ALS Update: why rehabilitation matters

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The Rehabilitation Medicine Scientist Training Program (RMSTP)
Amyotrophic Lateral Sclerosis (ALS)

• Motor Neuron Disease affecting upper and lower motor neurons
• “Progressive painless weakness”
• Asymmetric onset, regional spread

• Average age of onset is 55 y.o.
• Familial ALS (FALS) ~10-20% (usually AD inheritance)
• Average time from symptom onset to diagnosis is 12-14 months
  – Longer time = improved prognosis

• Average survival after symptom onset is 3-5 years
  – Wide variability
• Pathophysiology not well understood
• No known cure
• Only FDA-approved medication is riluzole

Upper and Lower Motor Neurons

Upper Motor Neurons

Lower Motor Neurons

Picture Credit: www.doctorexclusive.com
Amyotrophic Lateral Sclerosis (ALS)

- **Amyotrophy** – describes clinically evident muscle atrophy

- **Lateral Sclerosis** – describes the gross pathology finding of sclerosis (scarring) of the lateral corticospinal tracts in the spinal cord.

Picture Credits: [www.mdconsult.com](http://www.mdconsult.com); Bradley: Neurology in Clinical Practice, 5th ed; 2000 – M&N - Goetz (review)
Lou Gehrig and his disease

- Columbia engineering student
- Football scholarship; also played baseball
- Yankees player for 17 years
  - First Yankee with retired number (4).
- Known as “The Iron Horse”
  - Played 2,130 consecutive games
- Diagnosed with ALS on his 36th birthday - June 19, 1939.
- Died June 24, 1941
Clinical Features of ALS

• Weakness = disease onset for clinical trials

• Onset of weakness
  – 1/3 bulbar, 1/3 arms, 1/3 legs
  – Limbs: begins asymmetrically
  – Bulbar: CN XII typically first involved

• UMN Symptoms (weakness, stiffness, slow movements, imbalance, dysarthria, increased gag, excessive/painful yawning, muscle spasms)

• LMN Symptoms (weakness, muscle thinning, cramping, fasciculations, dysarthria, nasal rigurgitation)

• Bulbar Symptoms (dysarthria, dysphagia, drooling, nasal rigurgitation, aspiration)

• Non Motor Manifestations (pseudobulbar affect, fatigue, weight loss, pain secondary to immobility, cognitive changes)
Challenges in ALS Clinical Research

- **ALS is Rare, Degenerative, and Fatal**
- **No Prodrome**
  - When does disease begin?
- **Unclear Pathophysiology**
  - Appropriate drug targets?
- **Limited Preclinical Models**
  - Which candidate drugs move forward?
- **Lack of Biomarkers**
  - How do we identify patients early, follow intermediate outcomes, and unravel pathophysiology?
- **Heterogeneous patients**
- **Trials**
  - Size, Duration, Cost
  - Placebo Burden
ALS update: what’s new

1869
ALS described by Charcot

1939
Lou Gehrig

1993 - 2013

1993
1st gene: SOD1

1994
ALS Mouse
Riluzole

1995
Northeast ALS
Consortium
Trial group

2000
EEC
1st NIH funded trial

2011
Gene Discovery
Biomarker Research
Drug Trials
Gene Therapy
Stem cells

Adapted from www.alsconsortium.org
What’s new in collaborative research

• Collaborative Research Community
  – Nationwide and Worldwide
  – Basic Scientists and Clinical Researchers
  – Patients are increasingly involved

• Northeast ALS Consortium
  – Over 100 centers
  – Dedicated Trial Coordination Center
  – Dedicated Outcomes/Monitoring Center
  – Provides site and PI training
  – Conducting an increasing number of trials

From www.alsconsortium.org
What’s new in genetic discovery

• Initial hope: gene discovery would “solve” ALS.
  – 1993 Discovery of SOD1 was a leap forward for the field
    • Transgenic mouse created in 1994 and still used for preclinical screening
  – No clear disease-causing mechanism was found

• Discovery of subsequent genes has been exciting, but has complicated the genetic story
  – RNA binding protein mutations discovered
    • Gene expression dysregulation
  – Protein misfolding

