ALS and DEMENTIA
An Odd Couple?

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Amyotrophic Lateral Sclerosis

- First ALS case described by Sir Charles Bell in 1830
- Progressive Muscular Atrophy described by Aran in 1850
- Case series by Charcot (1874)
  Neuro-degenerative condition predominantly affecting upper
  and lower motor neurons (with preservation of cognition)

ALS HAS BEEN CONSIDERED A
NEUROMUSCULAR CONDITION

Lou Gehrig’s Batting Average Declined Sharply
During the 1938 Season

Most models are focused on the Lower Motor Neuron and Its Local Environment
Pathogenesis of SOD1-Associated ALS: Insights from the SOD1 Mouse

- Mutant SOD1 transgenic mice develop an “ALS-like phenotype” (of lower motor neurone disease)
- SOD1 mutations in vitro disrupt normal cellular function
- Effects are non-cell autonomous

Initiators and Propagators of disease in SOD1 Transgenics

- **Disease Initiation**
  - Retraction of axons from neuromuscular synapses
  - Inhibition of antergrade axonal transport
  - Protein misfolding,
  - mitochondrial injury

- **Disease Propagation**
  - Microglial activation
  - Continuing neuronal damage
  - Astrocyte injury (protein aggregation)
  - Excitotoxicity
  - Increased secretion of neurotoxic compounds (including misfolded SOD1?)

COGNITIVE IMPAIRMENT AND ALS

- Frontotemporal dementias can develop anterior horn cell degeneration
- Dementia can occur with “classical ALS”
- ALS PD Dementia complex occurs in Guam
- Occasional descriptions of “childish and credulous behaviour” in some ALS patients (Pierre Marie 1853-1940)

ALS is a Multisystem Disease

(Adenson 1981)

**MND - a multisystem disease**

- Clinical
  - dementia
  - parkinsonism
  - cerebellar signs
  - autonomic dysfunction
  - sensory abnormalities
- Pathology
  - extramotor neocortex
  - striatum
  - globus pallidus
  - thalamus
  - subthalamus
  - sub. nigra

ALS and FTD are biologically related
Neuropathologic Evidence

Pathology of ALS and FTD

Spongiform degeneration of Cortical Layers II and III

Familial ALS: Frequent Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Inheritance</th>
<th>Frequency</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOD1</td>
<td>16p11.2</td>
<td>AD</td>
<td>10-20%</td>
<td>Juvenile ALS</td>
</tr>
<tr>
<td>C9orf72</td>
<td>9p21-22</td>
<td>GCA</td>
<td>&lt;1%</td>
<td>FTLD, ALS</td>
</tr>
<tr>
<td>TARDBP</td>
<td>17p13.3</td>
<td>FTDP-17, FTD, AD</td>
<td>1-3%</td>
<td>FTLD, ALS</td>
</tr>
<tr>
<td>FUS</td>
<td>16p11.2</td>
<td>FTDP-17, FTD, AD</td>
<td>1-3%</td>
<td>FTLD, ALS</td>
</tr>
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<td>FTLD</td>
<td>17p13.3</td>
<td>FTDP-17, FTD, AD</td>
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<td>FTLD, ALS</td>
</tr>
</tbody>
</table>

GENETIC EVIDENCE
Single Genes of Large Effect
Chromosome 9 linked ALS FTD (Gwent Pedigree)

