Application of ALS Staging Systems to an American ALS Population

Justin Kwan, M.D.
Disclosure statement

• I have no conflicts of interest to report

• I do not have financial or other relationships with any commercial interest

• I will not be discussing off label use of pharmaceuticals or devices

"Under disclosure rules, I'm required to tell you I own stock in the company whose drug I'm prescribing."
Current ALS “classifications”

• Site of onset
• Gene mutation
• Cognitive impairment
Revised El Escorial diagnostic criteria

- Revised El Escorial diagnostic criteria
  - Characterizes the extent of upper and lower motor neuron signs

- Clinically definite ALS
  - Upper motor neuron (UMN) as well as lower motor neuron (LMN) signs in the bulbar region and at least two spinal regions or the presence of UMN and LMN signs in three spinal regions

- Clinically probable ALS
  - UMN and LMN signs in 2 regions with at least some UMN signs rostral to LMN signs

- Clinically probable ALS: laboratory supported
  - UMN and LMN signs are only in one regions or UMN signs alone are in one or more regions, and LMN signs defined by EMG criteria in at least two regions

- Clinically possible ALS
  - UMN and LMN in one region (together) or
  - UMN in 2 or more regions
  - UMN and LMN signs in 2 regions with no UMN signs rostral to LMN signs
El Escorial criteria limitations

- Goal of the criteria is to determine clinical certainty of ALS diagnosis
- Criteria is sensitive to the “extent of disease” rather than to the “burden of disease”
- Up to 10% of patients may not fulfill “definite ALS” criteria at the time of death
- Does not provide prognostic information
ALS-FRS-R

- 48 point scale with 4 major domains (48 = normal)
  - Bulbar
    - Speech
    - Salivation
    - Swallowing
  - Upper limb
    - Handwriting
    - Cutting food and handling utensil (with and without gastrostomy)
    - Dressing and hygiene
  - Lower limb
    - Turning in bed and adjusting bed clothes
    - Walking
    - Climbing stairs
  - Respiratory
    - Dyspnea
    - Orthopnea
    - Respiratory insufficiency
ALS-FRS-R

• Measure of disability and not “stage” of disease
• Patients with different stages of disease may have the same ALS-FRS-R
What is staging and why is it important?

• Define specific milestones over the course of the disease and reflects:
  – Disease severity
  – Prognosis
  – Options for treatment

• Purpose:
  – Tool of rehabilitation
  – Rapid functional assessment
  – Biomarker analysis
  – Effective research design
  – Health economics
Proposed staging systems

- King’s clinical staging (2012)
  - 5 stages based on disease burden as measured by clinical involvement and significant feeding or respiratory failure
  - Can be estimated from ALSFRS-R

  - Uses 6 stages based on functional ability as assessed by ALS Functional Rating Scale-Revised
• King’s clinical staging system differentiates early to mid disease
  – Focus on anatomical disease spread and significant involvement of respiration
• MiToS differentiate late stages in detail
  – Functional status tends to follow anatomical involvement therefore MiToS stages tend to lag behind King’s stages
King’s clinical staging

Stage 1:
Involvement of first region

Stage 2:
2A: Diagnosis
2B: Involvement of second region

Stage 3:
Involvement of third region

Stage 4:
4A: Nutritional failure
4B: Respiratory failure

Stage 5:
Death

ALS-MITOS functional staging

Stage 0:
Functional Involvement

Stage 1:
Loss of independence in 1 domain

Stage 2:
Loss of independence in 2 domains

Stage 3:
Loss of independence in 3 domains

Stage 4:
Loss of independence in 4 domains

Stage 5:
Death
• Objective:
  – Apply the King’s clinical staging to an American ALS population
Methods

• IRB approved retrospective chart review of 139 patients who presented to the University of Maryland ALS Clinic between January 2007 to August 2015

• ALS patient fulfilled the revised El Escorial Diagnostic criteria for clinical definite, probable, possible ALS
• Statistics:
  – Mean milestone time: Time elapsed from symptom onset to time of last clinical milestone reached
  – Fraction of total survival to onset of stages: Proportion of time spent in each milestone from symptom onset to death
## Demographics

