ALS Symptom Management

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Overview

- Historic timeline
- Epidemiology and ALS signs and symptoms
- Vignettes about ALS symptoms and their management
- Future direction
A Historic overview

- Charcot (1825–1893) is generally credited for first describing ALS.
  During his Tuesday lectures beginning in the late 1860s and culminating in a publication in 1874.
- Later work by Gowers and then by Charcot refined the description into a complete clinical spectrum with specific examination features.
- There has been little change in the clinical understanding of the phenotypic disease description for nearly 150 years.
ALS timeline

- 1830 Bell reports a case of a progressive paralysis of limbs and tongue with preservation of sensation
- 1850 Aran names the condition of progressive muscular atrophy
- 1865 Charcot describes progressive lateral sclerosis (PLS)
- 1870 Charcot describes progressive bulbar palsy
- 1874 Charcot names ALS (de la sclérose laterále amyotrophique)
- 1939 Lou Gehrig’s diagnosis and first clinical trial with vitamin E
- 1941 Lou Gehrig dies of ALS
- 1943 Vitamin E injections are shown not to be effective to treat ALS
ALS timeline

- 1952 Hirano describes the guam ALS/Dementia/Parkinson Complex
- 1969 Lambert – Diagnostic criteria using EMG
- 1980 report of nerve growth factor published
- 1984 Use of percutaneous endoscopic gastrostomy (PEG) reported in ALS.
- 1987 Glutamate metabolism abnormality theory reported in ALS.
- 1993 SOD-1 gene identified.
- 1994 El Escorial criteria for ALS clinical trial inclusion published.
- 1995 first positive clinical trial for ALS. Riluzole has an effect on survival, prolonging life by 3 months.
- 2011 C9orf72 gene discovered, a repeat expansion GGGGCC
ALS Demographics

- Incidence US: 2-3 per 100,000
- Prevalence US: 35,000
- Male slightly > Female
- Peak age onset: 6th decade, range <20 to >80
- 90-95% sporadic
- 5-10% familial. Of these
  - 30-50% C9orf72 hexanucleotide expansion GGGGCC
  - 15-20% SOD-1
  - 5% TDP-43, VCP, FUS, Ubiquitin mutations
Other than Riluzole, how do we treat these symptoms?

- Spasticity
- Pseudobulbar Affect
- Fasciculations
- Cramps
- Dysarthria
- Dysphagia
- Oral Secretions
- Respiratory Symptoms
- Arm weakness
- Leg weakness
Case 1

- 70 y/o F with 2 year history of bulbar-onset ALS presents with excessive drooling.
- Chokes constantly on saliva and uses a PEG for the majority of her nutrition.
- Unable to tolerate prior trial of amitriptyline, scopolamine, and hyosamine due to side effects.
- FVC = 60%
Case 1

What would you do next?

A. Refer for botulinum toxin type B injections into salivary glands.
B. Write prescription for glycopyrrolate (Robinul).
C. Refer for botulinum toxin type A injections into the salivary glands.
D. Order suction machine and refer to hospice.
E. Refer for low dose radiation therapy to salivary glands.
Conclusions:
- In patients with medically refractory sialorrhea, botulinum toxin B (BTxB) injections into the parotid and submandibular glands are probably effective (one Class I study).
- There are inadequate data on the effectiveness of botulinum toxin A (BTxA) (one Class III study).
- Low-dose irradiation is possibly effective for sialorrhea (two Class III studies).