<table>
<thead>
<tr>
<th>Type</th>
<th>Locus</th>
<th>Gene</th>
<th>Inheritance</th>
<th>Frequency</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS-1</td>
<td>21q22.1-22.2</td>
<td>SOD-1</td>
<td>AD</td>
<td>0-20%</td>
<td>variable</td>
</tr>
<tr>
<td>ALS-2</td>
<td>2q33</td>
<td>ALSin</td>
<td>AR</td>
<td>Rare, mostly Arab Juvenile ALS</td>
<td></td>
</tr>
<tr>
<td>ALS-3</td>
<td>18q</td>
<td>9q34</td>
<td>AD</td>
<td>Single family</td>
<td></td>
</tr>
<tr>
<td>ALS-4</td>
<td>9q34</td>
<td>SETX</td>
<td>AD</td>
<td>Ataxia oculomotor apraxia</td>
<td></td>
</tr>
<tr>
<td>ALS-5</td>
<td>15q15-22</td>
<td>SPG1</td>
<td>AR</td>
<td>Juvenile HSP</td>
<td></td>
</tr>
<tr>
<td>ALS-6</td>
<td>16q21</td>
<td>FUS</td>
<td>AD, AR</td>
<td>0.5%</td>
<td>Young onset, LMN, often sporadic</td>
</tr>
<tr>
<td>ALS-7</td>
<td>20p13</td>
<td></td>
<td></td>
<td>AD</td>
<td>-</td>
</tr>
<tr>
<td>ALS-8</td>
<td>17q21</td>
<td>VAPB</td>
<td>AD</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>ALS-9</td>
<td>14.q11</td>
<td>ANG</td>
<td>AD</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>ALS-10</td>
<td>1p36.22</td>
<td>TARDBP</td>
<td>AD</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>ALS-11</td>
<td>6p.21</td>
<td>FIG4</td>
<td>AD</td>
<td>ALS, CMT 4</td>
<td></td>
</tr>
<tr>
<td>ALS-12</td>
<td>10p.13</td>
<td>OPTN</td>
<td>AD/AR</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>ALS-13</td>
<td>12p23.12</td>
<td>ATXN2</td>
<td>AD?</td>
<td>ALS, SCA2</td>
<td></td>
</tr>
<tr>
<td>ALS-14</td>
<td>9p13.3</td>
<td>VCP</td>
<td>AD</td>
<td>0.5%</td>
<td>IBM, Paget's Disease, Dementia</td>
</tr>
<tr>
<td>ALS-15</td>
<td>Xp11.21</td>
<td>UBQLN2</td>
<td>X-linked</td>
<td></td>
<td>FTDP</td>
</tr>
<tr>
<td>ALS-16</td>
<td>9p13</td>
<td>SIGMAR1</td>
<td>AD</td>
<td>Mostly Arab Juvenile ALS</td>
<td></td>
</tr>
<tr>
<td>ALS-17</td>
<td>3-11.2</td>
<td>CHMP2B</td>
<td>AD</td>
<td>1%</td>
<td>LMN predominent</td>
</tr>
<tr>
<td>ALS-18</td>
<td>17p13.2</td>
<td>PFN1</td>
<td>AD</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>ALS-19</td>
<td>5q53.3</td>
<td>SQSTM1</td>
<td>AD</td>
<td>Paget's Disease</td>
<td></td>
</tr>
<tr>
<td>ALS-20</td>
<td>9p21</td>
<td>C9orf72</td>
<td>AD</td>
<td>50% Regional Variation</td>
<td></td>
</tr>
</tbody>
</table>

Hexanucleotide Repeat Expansion in C9orf72 causes ALS and FTD

Cognitive Impairment in ALS: Predominantly Fronto-Temporal Degeneration

Clinical Features of fvFTD

- Over-eating and food fads
- Blunted emotions
- Lack of judgement
- Impulsive buying
- New onset criminal behaviour
- Ignoring social etiquette
- Change in personal hygiene
- Hoarding

- FTD
- Dementia
- Motor neuron disease
- Frontal variant

Family members may not be aware that deficits of executive dysfunction / personality changes are features of the condition.

Classification of Frontotemporal Syndromes in ALS.

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS</td>
<td>A pure motor system disorder as defined by the El Escorial criteria with no clinical evidence of non-motor system involvement</td>
</tr>
<tr>
<td>ALSa</td>
<td>Cognitive impairment on standardised neuropsychological testing of at least one of the following: memory, visuospatial, language, executive function, attention, or processing speed, without final evidence of motor neuron degeneration</td>
</tr>
<tr>
<td>ALSb</td>
<td>Motor neuron disease with evidence of cognitive impairment on standardised neuropsychological testing</td>
</tr>
<tr>
<td>ALS-FTD</td>
<td>Defined criteria for FTLD limit</td>
</tr>
<tr>
<td>FTD-MND-like</td>
<td>Neuropathological examination of frontotemporal lobar degeneration (FTLD) but ALS shows a neuropathological evidence of motor neuron damage that is not classical frontotemporal dementia</td>
</tr>
<tr>
<td>ALS-dementia</td>
<td>ALS with dementia, not typical of the above (e.g. concomitant Alzheimer's disease or vascular dementia)</td>
</tr>
</tbody>
</table>
Population Based Study of Cognitive & Behavioural Impairment in ALS