<table>
<thead>
<tr>
<th>Onset</th>
<th>N (%)</th>
<th>Onset (years)</th>
<th>Duration to Diagnosis (months)</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Total</td>
<td>139</td>
<td>60.7</td>
<td>14.0</td>
<td>35.0</td>
</tr>
<tr>
<td>Male</td>
<td>82 (59%)</td>
<td>59.8</td>
<td>14.9</td>
<td>34.0</td>
</tr>
<tr>
<td>Female</td>
<td>57 (41%)</td>
<td>61.9</td>
<td>13.7</td>
<td>37.1</td>
</tr>
<tr>
<td>Bulbar Total</td>
<td>45 (32%)</td>
<td>62.7</td>
<td>13.9</td>
<td>27.3</td>
</tr>
<tr>
<td>Male</td>
<td>23 (51%)</td>
<td>61.3</td>
<td>15.2</td>
<td>27.4</td>
</tr>
<tr>
<td>Female</td>
<td>22 (49%)</td>
<td>64.4</td>
<td>12.3</td>
<td>27.3</td>
</tr>
<tr>
<td>Limb Total</td>
<td>91 (66%)</td>
<td>59.8</td>
<td>14.7</td>
<td>39.2</td>
</tr>
<tr>
<td>Male</td>
<td>57 (63%)</td>
<td>59.1</td>
<td>14.2</td>
<td>37.1</td>
</tr>
<tr>
<td>Female</td>
<td>34 (37%)</td>
<td>60.8</td>
<td>14.8</td>
<td>42.4</td>
</tr>
<tr>
<td>Spine Total</td>
<td>3 (2%)</td>
<td>56.7</td>
<td>12.0</td>
<td>33.5</td>
</tr>
<tr>
<td>Male</td>
<td>2 (66%)</td>
<td>60.5</td>
<td>15.5</td>
<td>33.5</td>
</tr>
<tr>
<td>Female</td>
<td>1 (33%)</td>
<td>49.0</td>
<td>5.0</td>
<td>--</td>
</tr>
</tbody>
</table>
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>UMD</th>
<th>King’s</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>139</td>
<td>1459</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>82 (59%)</td>
<td>892 (61%)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>57 (41%)</td>
<td>577 (39%)</td>
</tr>
<tr>
<td><strong>Bulbar onset</strong></td>
<td>45 (32%)</td>
<td>371 (25%)</td>
</tr>
<tr>
<td><strong>Limb onset</strong></td>
<td>91 (66%)</td>
<td>1088 (75%)</td>
</tr>
<tr>
<td><strong>Age at onset (years)</strong></td>
<td>60.7</td>
<td>60</td>
</tr>
<tr>
<td><strong>Survival (months)</strong></td>
<td><strong>All</strong></td>
<td>35</td>
</tr>
<tr>
<td></td>
<td><strong>Bulbar</strong></td>
<td>27</td>
</tr>
<tr>
<td></td>
<td><strong>Limb</strong></td>
<td>39</td>
</tr>
<tr>
<td>Stage</td>
<td>University of Maryland</td>
<td>King’s clinical staging</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Stage 2B</td>
<td>12.4 (8.5 - 16.3)</td>
<td>17.7 (15.5 - 19.8)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>15.4 (12.7 - 18.1)</td>
<td>23.3 (20.8 - 25.7)</td>
</tr>
<tr>
<td>Stage 4A</td>
<td>16.3 (9.7 - 23.0)</td>
<td>27.7 (25.1 - 30.2)</td>
</tr>
<tr>
<td>Stage 4B</td>
<td>24.4 (20.6 - 28.3)</td>
<td>30.3 (26.4 - 34.2)</td>
</tr>
</tbody>
</table>
## Fraction of total survival to onset of the stages (with 95% CI)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Overall Population</th>
<th>Bulbar Onset</th>
<th>Limb Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UMD</td>
<td>King’s</td>
<td>UMD</td>
</tr>
<tr>
<td>2</td>
<td>0.33 (0.27-0.39)</td>
<td>0.40 (0.37-0.42)</td>
<td>0.32 (0.19-0.46)</td>
</tr>
<tr>
<td>3</td>
<td>0.41 (0.37-0.46)</td>
<td>0.59 (0.57-0.62)</td>
<td>0.37 (0.30-0.43)</td>
</tr>
<tr>
<td>4a</td>
<td>0.67 (0.62-0.72)</td>
<td>0.76 (0.73-0.78)</td>
<td>0.68 (0.59-0.76)</td>
</tr>
<tr>
<td>4b</td>
<td>0.66 (0.61-0.70)</td>
<td>0.75 (0.72-0.79)</td>
<td>0.60 (0.51-0.70)</td>
</tr>
<tr>
<td>4</td>
<td>0.65 (0.61-0.70)</td>
<td>0.60 (0.50-0.69)</td>
<td></td>
</tr>
</tbody>
</table>

Note that time spent in each stage is expressed as a fraction of 1, which represents 100% of the illness course.
Time to reach each milestone

Figure 1 Boxplot showing standardized times to last recorded milestone (where 0 is onset of disease and 1 is death) for each stage in the entire cohort with ALS. Stage 1 (onset) is not explicitly shown but occurs at the origin; 2A = diagnosis; 2B = second region involved; 3 = third region involved; 4A = gastrostomy needed; 4B = respiratory support (non-invasive ventilation) needed. The line marks the median with the shaded box showing the interquartile range.

Roche et al 2012
Figure 2  Kaplan–Meier curve showing survival for entire cohort from last recorded milestone to death or censor date. The separation of the curves is evidence of construct validity. Blue = diagnosis; green = second region involved; grey = third region involved; black = gastrostomy needed; purple = respiratory support needed.

Roche et al 2012
US versus European data

**Similarities**
- Similar demographics
- Comparable time to reach the next milestone

**Differences**
- Shorter survival in US
  - May be driven by the limb onset group (39 [US] vs 48 [European] months)
- More time spent in the early stages in King’s and later stages in UMD
  - Bulbar onset patient spent more time in stage 4 in UMD
  - Limb onset transition faster to later stages in UMD
Summary

• Apply and validate the King’s staging in a US ALS population

• Differences in health insurance systems in US versus UK
  – Access to specialized equipment such as NPPV

• Limitation
  – Smaller US population
  – Retrospective review
Acknowledgement

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