ALS:
Evolution of disease conception and
the need for multidisciplinary care

Dan Larriviere MD, JD, FAAN
Director, Ochsner ALS Clinic
Disclosures

- I have no conflicts of interest to disclose
- I will mention off-label use of medications
ALS

- Rapidly progressive and fatal disease involving upper and lower motor neurones
- M:F = 1.5:1
- 20-30K pALS in the US with 5,000 diagnosed annually
Phenotype range

**Onset type**
- Bulbar (1860)
- Upper limb
- Lower limb
- Truncal
- Ventilatory

**Phenotype**
- Progressive muscular atrophy (1849)
- LMN dominant ALS
- ALS (1874)
- UMN dominant ALS
- PLS (1875)
Phenotypic range

- Most patients die within 2-5 yrs of symptom onset
  - Range: 1-10 yrs

- Cognitive dysfunction seen in 20-50%, with 8-15% meeting criteria for dementia

- Clinical findings include evidence for extrapyramidal and cerebellar dysfunction

Symptoms

- Hypoventilation
  - NIV
- Spasticity
  - Tizanidine
  - Baclofen
- Dysphagia
  - PEG
  - Change food consistency
- Depression
  - TCS
  - SSRI

- Sialorrhea
  - Glycopyrrolate
  - Tricyclic antidepressants (TCA)
  - Atropine
  - Scopolamine patch
  - Salivary gland radiation

- Pseudobulbar affect
  - Dextromethorphan hydrobromide and quinidine sulfate
  - TCA
  - SSRI

- Mobility issues
  - myriad
Symptoms

• Behavioral
  o Apathy
  o Altered social and interpersonal conduct
  o Emotional blunting
  o Loss of insight

• Language
  o Expressive difficulty – paraphasic errors, word finding difficulties
  o Receptive language difficulty

• Poor executive functioning
  o Planning, organizing, shifting sets
Etiology

- Sporadic

- Genetic
  - SOD1 discovered ~ 1993
  - Possible gain of function mutation -> oxidative damage, excitotoxicity, impairment of mitochondrial function
<table>
<thead>
<tr>
<th>Locus</th>
<th>Gene</th>
<th>Gene name</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS 1</td>
<td>SOD1</td>
<td>Cu/Zn superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))</td>
</tr>
<tr>
<td>ALS 2</td>
<td>ALS2</td>
<td>amyotrophic lateral sclerosis 2 (juvenile) homolog (human). Alsin</td>
</tr>
<tr>
<td>ALS 3</td>
<td>ALS3</td>
<td>Unknown</td>
</tr>
<tr>
<td>ALS 4</td>
<td>SETX</td>
<td>Senataxin</td>
</tr>
<tr>
<td>ALS 5</td>
<td>SPG11</td>
<td>spastic paraplegia 11 (autosomal recessive)</td>
</tr>
<tr>
<td>ALS 6</td>
<td>FUS</td>
<td>fusion (involved in t(12;18) in malignant liposarcoma)</td>
</tr>
<tr>
<td>ALS 7</td>
<td>ALS7</td>
<td>Unknown</td>
</tr>
<tr>
<td>ALS 8</td>
<td>VAPB</td>
<td>Vesicle-associated membrane protein-associated protein B</td>
</tr>
<tr>
<td>ALS 9</td>
<td>ANG</td>
<td>Angiogenin</td>
</tr>
<tr>
<td>ALS 10</td>
<td>TARDPB</td>
<td>TAR DNA binding protein</td>
</tr>
<tr>
<td>ALS 11</td>
<td>FIG4</td>
<td>FIG4 homolog, SAC1 lipid phosphatase domain containing (S. cerevisiae)</td>
</tr>
<tr>
<td>ALS 12</td>
<td>OPTN</td>
<td>optineurin</td>
</tr>
<tr>
<td>ALS 13</td>
<td>ATXN2</td>
<td>ataxin 2</td>
</tr>
<tr>
<td>ALS 14</td>
<td>VCP</td>
<td>valosin-containing protein</td>
</tr>
<tr>
<td>ALS 15</td>
<td>UBQLN2</td>
<td>ubiquinol 2</td>
</tr>
<tr>
<td>ALS 16</td>
<td>SIGMAR1</td>
<td>sigma non-opioid intracellular receptor 1</td>
</tr>
<tr>
<td>ALS 17</td>
<td>CHMP2B</td>
<td>chromatin modifying protein 2B</td>
</tr>
<tr>
<td>ALS 18</td>
<td>PFN1</td>
<td>profilin 1</td>
</tr>
<tr>
<td>ALS 19</td>
<td>ERBB4</td>
<td>v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 4</td>
</tr>
<tr>
<td>ALS 20</td>
<td>HNRNPA1</td>
<td>heterogeneous nuclear ribonucleoprotein A1</td>
</tr>
<tr>
<td>ALS 21</td>
<td>MATR3</td>
<td>matrin 3</td>
</tr>
<tr>
<td>ALS</td>
<td>CHCHD10</td>
<td>coiled-coil-helix-coiled-coil-helix domain containing 10</td>
</tr>
<tr>
<td>FTD2</td>
<td></td>
<td>chromosome 9 open reading frame 72</td>
</tr>
<tr>
<td>FTD1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALS</td>
<td>UNC13A</td>
<td>unc-13 homolog A (C. elegans)</td>
</tr>
<tr>
<td>ALS</td>
<td>DAO</td>
<td>D-amino-acid oxidase</td>
</tr>
<tr>
<td>ALS</td>
<td>DCTN1</td>
<td>Dynactin</td>
</tr>
<tr>
<td>ALS</td>
<td>NEFH</td>
<td>neurofilament, heavy polypeptide 200kDa, heavy chain</td>
</tr>
<tr>
<td>ALS</td>
<td>PRPH</td>
<td>peripherin</td>
</tr>
<tr>
<td>ALS</td>
<td>SQSTM1</td>
<td>sequestosome 1</td>
</tr>
<tr>
<td>ALS</td>
<td>TAF15</td>
<td>TAF15 RNA polymerase II, TATA box binding protein (TBP)-associated factor,</td>
</tr>
<tr>
<td>ALS</td>
<td>SPAST</td>
<td>Spastin</td>
</tr>
<tr>
<td>ALS</td>
<td>ELP3</td>
<td>elongation protein 3 homolog (S. cerevisiae)</td>
</tr>
<tr>
<td>ALS</td>
<td>LMNB1</td>
<td>lamin B1</td>
</tr>
</tbody>
</table>
Etiology

