Breathing Life into Motor Neurone Disease

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Progressive neurodegenerative disorder (UMN & LMN)

- Loss of motor neurons in cortex, brainstem and spinal cord. Denervation atrophy in affected muscles

Familial 10%, Sporadic 90%

- Genetics rapidly evolving (SOD$_1$, TDP$_{45}$, FUS, C9orf72............. Present in ~ 65% “spontaneous” MND)

Incidence 1.5 - 2.5 / 100,000 / year. Prevalence ~ 1200

Male > female (ratio 3:2), Mean age of onset ~ 58 yrs

Progressive Respiratory Failure → death

Median survival 2-4 yrs

- Dependent on type / location of symptom onset, age, rate of respiratory decline, nutritional state
MND disease progression affected by phenotype

**ALS**
- Bulbar Onset: 25%
- Cervical Onset: 65%
- Lumbar Onset

**Flail**
- Cervical Onset: 9%
- Lumbar Onset

**PLS**
- Bulbar Onset: 1%
- Cervical Onset
- Lumbar Onset
Phenotype affects survival in MND/ALS

Talman et al 2009 & 2016
Sleep study on a person with MND before NIV
NIV improves QOL

Bourke 2003

- N = 15, prospective study, NIV users
- Disease progressed

Peak improvement in QOL 3-5 months after starting NIV

- SF-36: Mental health, emotional
- CRQ: Fatigue, mastery
- SAQLI: Social isolation, symptoms

- Large improvements in sleepiness (ESS)
Single RCT suggests NIV increases survival

Bourke et al. Lancet Neurol 2006
Figure 2: Survival from randomisation

- All patients
- B: patients with normal or moderately impaired bulbar function
- C: patients with severe bulbar impairment

Numbers at risk

<table>
<thead>
<tr>
<th></th>
<th>NIV</th>
<th>Standard care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22</td>
<td>19</td>
</tr>
</tbody>
</table>

Proportion surviving

- B: p = 0.0059
- C: p = 0.92
Melbourne cohort study

• Started with 2002-2004 Bethlehem Griffith Research Foundation grant support
  
  • “Prospective evaluation of sleep and breathing in Motor Neurone Disease.” DJ Berlowitz, P Talman, R Pierce & L Irving

  – Data collection integrated into usual care / routine OP clinic visit. Analyses supported by MNDRIA

• Aim

  – evaluate the effect of NIV on survival in a clinical cohort,

  – examine whether the effect of NIV on survival is different in patients with different clinical phenotypes
All patients with ALS/MND treated at a specialist, multidisciplinary clinic at the Bethlehem Hospital from 1991-2011.

Patients excluded if data regarding disease phenotype, date of disease onset, of death or last follow up were not recorded.

Tracheostomy-free survival (in months) was the primary outcome of interest.

- Survival was considered from onset of symptoms to either death, date of tracheostomy or censoring date of 31/12/2011.
<table>
<thead>
<tr>
<th></th>
<th>NIV</th>
<th>No-NIV</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total sample</strong></td>
<td>219</td>
<td>710</td>
<td></td>
</tr>
<tr>
<td><strong>Age at disease onset, years</strong></td>
<td>58.3±11.5</td>
<td>64.0±11.9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Gender, Male</strong></td>
<td>157 (71.7)</td>
<td>375 (52.8)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td><strong>Riluzole prescription</strong></td>
<td>164 (74.9)</td>
<td>250 (35.2)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td><strong>PEG insertion</strong></td>
<td>129 (58.9)</td>
<td>180 (25.3)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td><strong>Phenotype</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALS- Bulbar Onset</td>
<td>58 (18.6)</td>
<td>254 (81.4)</td>
<td></td>
</tr>
<tr>
<td>ALS– Cervical Onset</td>
<td>61 (25.4)</td>
<td>179 (74.6)</td>
<td>0.08†</td>
</tr>
<tr>
<td>ALS– Lumbar Onset</td>
<td>78 (26.5)</td>
<td>216 (73.5)</td>
<td></td>
</tr>
<tr>
<td>Flail Limb</td>
<td>22 (26.5)</td>
<td>61 (73.4)</td>
<td></td>
</tr>
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</table>

* Independent sample t test
† Chi-square test

Data presented as mean + standard deviation or number (percentage). NIV = non-invasive ventilation
<table>
<thead>
<tr>
<th>Sample, n</th>
<th>Median survival, months</th>
<th>Univariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIV</td>
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</tr>
<tr>
<td>All Phenotypes*</td>
<td>219</td>
<td>710</td>
</tr>
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NIV = non-invasive ventilation; CI = confidence interval.

* Analysis stratified by phenotype and year of index in the database (i.e. before 2003 and after 2003)
All Phenotypes (n = 929)

![Graph showing time since symptom onset (months) for different treatment groups.](image)
### Sample, n Median survival, months Univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Sample, n</th>
<th>Median survival, months</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
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<td>28.63</td>
<td>15.02</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.61 (0.51-0.73)</td>
<td>0.000</td>
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<tr>
<td>Global - Bulbar Onset†</td>
<td>58</td>
<td>254</td>
<td>32.61</td>
<td>13.57</td>
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<tr>
<td></td>
<td></td>
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<td>0.50 (0.36-0.70)</td>
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<td>Global - Cervical Onset†</td>
<td>61</td>
<td>179</td>
<td>27.15</td>
<td>17.55</td>
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<td></td>
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<td>0.77 (0.55-1.06)</td>
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<td>27.55</td>
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<td></td>
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<td>0.62 (0.45-0.84)</td>
<td>0.003</td>
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<td>Flail Limb Onset†</td>
<td>22</td>
<td>61</td>
<td>55.92</td>
<td>24.92</td>
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<td></td>
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<td>0.57 (0.31-1.05)</td>
<td>0.07</td>
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NIV = non-invasive ventilation; CI = confidence interval.