• Pace of gene discovery is quickening
<table>
<thead>
<tr>
<th>Causative Gene</th>
<th>Normal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOD1</strong></td>
<td>Anti-oxidant</td>
</tr>
<tr>
<td><strong>TARDBP</strong></td>
<td>DNA and RNA binding protein</td>
</tr>
<tr>
<td><strong>FUS/TLS</strong></td>
<td>DNA and RNA binding protein</td>
</tr>
<tr>
<td><strong>ALS2</strong></td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>DCTN1</strong></td>
<td>Links dynein and kinesin to transport vesicles</td>
</tr>
<tr>
<td><strong>ANG</strong></td>
<td>Stimulates blood vessel growth; hydrolyze tRNA &amp; ↓ transc</td>
</tr>
<tr>
<td><strong>VAPB</strong></td>
<td>Likely involved in vesicle transport</td>
</tr>
<tr>
<td><strong>SPG11</strong></td>
<td>Unknown; possible role in vesicle trafficking</td>
</tr>
<tr>
<td><strong>OPTN</strong></td>
<td>Role in vesicle trafficking, apoptosis and innate immunity</td>
</tr>
<tr>
<td><strong>FIG4</strong></td>
<td>Presumably affects signaling pathways</td>
</tr>
<tr>
<td><strong>CHMP2B</strong></td>
<td>Involved in endosome invagination</td>
</tr>
<tr>
<td><strong>SETX</strong></td>
<td>Probably a DNA helicase</td>
</tr>
<tr>
<td><strong>VCP</strong></td>
<td>Cell survival, division, and DNA repair</td>
</tr>
<tr>
<td><strong>UBQLN2</strong></td>
<td>Ubiquitin-like protein involved in protein degradation</td>
</tr>
<tr>
<td><strong>C9ORF72</strong></td>
<td>Unknown; hexanucleotide repeat expansion causes disease</td>
</tr>
<tr>
<td><strong>ATXN2</strong></td>
<td>Causative of SCA-2 when PolyQ repeats are &gt;34; Risk factor for ALS if &gt;23 and &lt;34</td>
</tr>
</tbody>
</table>
C9ORF72
The Most Common FALS Gene?

- 2006-10: 7 papers identified locus of interest in ALS, FTD and ALS-FTD on Chromosome 9
- 2011: 2 papers show GGGGCC hexanucleotide repeat expansion in C9ORF72 on Chromosome 9
  - In Finland, 46% of FALS and 21% of SALS; 38% of FALS outside Finland
  - In the US (Mayo), 21% of FALS and 4% of pure SALS

What’s new in risk factors

• Various factors have been reported – none confirmed
  – Smoking
  – Pesticide exposure
  – Cyanobacteria
  – Head trauma
    • Italian soccer players
    • War Veterans
  – Low BMI

What’s new in ALS pathogenesis

Excitatory aminoacids/ neurotransmitters
Inflammation/ oxidative stress
Neurofilament/ impaired axonal transport
Growth factors/ cytokines
Mitochondrial damage
Protein aggregation/ misfolding
What’s new in preclinical models

SOD1 G93A Transgenic Mouse

✓ It remains the most predictable and well-studied preclinical model.
✓ Successes in this model have not yet translated into human successes.

New Directions

- New transgenic animal models based on novel mutations
- Induced pluripotent stem cells and iPS-derived motor neurons may be useful disease models

Induced-Pluripotent Stem Cells (iPSC)

Skin Biopsy

↓

Fibroblast

↓

iPSC

↓

Motor Neuron

Picture: 2002 - PNAS - Howland et al.
What’s new in drug discovery

- Riluzole: only FDA-approved disease modifying therapy
  - RCT: Increases trach-free survival by 2-3 months. (Class I)

- $800 - $1200 per month
  - Copay $2-300

- AE: Nausea, Asthenia, LFT increases

- Monitor LFT’s monthly for 3 months, then every 3 months

Number of ALS Treatment Trials Published Per Year

Year
Number of Trials
Trials with <100 Subjects
Trials with >100 Subjects

2011 – Clinical Investigation - Berry and Cudkowicz
Multiple drugs have been tested

**Anti glutamate:**  riluzole, gabapentin, topiramate, dextromethorphan, ONO-2506, memantine, talampanel, ceftriaxone

**Anti oxidants/ bioenergetics:**  creatine, vitamin E, acetylcysteine, CoQ, olexosome, tamoxifen, pioglitazone, dexpramipexole

**Growth factors:**  IGF-1, BDNF, CTNF, Xaliproden

**Anti-apoptotic:**  pentoxyfilline, TCH346

**Anti-inflammatory:**  celebrex, minocycline, numesulide, NP001

**Protein aggregation:**  lithium, arimocloclomol

Adapted from alsconsortium.org
Current Trials - Examples

• Creatine/Tamoxifen – Phase II trial. Oral drugs aimed at 1) improving cell energy metabolism and 2) changing hormonal response.

• Tiramsemtiv – Phase IIb trial. Troponin activator to improve muscle strength.