- Environmental + genetic
  - Disease manifests later in life, even in those with genetic mutation
  - Same gene can result in different diseases
  - Not all carriers develop disease
Current concept

• ALS is a multisystem disease with variable phenotypic expression
Heterogenous pathophysiologic processes

- **Stress granules**
  - FUS
  - TDP-43
  - VCP

- **Autophagy**
  - OPTN
  - VCP
  - FIG4

- **Protein aggregation**
  - SOD1
  - C9ORF72

- **Prion-like**
  - TDP-43
  - FUS
  - TAF15
  - EWSR1
  - hnRNPs

- **RNA Processing**
  - TDP-43
  - FUS
  - C9ORF72

- **Proteosome**
  - SQSTM1
  - UBQLN2

- **Axonal transport**
  - TDP-43
  -PFN1
# ALS Trials

<table>
<thead>
<tr>
<th>Neurotrophic</th>
<th>Excitotoxicity</th>
<th>Inflam</th>
<th>Oxidative</th>
<th>Viral</th>
<th>Mitoch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone</td>
<td>Ceftriaxone</td>
<td>Celecoxib</td>
<td>Vitamin E</td>
<td>Amantadine</td>
<td>Lithium</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Dextromethorphan</td>
<td>Cytoxan</td>
<td>Selegiline</td>
<td>Guanidine</td>
<td>Co-Q 10</td>
</tr>
<tr>
<td>Memantine</td>
<td>IVIg</td>
<td>Glutathione</td>
<td>Indinavir</td>
<td>Creatine</td>
<td></td>
</tr>
</tbody>
</table>
# ALS Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>Survival, function</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Strength – upper limb</td>
</tr>
<tr>
<td>Selegiline</td>
<td>Function</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Strength – upper limb</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Strength – upper limb</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Function</td>
</tr>
<tr>
<td>Pentoxyfilline</td>
<td>Survival</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Function</td>
</tr>
<tr>
<td>Lithium</td>
<td>Survival</td>
</tr>
<tr>
<td>Creatine</td>
<td>Strength – upper limb; survival</td>
</tr>
<tr>
<td>Dexpramipexole</td>
<td>Survival + function</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Strength</td>
</tr>
<tr>
<td>BDNF</td>
<td>FVC, survival</td>
</tr>
<tr>
<td>Riluzole</td>
<td>Survival</td>
</tr>
</tbody>
</table>
Old model

Motor neuron function

Disease onset

Diagnosis

Time
Motor neuron function

Etiology
Pathophysiologic processes

Outcome measures
Phenotypic characterization
Therapeutics

Disease onset
Symptom onset
Pre-symptomatic phase
Diagnosis

Time
Motor neuron function

- Early intervention
- Research participation
- Biomarkers
- Etiology
- Pathophysiologic processes
- Outcome measures
  - Phenotypic characterization
  - Therapeutics

Disease onset → Symptom onset → Diagnosis

Pre-symptomatic phase

Time
~ 170 patients being served, but prevalence rates would suggest double that number in the state.
~ 75 patients being served, but prevalence rates would about 30% more in the state

