What causes motor neuron disease?

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“Are there different types of MND?”

“What type have I got?”
Damage causes weakness, stiffness and brisk reflexes.

Upper motor neuron damage causes weakness, wasting, twitching, and loss of reflexes.

Lower motor neuron damage causes weakness.
Types of MND - Neurologists

- **Clinical experience**
  - Bulbar palsy
  - Limb onset ALS
  - Flail arm syndrome
  - Flail leg syndrome
  - Primary lateral sclerosis
  - Progressive muscular atrophy
Types of MND - Neurologists

• Neurologists
  – classifications predict survival

*Wijesekera LC et al, Neurology 2009*
Types of MND - Neurologists

- Neurologists
  - classifications predict survival

Bulbar onset

50% survival = 2 years

Wijesekera LC et al, Neurology 2009
Types of MND - Neurologists

- Neurologists
  - classifications predict survival

Flail leg syndrome
50% survival = 6 years

*Wijesekera LC et al, Neurology 2009*
Types of MND - Machines

- **Machine classification**
  - Statistical patterns extracted using latent class cluster analysis

- **5 groups identified**
  - Match mainly to bulbar onset, age of onset, diagnostic delay
Types of MND - Machines

- Neurologists
  - classifications predict survival

- Machines
  - classifications predict better

Wijesekera LC et al, Neurology 2009

Ganesalingam J et al, PLoSOne 2009
Types of MND - Machines

- Machines
  - classifications predict better

Group 3
No deaths in study

Ganesalingam J et al, PLoSOne 2009
Types of MND - Machines

- Machines
  - classifications predict better

Group 4
50% survival = 7 years

Ganesalingam J et al, PLoSOne 2009
Types of MND - Machines

- Machines
  - classifications predict better

Group 5
50% survival = 14 years

Ganesalingam J et al, PLoSOne 2009
Collaborations needed to study subtypes of MND

- **EuroMotor**
  - Population registers and DNA Banks to collect data

- **SOPHIA**
  - Collect huge amounts of data in a standardized way

- **STRENGTH**
  - Multiple layers of data to find subtypes of MND

- **ALS-CarE**
  - Generate the ideal care pathway for the subtypes
“I thought it was a rare condition”
How common is MND?

- Most common neurodegenerative disease of mid-life

- At least 3 people diagnosed per day in the UK
  - Average GP sees one affected person in their lifetime
  - Average neurologist sees two affected people per year
  - We see 200 newly diagnosed people per year
Lifetime risk of MND

1 in 300 risk

“Is it something I did?”

“What causes MND?”
Exercise and MND risk

- **Anecdotal experience of neurologists**
  - But biased selection

- **Gulf war veterans**
  - Deployment rather than fitness

- **Studies of exercise**
  - Inconclusive but suggest a risk factor
Handedness and MND

- Arms exercised asymmetrically based on dominance
- Legs exercised equally regardless of dominance
- Natural test of relationship between exercise and MND

*Turner M et al., JNNP 2010*
Handedness and MND

• 151 upper limb onset patients
  – 64% onset in dominant limb
    • Statistically different from 50:50

• 181 lower limb onset patients
  – 55% onset in dominant limb
    • Statistically same as 50:50

• Exercised limb more likely to be affected first
  – Other explanations too

Turner M et al., JNNP 2010
Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players

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Football and MND

• Italian professional players
  – Serie A, B and C

• 7325 in study cohort
• Age range 18 – 69

• 5 cases identified
  – Expect 0.77

• Excess risk of death 6.5 times average

• Different analysis suggests no increased risk
UK football cluster

Three soccer playing friends with simultaneous amyotrophic lateral sclerosis

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*Amyotrophic Lateral Sclerosis*
2007, 1–3, article
UK football cluster

• **Three friends**
  – Grew up in the same small village in Kent
  – Played amateur football
    • Several times a week for 12 to 28 years
    • Two on same team
    • Same pitches
  – All had MND at the same time
    • Two died the same weekend

• **Shared other potential risk factors**
  – Smoking, electric shock, trauma, exercise
Smoking and MND

- Best quality studies show smoking increases risk
  - Dose response

- Dutch study shows worsens survival too
  - Clinic populations unlikely to have many smokers

- Some studies suggest women more at risk
“There is a cluster of cases near me”
Geographic distribution of ALS in South East England 1996 - 2006

Scott KM et al, Neuroepidemiology, 2008
Geographic distribution of ALS in South East England 1996 - 2006

Scott KM et al, Neuroepidemiology, 2008
Geographic clustering in South East London 1996 - 2006

Scott KM et al, Neuroepidemiology, 2008
Geographic clustering in South East London 1996 - 2006

Scott KM et al, Neuroepidemiology, 2008
Geographic clustering in Finland 1990

Clustering in Piedmont region, Italy

Migliaretti G, ALS 2012
Relative Risk of ALS – all cases 1995 – 2013
National MND Register

- Aim to capture information on every person with MND in the UK
  - Significant challenges
  - Many benefits
“How long have I got?”
How long have I got?