Methodology

Inclusion Criteria
- Incident cases
- Age 18 or more
- Possible, probable or definite ALS as per the Revised El Escorial Criteria

Exclusion Criteria
- History of neurological conditions that could affect cognition (major hemispheric stroke, traumatic brain injury, learning disability, severe active epilepsy)
- Alcohol dependence syndrome
- Severe active mental illness, and/or use of high dose psychoactive medications.

Clinical Data

- Demographic data
- Clinical details
- Brief Family History
- ASFRS-R
- Transcutaneous O2/CO2 levels
- Genetic status (C9orf72)

Background Demographics
(n=206 patients, 120 controls)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age at assessment (SD)</td>
<td>62.9 (10.3)</td>
</tr>
<tr>
<td>Percentage of Males</td>
<td>59.0%</td>
</tr>
<tr>
<td>Mean Education in years (SD)</td>
<td>12.1 (3.3)</td>
</tr>
<tr>
<td>Spinal-onset disease</td>
<td>63.9%</td>
</tr>
<tr>
<td>Bulbar-onset disease</td>
<td>34.3%</td>
</tr>
<tr>
<td>Respiratory-onset disease</td>
<td>1.5%</td>
</tr>
<tr>
<td>Baseline median ALSFRS-R</td>
<td>38</td>
</tr>
<tr>
<td>NIV use at baseline</td>
<td>11.2%</td>
</tr>
<tr>
<td>Enteral tube in situ at baseline</td>
<td>15.6%</td>
</tr>
<tr>
<td>Use of Riluzole at baseline</td>
<td>82.9%</td>
</tr>
<tr>
<td>Median Time to diagnosis (months)</td>
<td>11 months</td>
</tr>
</tbody>
</table>

Neuropsychological Battery

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

- **Memory**
  - Logical memory (WMS-III)
  - California Verbal Learning Test
  - Paired Associate Learning Test (WMS-III)
  - Rey Complex Figure Test (immediate and delayed)

- **Language**
  - Boston Naming Test

COGNITIVE PROFILE
CLASSIFICATION OF IMPAIRMENT

- Normal
- ALS with cognitive impairment
  - Executive impairment
  - Non-executive impairment
- ALS with FTD

SubClassification of Non-Demented ALS Patients

Cognitive & Behaviour Impairment in ALS: Unanswered Questions

Longitudinal Study of Cognition in ALS
**Percentage of ALS Patients with No Cognitive Impairment**

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS Patients</td>
<td>32%</td>
<td>86%</td>
<td>57%</td>
<td>3%</td>
</tr>
<tr>
<td>HC</td>
<td>205</td>
<td>136</td>
<td>103</td>
<td>57</td>
</tr>
</tbody>
</table>

**Motor Decline & Cognitive Function are Linked**

<table>
<thead>
<tr>
<th>ALSFRS-R slope points/mth</th>
<th>ALS-FTD</th>
<th>Executive dysfunction</th>
<th>NECI Abnormality</th>
<th>No Abnormality</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 data</td>
<td>1.8</td>
<td>1.2</td>
<td>1.2</td>
<td>0.83</td>
<td>0.55</td>
</tr>
<tr>
<td>T3 data</td>
<td>1.4</td>
<td>0.78</td>
<td>0.42</td>
<td>0.032</td>
<td></td>
</tr>
</tbody>
</table>

**Change in Cognitive Status on Repeated assessments**

Those with executive dysfunction at presentation
- 5/6 “single domain” → multi-domain (by T2)
- 2/12 → co-morbid FTD (by T2)