* Analysis stratified by phenotype and year of index in the database (i.e. before 2003 and after 2003)
† Analysis stratified by year of index in the database (i.e. before 2003 and after 2003).
‡ Multivariate model includes the variables: percutaneous endoscopic gastrostomy, riluzole, age of onset & gender
Other cohorts; similar survival results

• Survival advantage in those who tolerated NIV
  • Risk of death 3.1 times greater in non-users
  • Still present in severe bulbar dysfunction
  • Still present once adjusted for confounders

• Median survival after NIV
  – 18 months vs 6 months

• Mean survival after NIV
  – Gp 1 = tolerated > 4 hrs/night = 14.2 months
  – Gp 2 = tolerated < 4 hrs/night = 7.0 months
  – Gp 3 = refused to try = 4.6 months
Does NIV modify disease and if yes, how?

- Sleep disordered breathing is a potent source of chronic intermittent hypoxia and reactive oxygen species
  - Lavie 2015
- Reactive oxygen species are a therapeutic target in MND
  - Barber 2006
- Chronic Intermittent Hypoxia (cycles over 12 hours for 2 weeks) aggravates motor neuronal loss and impairs memory in (n=16) SOD1 mouse model of MND
  - Kim 2013

Figure 3. Percent alteration in the Y-maze test. The Y-maze test was performed to evaluate the effect of CH on spatial memory in mice. After 2 weeks of CH, ALS mice exhibited significantly lower percent alteration (PA) in the Y-maze test than did the ALS-NOX mice ($p < 0.05$). In addition, the ALS-CH mice showed poorer spatial memory compared with the WI-CH mice, an effect which suggests that ALS mice are more vulnerable to CH than the WI mice are.

* $p < 0.05$, ** $p < 0.01$

Figure 4. Immunohistochemistry with anti-choline acetyltransferase (ChAT) to assess the number of ventral horn motor neurons. Motor neurons in the ventral horn were stained with ChAT. Existing motor neurons and the number of motor neurons were counted in all mice. Significantly more motor neurons were counted in the ALS-CH mice than in the ALS-NOX mice ($p < 0.05$). The number of motor neurons did not differ significantly between the WI-CH mice and the ALS-NOX mice ($p > 0.05$).

* $p < 0.05$, ** $p < 0.01$, n.s. = no statistical significance

Figure 5. Western blot for markers of oxidative stress (4-HNE) and activation of the NF-κB pathway (IkB, p-IkBα, p-NF-κB). Generation of reactive oxygen species and/or activation of inflammatory pathways might be involved in the increased loss of motor neurons in ALS mice due to CH. Although the wild-type mice (WT) used in the study did not induce oxidative stress or activation of the NF-κB pathway in the WI mice, significant oxidative stress (A and B) and activation of the NF-κB (A and C) pathway were demonstrated in ALS mice.
Results from this cohort study involving a large scale Australian database confirm the positive effect of NIV on survival of patients with ALS/MND

In our subgroup analysis within ALS/MND phenotypes, patients with bulbar disease onset showed the greatest survival advantage with the use of NIV

Similar improvement observed in reduction in breathing capacity decline

NIV works in MND, so we should always consider it
Thank you

2002
Bethlehem Griffith Research Foundation
2010 and 2017
Motor Neurone Disease Research Institute of Australia
Pulmonary function slopes pre & post NIV

208 of the 219 patients who used NIV had sufficient pre and post-NIV data for model inclusion.

FVC slopes before and after NIV (Litres per year)

<table>
<thead>
<tr>
<th>Sample</th>
<th>Before NIV</th>
<th>After NIV</th>
<th>Difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All phenotypes</td>
<td>-1.22</td>
<td>-1.06</td>
<td>0.16 (0.04 to 0.29)</td>
<td>0.009</td>
</tr>
<tr>
<td>ALS-Bulbar</td>
<td>-1.36</td>
<td>-1.00</td>
<td>0.36 (0.09 to 0.64)</td>
<td>0.009</td>
</tr>
<tr>
<td>ALS-Cervical</td>
<td>-1.08</td>
<td>-1.26</td>
<td>-0.18 (-0.42 to 0.06)</td>
<td>0.141</td>
</tr>
<tr>
<td>ALS-Lumbar</td>
<td>-1.41</td>
<td>-1.24</td>
<td>0.17 (-0.06 to 0.41)</td>
<td>0.159</td>
</tr>
<tr>
<td>ALS-Flail limb</td>
<td>-0.80</td>
<td>-0.33</td>
<td>0.47 (0.24 to 0.70)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
NIV slows rate of decline in lung function

FVC % is predictor of death

FVC best correlates to symptoms

Rate of decline in RFT was related to mortality
- Average drop FVC = -3.5% / mth

Similar in Bourke 2003, Lo Coco 2006
- -0.5% / month on NIV
- -3.46% / month intolerant of NIV

FVC before and after NIV

Kleopa 1999