Upcoming Trials - Examples

• Mexiletine
• Nuedexta
• NogoA inhibitor
More Research

- Stem cells
- Diaphragm pacing
- Nutrition
- Exercise
- Biomarkers
- Antisense oligonucleotides

ALS research is an extremely active field. But what can we do for our patients while we are waiting for a cure?
Why rehabilitation matters

Rehabilitation is the process of helping a person to maximize function and quality of life. Therefore, rehabilitation matters to patients with ALS because it helps them reach their fullest potential despite the presence of a disability.

Rehabilitation concerns in ALS

- Symptom management
- Exercise
- Mobility
- Activities of daily living
- Speech
- Swallowing function
- Nutrition
- Breathing
- Psychosocial/ family support
- Quality of life
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**Why rehabilitation matters**

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- Breathing
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- Quality of life
ALS Care is Improving

- Multidisciplinary care improves QOL and survival
  (Traynor et al., 2003; Van den Berg et al., 2005)

What’s new in symptom management

- **Pseudobulbar Affect** - dextromethorphan/quinidine (Nuedexta); SSRIs and TCAs have small benefit

- **Drooling/Saliva Problems** — TCAs, glycopyrrholate, scopolamine, hyoscyamine, botulinum toxin, low-dose radiation

- **Pain** — TCAs, gabapentin/pregabalin, NSAIDs, opiates, non-pharmacological modalities

- **Depression** — SSRIs, SNRIs

- **Spasticity** — baclofen, tizanidine, dronabinol, medical marijuana?
What’s new in exercise

• **Studies in ALS mouse models**: 2 studies of moderate intensity aerobic exercise showed slowing of progression and 1 study of high intensity aerobic exercise resulted in decreased survival.
  
  (Kirkinezos et al, 2003; Veldink et al., 2003; Mahoney et al., 2004)

• **Studies in ALS patients**: 1 small trial of moderate intensity aerobic exercise and 1 small trial of moderate resistance training were safe and well tolerated. Positive trend in QOL scores.
  
  (Drory et al, 2002; Dal Bello-Haas et al., 2007)

→ Currently enrolling: A Trial of Endurance and Resistance Exercise in ALS
General exercise recommendations

More research is needed before ALS-specific exercise recommendations can be made.

1) **Stretching and range of motion** (standard of care)
   - Especially Shoulder, Gastroc/Soleus

2) **Aerobic Exercise**
   - No clear contraindications to moderate program, benefits similar to healthy, watch respiratory status
   - Choose activity with minimal risk of injury from falls, low impact
     - Walking, elliptical, recumbent (stationary) bicycle, minicycle, pool

3) **Strengthening** (proper supervision)
   - Goal - maximize strength of unaffected or minimally affected muscles to delay onset of impairment
   - Low weight, avoid eccentric contractions

*General principle*: careful monitoring of exercise response → if excessive muscle soreness or fatigue, reduce activity. Exercise-related fatigue should not interfere with ability to perform daily activities. Describing “moderate, sub-fatigue” to patients: “OK to feel tired when finished exercising, but if you rest for 30-60 minutes (recovery), you should feel like you could do it again”.
The role of PTs and OTs

Treatment focuses on preserving function, safety, and teaching.

Equipment is available for many aspects of daily living and to help with mobility. Be pro-active and think ahead. Consider loaners.

Therapists also play a major role in treating musculoskeletal dysfunction

Joint problems
  - Adhesive capsulitis of shoulder

Contractures
  - Gastroc/Soleus very common
  - Shoulder elevation
  - Hamstrings (especially those using wheelchair)

Pain
  - Cervical
  - Shoulder
  - Low back
ALS “stages” from a therapist’s perspective

**Early Stages** -
- Gait and balance evaluation and training
  - Assess need for assistive devices, AFOs, changes in shoewear
- Patient and caregiver education regarding activity tolerance, energy conservation techniques
- General stretching program
  - Shoulders, ankles
- Exercise program – modified for safety and tolerance

**Middle Stages** -
- Focus on safety and maintaining independence
  - Assess need for assistive devices and adaptive equipment
- Home modifications
- Community Resources

**Later Stages** -
- Mobility (wheelchair, bed mobility, transfers)
- Family/Caregiver training
- Help at home, available services
- ROM exercises to prevent/minimize contractures
- Monitor skin for pressure areas
- Positioning
- Monitor for signs/symptoms of DVT
What’s new in the management of respiratory failure

– Input from respiratory therapist and/or pulmonologist
– Monitor symptoms of hypoventilation (note: nocturnal hypoventilation may present as poor sleep, daytime fatigue/sleepiness, early AM headaches)
– Pneumococcal and influenza vaccination
– Periodic PFTs
– BiPAP/NIV: evidence suggests NIV prolongs survival
  • Insurance typically pays if FVC <50% or MIP <60 or nocturnal desaturations are identified
  • Early implementation may be beneficial – uncertain
– Cough assist and suction machines
– Diaphragmatic pacer?
– Tracheostomy
What’s new: focus on nutrition