Recommendations:
- In patients with ALS who have medically refractory sialorrhea, BTxB should be considered (Level B) and low-dose radiation therapy to the salivary glands may be considered (Level C).
Sialorrhea Treatments

- Amitriptyline (Elavil) 25-100 mg qhs
- Nortriptyline (Pamelor) 20-100 mg qhs
- Diphenhydramine (Benadryl) 25-50 mg TID
- Glycopyrrolate (Robinul) 1-2 mg q 4h
- Hyoscyamine sulfate (Levsin) 0.125-0.25 mg q 4-6h
- Transdermal scopolamine 0.5mg behind ear q 3 days
- Atropine sublingual drops (ophthalmic drops) 1-2 drops SL q 4-6h
Case 2

- 67 y/o WM with a history of ALS presents with frequent episodes of uncontrolled crying.
- These are out of proportion to the triggers and are a source of embarrassment to the patient.
Case 2

- What would you recommend?
  A. Ativan 0.5mg TID
  B. Amitriptyline 50mg qhs (Elavil)
  C. Dextromethorphan/quinidine (Nuedexta)
  D. Paroxetine 10mg qam (Paxil)
AAN Conclusion/Recommendation: Treatment of PBA

Conclusion:
- The combination of dextromethorphan/quinidine (DM/Q) is probably effective for pseudobulbar affect in ALS (one Class I study).

Recommendation:
- DM/Q should be considered for symptoms of pseudobulbar affect in patients with ALS (Level B).

STAR Pivotal Trial Study Design

- **PBA**
  - ALS (n = 197)
  - MS (n = 129)

- **64 study sites**
  - North America (47 sites)
  - Latin America (17 sites)

**Study Design**

**Randomized**

- **N = 326**

**Double-Blind Phase**

- **12 weeks**
- **N = 110**
  - DM/Q 30/10 BID

**Open-Label Phase**

- **12 weeks**
- **N = 207**
  - DM/Q 20/10 BID
  - Placebo BID

PBA STAR Trial Results

Mean Weekly Episode Decrease

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
<th>Week 8</th>
<th>Week 9</th>
<th>Week 10</th>
<th>Week 11</th>
<th>Week 12</th>
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<tbody>
<tr>
<td>0</td>
<td>-20</td>
<td>-40</td>
<td>-60</td>
<td>-80</td>
<td>-100</td>
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</table>

**Placebo**

**DM/Q**

*P < .05

STAR Trial. Avanir Pharmaceuticals, Aliso Viejo, CA; 2009.
# PBA STAR Trial Adverse Reactions

Adverse Drug Reactions With an Incidence of $\geq 3\%$ of Subjects and $\geq 2\times$ Placebo in NUEDEXTA-Treated Subjects

<table>
<thead>
<tr>
<th></th>
<th>Adverse Reaction</th>
<th>NUEDEXTA n = 107</th>
<th>Placebo n = 109</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>13%</td>
<td>6%</td>
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</tr>
<tr>
<td>Dizziness</td>
<td>10%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>5%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>5%</td>
<td>1%</td>
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</table>

PBA DM/Q (Nuedexta) Dosing

- One capsule daily by mouth for initial 7 days of therapy
- Then 1 cap twice daily.
- Other meds that may help with PBA, although no controlled trial has been conducted include:
  - Amitriptyline
  - SSRIs
Case 3

- 56 y/o F with bulbar ALS
- Has severe difficulty swallowing
- 20 pound weight loss over the past 3 mo
- FVC = 20%
- Refused PEG in the past and prior neurologist said her FVC was now too low.
Case 3

- What would you recommend?

A. Refer to Speech Pathologist for education on techniques to minimize risk of aspiration since PEG is too dangerous.
B. Refer patient to hospice for supportive care.
C. Proceed with PEG placement using NIV support during procedure.
E. Refer to Radiology for a RIG tube under local anesthesia.
Conclusion:
- There are no studies of ALS-specific indications for the timing of PEG insertion, although patients with dysphagia will possibly be exposed to less risk if PEG is placed when forced vital capacity (FVC) is above 50% of predicted (one Class III study).

Recommendation:
- There are insufficient data to support or refute specific timing of PEG insertion in patients with ALS (Level U).

Dysphagia

- Indications for PEG Placement:
  - Significant weight loss
  - Frequent choking/swallowing difficulty
  - Prolonged meal times
  - FVC < 50%
  - Aspiration pneumonia
PEG Placement in “High Risk” Patients

- Uncontrolled, retrospective experience of 33 patients with erect or supine FVC <50% underwent PEG placement with NIV support.
- All PEGs were successfully placed.
- Mean survival was 211 days with most patients (67%) surviving more than 180 days.
- FVC at time of PEG did not predict survival.