LA-MS Chapter ALSA
Goals

• Develop an ALS Center to provide the highest quality, comprehensive, and supportive care for patients and caregivers

• Include all necessary and appropriate medical personnel, clinic space, equipment, access to clinical trials, and support services that our patients need.
Care Model

• Multidisciplinary clinic and care plans
  
  o Quality measure, endorsed by the American Academy of Neurology\(^1\)
  
  o Has been shown to improve QOL and extend life\(^2\)


## Resources

### In Clinic
- ALS Neurologist
- APC
- RN
- Pulmonary critical care
- PM&R
- ALSA Chapter Liaison
- LMSW
- Registered dietician
- OT/PT/Speech
- DME rep

### Available
- Gastroenterologist
- Internal medicine
- Infectious disease
- Psych/neuropsych
- Geneticist
- Genetics counselor
- Radiologist
- Attorney for EOL planning
Clinic
Large rooms, easy access, comfortable for pALS and families

Building
Ease of access, valet, dedicated entrance
Markers of Success

• Ease of access
  o Maria Arcuri, Clinic Coordinator: 504.842.0113
  o Dr Dan Larriviere, Director: 434.806.9823

• Patient and caregiver focused
  o Short wait times for clinic appointments
  o Same day/next day resolution of patient requests

• Efficient communication with referring providers
Markers of Success

• Offer clinical trials/Research/advance knowledge
  o NEALS (www.alsconsortium.org/)
  o National registry
  o ALS Untangled (http://www.alsuntangled.com/)

• Advocacy
  o National ALS Advocacy Day and public policy conference
    • http://www.als.org/advocacy/
  o Louisiana State Advocacy Day
Front row: Deborah Ross, RD; Sadie Chotto, PA; Sarah Stollberg, PT; Esther Hendler, OT; Maria Arcuri, Coordinator
Back row: Dan Larriviere, MD, JD; Jayne Stillman, LMSW; Jena Hampton, RN; Alicia Cantrell, MCD, CCC-SLP; Mahmoud Sarmini, MD; Letty Barras, RRT; Steve Kantrow, MD
Thank you

• ALS Clinic team
• Neuroscience Team
  o Chair, Rich Zweifler, MD
  o VP: Emily Wiltenmuth
  o Mgr: Andrew Hancher
• Primary Care
  o Chair, Pedro Cazabon, MD

• ALSA, LA-MS Chapter
  o Kelly Viator, Executive Director
  o Chrissie Trosclair, CSC
New Copper Therapy Shows Initial Promise in ALS Mice

www.als.org/newsarchive/new-copper-therapy.html  AL's Association  Jan 29, 2016 - The paper, titled "Copper delivery to the CNS by CuATSM effectively treats ... while the treatment delivered major benefit to the mice in the ...

Copper to the Rescue in ALS Mice | ALZFORUM

www.alzforum.org/news/research-news/copper-rescue-als-mice  Feb 5, 2016 - As reported in the January 27 Neurobiology of Disease online, the researchers treated the mice with CuATSM, a reddish copper chelator that...

New therapy halts progression of Lou Gehrig's disease in mice

oregonstate.edu/news/new-therapy-halts-progressio...  Oregon State University  Jan 29, 2016 - In decades of work, no treatment has been discovered for ALS that can...

to this treatment, which consists of a compound called copper-ATSM.

Story: Copper Compound (CuATSM) Shows Promise in ALS ...

www.als.net/new/copper-compoun...  ALS Therapy Development Foundation  Jan 29, 2016 - Copper Compound (CuATSM) Shows Promise in ALS Lab Studies ... know about the potential of CuATSM as a potential treatment for ALS.

Researchers: Copper Treatments Stopped ALS Progression ...

https://mobiilitymort.com/articles/research-copper-treatment-als.aspx  Results of the study were published in Neurobiology of Disease. The study involved using a compound called Copper-ATSM "that helps deliver copper specifically to cells with damaged mitochondria, and reaches the spinal cord, where it's needed to treat ALS," a Jan. 26 news announcement said.

ALS: 'Shocking success!' Copper+ATSM mice trials show ...

www.ibtimes.co.uk/Science/Health...International Business Times  Jan 29, 2016 - A new treatment for ALS could be the way, as researchers say they have stopped the progression of the disease in mice for two years.

Copper compound could form basis for first Lou Gehrig's ...

www.medicalnewstoday.com/articles/276926.php  Medical News Today  ★★★★★ Rating: 3.9 7 votes  Jun 13, 2014 - The team explains that ALS has been traced to mutations in copper, zinc ... the Food and Drug Administration approved the first drug treatment ...

Lou Gehrig's Disease: Promising New Drug Therapy ...

www.medicaldaily.com/lou-gehrigs-disease-therapy-lifespan-2-years-37... Jan 31, 2016 - Copper compound shown to improve ALS lifespan by up to two ... at home and that treatment also shows the potential of ALS drug study.