 Language
 Planning, Problem-solving
 Behaviour

Neuropsychological Battery

Executive function:
- Verbal fluency (phonological and category)
- Brixton Test
- Stroop Interference Test
- Digit span

Memory:
- Logical memory (WMS-III)
- Paired Associate Learning Test (WMS-III)
- Rey Complex Figure Test (immediate and delayed)
Cognitive Impairment in ALS

MND and Cognitive Impairment

MND and Behavioural Impairment

Up to 50%

MND and Behavioural Impairment

Cognitive Impairment in ALS

Neuropsychology

At Least 3 groups of MND Patients

No Thinking Problems

Mild Changes in Thinking

Severe Changes in Thinking

Cognitive & Behaviour Impairment in ALS:
Unanswered Questions

Cognitive changes predict functional decline in ALS

A population-based longitudinal study

Executive Dysfunction is a Negative Prognostic Indicator

INTERPRETATION

- Cognitive decline progresses but is difficult to detect
- Cognitive status is linked with:
  - rate of motor decline and risk of attrition
  - rate and pattern of cognitive decline
- Cognitively intact patients tend to remain cognitively intact
- Cognitive status may be phenotypic marker for distinct disease subtypes
Genetics of MND in Ireland

- Ideal for gene-finding projects
- Island
- Remote geographical position
- Gene-pool stable
- Well studied, 2 main genetic ancestries, "Irish/Celtic" and "Anglo-Saxon" origins

Population Structure Within Europe
(Novembre et al Nature 456:6, 2008)

IRISH POPULATION ALSO DEMONSTRATES GENETIC SUBSTRUCTURE:
Comparison With Dutch & US populations

Identity by Descent within Irish & British Individuals

DEFINING FAMILIAL ALS

<table>
<thead>
<tr>
<th>Definition</th>
<th>History</th>
<th>Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite FALS</td>
<td>Patient with two first or second degree relatives with ALS</td>
<td>Patients with an allele with ALS and gene positive segregation</td>
</tr>
<tr>
<td>Probable FALS</td>
<td>Patient with one first or second degree relative with ALS</td>
<td></td>
</tr>
<tr>
<td>Possible FALS</td>
<td>Patients with one or more third degree relative with ALS</td>
<td></td>
</tr>
<tr>
<td>Degeneration</td>
<td>Patient with a first or second degree relative with confirmed FTD</td>
<td></td>
</tr>
</tbody>
</table>
Most common reported genes in Familial MND worldwide

- C9orf72 0-70% (geographic variation)
- SOD1 5-20% (geographic variation)
- TDP43 4%
- FUS 4%
- ANG 2%

Hexanucleotide Repeat Expansion in C9orf72 causes ALS and FTD

Known Genes Causing Familial MND in Ireland

- C9orf72 - 50% of familial MND
- Other known genes very rare in the Irish MND population

Frequency of known Genes is Not Uniform Across Populations: Ireland vs Italy

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANY GENE</td>
<td>67%</td>
<td>4.5%</td>
</tr>
<tr>
<td>C9orf72</td>
<td>41%</td>
<td>1.9%</td>
</tr>
<tr>
<td>SOD1</td>
<td>12.5%</td>
<td>1.4%</td>
</tr>
<tr>
<td>TDP43</td>
<td>9.2%</td>
<td>1.2%</td>
</tr>
<tr>
<td>FUS</td>
<td>0.7%</td>
<td>0.0%</td>
</tr>
<tr>
<td>ORF71</td>
<td>1%</td>
<td>0.0%</td>
</tr>
<tr>
<td>UNKNOWN</td>
<td>32%</td>
<td>52%</td>
</tr>
</tbody>
</table>

The Effect of the C9orf72 gene

C9orf72 gene variant -

C9orf72 repeats and protein

C9orf72 gene variant +

C9orf72 repeat expansion in C9orf72 and the cause of C9orf72

Neuron

C9orf72 variants and repeat expansion in C9orf72 and the cause of C9orf72

Neuron

C9orf72 variants and repeat expansion in C9orf72 and the cause of C9orf72

Neuron
**Behaviour: population based cohort**

C9orf72 gene Negative  
C9orf72 gene Positive

**C9orf72 Screening Algorithm**

- Family history ALS or FTD?
  - Yes (26)
  - No (86)

- Behaviorally impaired on FARS?
  - Yes (71)
  - No (35)

- Clinical Trials
  - Dexpramipexole
    - Negative
  - Tirazemtiv
    - Ongoing
  - TCD Lead Compound
    - Under development

**Brain Imaging & EEG**

**Health Services**

- Patient Journey
- Triggers for Palliative Care intervention
- Modelling of costs

**Patient Journey**

- Mapping the experience of the person with MND
- Identifying gaps in service delivery
- Mapping effects of illness on quality of life
- Understanding decision making
Developing a Framework for Palliative Care Intervention

Clinical/Palliative Care

- Research to identify preferences of patients & carers who interact with palliative care services
- Development of a measure for health economic assessment of palliative interventions

Clinical /Palliative Care

- Integrated with laboratory based research group
- Integrated with health services research group
- Participation in current /new clinical trials

Team

Clinical
Bernie Corr
Ger Foley
Dundre Murray
Lisley Doyle
Leslie Wheats
Kitty McEligott

Imaging & EEG
Dr. Peter Bede
Dr. Parames Iyer
Barth Michaels

Laboratory
Dr. Julia Kelly
Dr. Alan Wade
Gill Bater

Neuropsychology
Dr. Niall Pender
Dr. Malav Dhar
Tom Burke
Caroline McHugh

Epidemiology
Dr. Susan Byrne
Dr. James Rooney
Mark Heretik (Register)
Emma Quinnan
Emma Kirby

Genetics
Dr. Russell McLaughlin
Kevin Hanna

Health Services
Dr. Miriam O’Dea
Dr. Brighd Connolly
Dr. Katy Taylor
Dr. David Maguire

EMG & Biomarkers
Dr. Taha Omar

Clinical Trials
Lisa Fingher
Fiona McSween
San Kassamia

TCD Admin
Dominique Plant

International Collaborators

- European Network for the Cure of ALS
  - EMPOWER
  - SOPHIA
  - ALSCarE
  - STRENGTH
- University of Utrecht
- Kings College London
- University of Edinburgh
- Massachusetts General Hospital & Harvard
- University of Massachusetts
- Institute of Neurology, Havana

FUNDING

18/11/2013