Those with non-executive cognitive impairment at presentation
- 36% developed executive dysfunction (by T2)
- Remaining patients continued to have NECI

- Those who were cognitively intact at presentation:
  - Majority remained cognitively intact:
    - T2: 52/65, (80.0%)
    - T3: 31/38 (81.6%)
    - T4: 6/7, (85.7%)
  - Most common new cognitive change: language: 18.1% at T2, 7.9% at T3
  - Executive dysfunction rare T2: 3/65 (4.6%) T3: 2/38 (5.2%)
  - Subtle changes at baseline

**DOES COGNITIVE IMPAIRMENT IN ALS INFLUENCE SURVIVAL?**

**ALS-FTD vs ALS without FTD**

- ALS-FTD (n=21) 25 mths (95% CI 20.7 - 29.2)
- ALS without FTD (n=126) 42 mths (95% CI 32.5 - 51.5)

**Executive Dysfunction (n=126)**

- Executive dysfunction (n=16) 27 mths (95% CI 19.7 - 39.7)
- No executive dysfunction (n=110) 48 mths (95% CI 30.2 - 65.7)

HR 3.9 (95% CI 2.0 to 7.2)
Summary so far

- ALS is a spectrum disease
- A subgroup of ALS patients remain cognitively intact
- Cognitive phenotype correlates with disease trajectory
- Executive impairment is a negative prognostic indicator

Phenotype Genotype Correlation

C9orf72 Repeat Negative

C9orf72 Repeat Positive

Cognitive and clinical characteristics of patients with amyotrophic lateral sclerosis carrying a C9orf72 repeat expansion: a population-based cohort study

C9orf Expansion has a Distinctive Imaging Signature

Subcortical Grey Matter is Involved

(Bede et al Neurology 2014)
ALS ENDOPHENOTYPES?

172 ALS and 198 Control kindreds, 12,000 relatives

Table:

<table>
<thead>
<tr>
<th>Allele</th>
<th>Haplo ID</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>172 ALS</td>
<td>0.3</td>
<td>0.017</td>
</tr>
<tr>
<td>198 Control</td>
<td>0.07</td>
<td>0.0011</td>
</tr>
<tr>
<td>ALS</td>
<td>0.3</td>
<td>0.0015</td>
</tr>
<tr>
<td>Control</td>
<td>0.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>ALS</td>
<td>0.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Control</td>
<td>0.1</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

C9orf72 Screening Algorithm

Is Cognitive Impairment Important?

- Survival
- Decisions: finance, end-of-life decisions
- Compliance with NIV, RIG, multidisciplinary care
- Safety awareness e.g. Fall avoidance, coping with choking episodes
- Carer burden impact
- Critical to our understanding of the biology of ALS

ALS and DEMENTIA
No longer an “odd couple!”

Team

- Clinical
  - Bernie Corr
  - Ger Foley
  - Deirdre Murray
  - Lesley Doyle
  - Louise Whelan
  - Kitty McElligott
  - Bernie Corr
  - Ger Foley
  - Deirdre Murray
  - Lesley Doyle
  - Louise Whelan
  - Kitty McElligott

- Imaging & EEG
  - Dr. Peter Bede
  - Dr. Arun Bokde
  - Dr. Ed Lalor
  - Dr. Parames Iyer

- Laboratory
  - Dr. Julie Kelly
  - Dr. Alice Veiga
  - Dr. Vidya

- Health Services
  - Prof. Anthony Staines
  - Dr. Miriam Galvin
  - Dr. Shovaghy Chetkowitz
  - Dr. Kay Tobin

- Genetics
  - Prof. Dan Bradley
  - Dr. Russell McLaughlin
  - Dr. Kevin Keane

- Neuropsychology
  - Dr. Niall Pender
  - Dr. Marwa Elamin
  - Dr. Cara McDaniel

- Epidemiology
  - Dr. Susan Byrne
  - Dr. James Rooney
  - Dr. Helen Herron

- EMG & Biomarkers
  - Dr. Ger Mullins
  - Dr. Taha Omar

- Clinical Trials
  - Liz Foley
  - Fiona McLean

- TCD Admin
  - Dominique Platt