Gregory et al., Neurol 2002;58:485-487.
What is the efficacy of PEG on survival?

Studies using appropriate controls or multivariate analysis demonstrated that PEG is probably effective in prolonging survival in ALS, although insufficient data exist to quantitate the survival advantage (2 Class II studies).

Del Piano et al 1999, Desport JC et al 2005
Case 4

- 62 y/o male with ALS complains of restless sleep.
- Arises 4-5 times a night to urinate.
- Severely fatigued during the day and having trouble concentrating.
- FVC = 80%
- No improvement with Triazolam.
Case 4

What would you recommend?

A. Refer for sleep study since FVC is normal.
B. Initiate NIV with no further workup.
C. Refer for evaluation of possible BPH.
D. Check supine FVC and/or MIP.
E. Prescribe Zolpidem (Ambien).
AAN Recommendations: PFTs

Recommendations:

- Nocturnal oximetry may be considered to detect hypoventilation (regardless of the FVC) (Level C).
- Supine FVC and MIP may be considered useful in routine respiratory monitoring, in addition to the erect FVC (Level C).
- Sniff nasal pressure (SNP) may be considered to detect hypercapnia and nocturnal hypoxemia (Level C).
AAN Conclusions/Recommendation: Impact of NIV on Survival

Conclusions:

- NIV is probably effective in prolonging survival (one Class I, three Class III studies).
- NIV is probably effective in slowing the rate of FVC decline (one Class I, one Class III study).

Recommendation:

- NIV should be considered to treat respiratory insufficiency in ALS, both to lengthen survival and to slow the rate of FVC decline (Level B).

Respiratory Insufficiency
Early Symptoms

- Dyspnea on exertion
- Supine dyspnea
- Marked fatigue
- Excessive daytime somnolence
- Frequent nocturnal arousals
- Vivid dreams
- Morning headaches
Respiratory Insufficiency
Late symptoms

- Dyspnea at rest
- Tachypnea
- Fatigue while talking or eating
- Weak cough
- Inability to clear secretions
- Drowsiness
Respiratory Insufficiency
Medicare Criteria for Implementing NIV

- FVC < 50% of predicted or
- MIP < -60 cm H2O or
- PCO2 > 45mm Hg or
- Nocturnal SpO2 < 88% for 5 minutes
Respiratory Insufficiency
Treatment of Hypoventilation

- Order Bi-PAP ST
- Start with IPAP of 8 cm H20 and EPAP of 3-4 cm H20.
  Initially use at night only.
- Titrate IPAP by 2-3 cm H20 increments based on symptoms and tolerability.
Respiratory Insufficiency
Treatment of Hypoventilation

- Prescribe at least 2 different interfaces. (nasal mask, nasal pillows, full-face/oronasal mask)

- Perform nocturnal oximetry studies every 3 months to avoid desats < 90%.
Respiratory Insufficiency Bi-level with AVAPS

- Average Volume Assured Pressure Support (AVAPS)
- Provides a fixed tidal volume.
- Automatically adjusts the inspiratory pressure.
How to Set Up AVAPS

- Choose a mode: ST or PC
- Set EPAP 4-5 cm
- Set IPAP min at target and IPAP max
- Choose a target tidal volume
  - For the average patient, set at 8cc/kg IBW
  - For those with bulbar disease, set at 6cc/kg IBW
Respiratory Insufficiency
Respiratory symptom management

- Loosen phlegm
  - Nebulized acetylcysteine or saline
  - Guaifenesin
  - Hydration
  - Alkalol mucus wash

- Treat nasal congestion
  - Nasal steroid inhaler
  - Heated humidifier
  - Antihistamine
  - Pseudoephedrine

- Provide sedation
  - Zolpidem 5-10mg qhs
  - Amitriptyline 25-50mg qhs
Respiratory Insufficiency Exacerbation Prevention

- Pneumococcal, and influenza vaccines
- Swallowing evaluation
- PEG placement before FVC < 50%
- Maintain adequate hydration
- Control secretions
Case 5

- 80 y/o female with bulbar onset ALS presents with frequent cough for the past 2 months. Cough worsens when lying supine.
- Dependent on PEG for majority of nutrition.
- FVC = 20%.
- Unable to clear airway secretions despite frequent use of suction machine.
Case 5

- What would you recommend?