- We can make a reasonably good prediction
  - Main factors are age of onset, site of onset, diagnostic delay and Riluzole use
NO

Respiratory failure

YES

Mortality rate per month

<table>
<thead>
<tr>
<th>Mortality rate per month</th>
<th>NIV</th>
<th>NO NIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>BULBAR ONSET</td>
<td>20%</td>
<td>54%</td>
</tr>
<tr>
<td>LIMB ONSET</td>
<td>10%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Use nomogram
Respiratory failure

- NO: Use nomogram
- YES:
  - One year survival
    - NIV
      - BULBAR ONSET: 7%
      - LIMB ONSET: 28%
    - NO NIV
      - BULBAR ONSET: 0%
      - LIMB ONSET: 1%
limb onset, riluzole

median survival from diagnosis (months)

age at onset

diagnostic delay (months)
“Will others in my family develop MND?”
Is there a genetic component to MND?

- **Meta-analysis**
  - British MND Twin Study
  - Swedish Twin Registry
  - King’s ALS Register

<table>
<thead>
<tr>
<th>At least one affected</th>
<th>MZ</th>
<th>DZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concordant pairs</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Discordant pairs</td>
<td>44</td>
<td>122</td>
</tr>
</tbody>
</table>

- **Heritability**
  - 0.61 (0.38-0.78)

- **Environmental component**
  - 0.39 (0.22 – 0.62)

*Al-Chalabi et al, JNNP 2010*
MND inheritance is complex

With kind permission of Peter Andersen
Genes are an important risk factor

- Genes found for familial and sporadic MND
  - Need large collaborations for gene discovery
    - 14,000 cases
    - 25,000 controls
Some important genes in MND

- VAPB
- OPTN
- VCP
- SOD1?
- FIG4, SIGMAR1, ALS2, SPG11

- TDP43
- ANG
- TAF15
- FUS
- ELP3
- SETX
- UBQLN2
- UNC13A
- ATXN2
Project MinE

- Aim to sequence whole genomes
  - 25,000 ALS genomes
  - 7,500 control genomes

- Nine countries participating so far
Is there a risk to relatives?

- Background risk of MND is 1 in 300
  - Means risk of not developing MND is 99.7%
  - Risk for relatives not developing MND is ~98%

Hanby MF et al, Brain, 2011
Is there a risk to relatives?

- Background risk of MND is 1 in 300
  - Means risk of not developing MND is 99.7%
  - Risk for relatives not developing MND is ~98%

- There is no great change in risks for those with no family history

*Hanby MF et al, Brain, 2011*
“So how come I have MND?”
A simple model of MND risk

Health

Genetic load (G)

Cell damage with time (T)

Environmental exposures (E)

Burden of disease causing factors

No disease

Disease

Al-Chalabi and Hardiman, Nature Reviews Neurol 2013
A simple model of MND risk

Health

Burden of disease causing factors

Birth
G
T
E
Onset

No disease
Disease

Al-Chalabi and Hardiman, Nature Reviews Neurol 2013
A simple model of MND risk

Health

Birth

Onset

Death

Burden of disease causing factors

No disease

Disease

Self-perpetuating process

Al-Chalabi and Hardiman, Nature Reviews Neurol 2013
A simple model of MND risk

Health

Burden of disease causing factors

No disease  Disease

Birth  Onset  Death

Self-perpetuating process

Al-Chalabi and Hardiman, Nature Reviews Neurol 2013
A simple model of MND risk

Health

Burden of disease causing factors

No disease  Disease

Birth

Onset

Death

Al-Chalabi and Hardiman, Nature Reviews Neurol 2013
Is MND a multistep process?

• If MND is a multistep process
  – Plot
    • $\log(\text{incidence})$ vs $\log(\text{age})$
  – Straight line?
  – Slope + 1 = number of steps needed

Al-Chalabi A, Lancet Neurology 2014
SEALS (England)

Slope of $5 = 6$ steps

$r^2 = 0.95$
Netherlands

Slope of 5 = 6 steps

$r^2 = 0.99$
Piedmont

Slope of 5 = 6 steps

$r^2 = 0.95$
Ireland

Slope of 5 = 6 steps

\[ r^2 = 0.99 \]
Scotland

Slope of 5 = 6 steps

\[ r^2 = 0.97 \]
Overall findings

Slope of 5 = 6 steps

$r^2 = 0.99$
A simple model of MND risk

6 STEPS

Burden of disease causing factors

No disease  |  Disease

Self-perpetuating process

Al-Chalabi and Hardiman, Nature Reviews Neurol 2013
Conclusions

• Genes and environment combine to cause MND

• Research helps answer patient questions
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