• Most ALS patients are deficient in energy intake
  – Consume 84% RDA for calories (Kasarskis, 1996)

• Causes of negative energy balance
  • Bulbar dysfunction and dysphagia
  • Arm weakness and inability to feed self
  • Too much time required
  • Depression
  • Possible hypermetabolism
Importance of Maintaining Nutrition

- Malnourished patients have 7.7 fold increased risk of death (BMI < 18.5)

Desport et al, Neurology, 1999

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A decrease in body mass index is associated with faster progression of motor symptoms and shorter survival in ALS

**Table II. Comparison (ANOVA) of survival and the rate of motor disease progression between different BMI change groups.**

<table>
<thead>
<tr>
<th>BMI change</th>
<th>Survival (years)</th>
<th>Rate of motor disease progression (AALSS/month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI loss &gt;1 (n=131)</td>
<td>4.04±1.90</td>
<td>3.27±2.36</td>
</tr>
<tr>
<td>BMI stable (n=88)</td>
<td>5.41±3.53</td>
<td>2.16±2.11</td>
</tr>
<tr>
<td>BMI gain &gt;1 (n=57)</td>
<td>4.89±3.21</td>
<td>1.88±2.00</td>
</tr>
</tbody>
</table>

F        p-value
---
4.24     0.02
10.6     0.001
BODY MASS INDEX, NOT DYSLIPIDEMIA, IS AN INDEPENDENT PREDICTOR OF SURVIVAL IN AMYOTROPHIC LATERAL SCLEROSIS

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1 Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, Massachusetts, USA

Kaplan-Meier Curves: survival probability in ALS patients with different BMI/Lipid profile

U-shaped correlation between % mortality & BMI class. Least % mortality for BMI group 30-35

Kaplan-Meier Curves: survival probability in ALS patients with different BMI/Lipid profile
Dysphagia management and nutritional supplementation

- Compensatory strategies
  - double swallow
  - chin tuck
  - head turning
- Dietary modification
  - thicken liquids
  - soft, moist solids easiest
  - modify temperature, texture
- High calorie supplements
- PEG - supplemental or complete nutritional support
Clinical indications for PEG/ RIG

• Aspiration pneumonia
• Loss of > 10% body weight
• Quality of life impaired by time required to maintain nutrition
• FVC approaching 50% of predicted - morbidity and mortality increase with lower FVC (AAN Practice Parameter, 2009)
• With low FVC, consider RIG (radiologically inserted gastrostomy) (Thornton et al., Radiology, 2002)

• Nutritional support by PEG might prolong survival (AAN Practice Parameter, 2009)
Targeting nutrition as a treatment tool?

**Trial of High fat/High Calorie Diet versus Optimal Nutrition in Amyotrophic Lateral Sclerosis**

<table>
<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
</tr>
</thead>
</table>
| Experimental: High fat/high calorie High fat/high calorie diet: Oxepa | Dietary Supplement: Oxepa  
  Oxepa: Tube feed containing 1.5 calories/ml of which 55% calories are from fat, including eicosapentaenoic acid and gamma-linolenic acid. Subjects will receive 1.25 times their daily caloric requirements based on their measured resting energy expenditure. Subjects will receive 4 months of tube feeds and be followed for an additional 1 month to measure adverse events and tolerability. |
| Active Comparator: High calorie High calorie diet: Jevity 1.5   | Dietary Supplement: Jevity 1.5  
  Jevity 1.5: Tube feed containing 1.5 calories/ml of which 29.4% are from fat. Subjects will receive 1.25 times their daily caloric requirements based on their measured resting energy expenditure. Subjects will receive 4 months of tube feeds and be followed for an additional 1 month to measure adverse events and tolerability.                                             |
| Placebo Comparator: Control Control diet: Jevity 1.0           | Dietary Supplement: Jevity 1.0  
  Jevity 1.0: Control tube feed. Subjects will receive 1.0 times their daily caloric requirements based on their measured resting energy expenditure. Subjects will receive 4 months of tube feeds and be followed for an additional 1 month to measure adverse events and tolerability.     |
Conclusions

1) ALS research is moving at a fast pace.

2) Advances in our understanding of ALS genetics and pathophysiology have not translated into an effective cure yet.

3) Many drugs and treatment strategies are currently being investigated.

4) While ALS is not curable, many disease manifestations are treatable, with the goal of maximizing function and quality of life despite the presence of progressive disability.

5) Rehabilitation specialists play a major role in multidisciplinary ALS treatment.