A. Antibiotic therapy for empiric treatment of aspiration pneumonia
B. Prescription for cough medication
C. Prescribe Mechanical Insufflation/Exsufflation device (MIE)
D. Prescribe High Frequency Chest Wall Oscillation device (HFCWO)
E. Hospice referral
AAN Recommendations: Airway Secretion Clearance

Recommendations:

- MIE (cough assist) may be considered to clear secretions in patients with ALS who have reduced peak cough flow, particularly during an acute chest infection (Level C).

- There are insufficient data to support or refute HFCWO for clearing airway secretions in patients with ALS (Level U).
Secretion Management

- Use expiratory aids when FVC<50% or PECF < 160 l/min:
  - Mechanical insufflator/exsufflator (MIE)
    - Cough Assist
  - High Frequency Chest Wall Oscillation (HFCWO)
    - (The Vest, MedPulse Smart Vest)
Secretion Management
Mechanical Insufflation-Exsufflation

- Assists patients to clear retained secretions non-invasively.
- Applies a positive pressure to the airway (insufflation) followed by a rapid shift to a negative pressure (exsufflation) simulating a cough.
- May be applied by mask or mouthpiece or invasively via endotracheal or tracheostomy tube.
Secretion Management
Typical MI-E Settings

- Pressures (positive and negative)
  - Start low, 10 to 15 cm H₂O
  - Get patient acclimated to device
  - Increase pressures as tolerated, ideally 35 to 45 cm H₂O

- Times (Inhale, Exhale and Pause)
  - Adults: 2 to 3 sec
Secretion Management
HFCWO

- Air generator rapidly inflates and deflates the vest, gently compressing the chest wall up to 25 times per second.
- Thins secretions
- Mucus is dislodged from the bronchial walls and moves it to more central airways.
- Once mucus has moved to more central airways it is removed by coughing or suctioning.
Secretion Management
HFCWO

- 10-20 minutes twice a day or more frequently if respiratory infection
- Use with NIV when FVC < 30%
- May require concomitant use of a suction machine or Cough Assist
- Frequency settings: 10-14 Hz (5-20 Hz)
- Pressure settings: 30-40 cm (10-100 cm)
Mexiletine trial

- 60 patients
- 12 week study
- 300mg/d or 900mg/d or placebo
- Safe but 30% at 900mg discontinued
- No diff ALSFRS-R
- Significant decrease in cramp frequency and intensity

## Symptomatic Rx for ALS

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Rx</th>
</tr>
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<tbody>
<tr>
<td>Sialorrhea</td>
<td>Anti-cholinergics Botulinum toxin</td>
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<tr>
<td>Pseudobulbar affect</td>
<td>Dextromethorphan/quinidine (NuedexTa)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>PEG</td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
<td>NIV</td>
</tr>
<tr>
<td>Cramps</td>
<td>Mexilitene</td>
</tr>
<tr>
<td>Spasticity</td>
<td>Botox or baclofen</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Modafinil</td>
</tr>
</tbody>
</table>

AAN ALS Practice Parameters. Miller et al, Neurology 2009;1218 and 1227. Miller et al Neurology 2013;2136
Conclusion

- We have improved the clinical management of ALS to help patients and families:
  - Multidisciplinary clinics
  - Symptomatic management
- Our goal is to provide hope to patients and families and search for better treatments
Future Directions

- We continue to have many questions unanswered (timing of NIV, which NIV device is better, PEG and survival, siahlorrhea meds, cramp meds)
- We need more clinical trials in ALS for both disease modifying agents and symptom management.
- New opportunities for comparative effectiveness and real time clinical trials
Thank You!