ALS and Frontotemporal Dementia

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Clinical Features

• Upper motor neuron findings
  • Slow speech
  • Brisk gag and jaw jerk, brisk limb reflexes
  • Spasticity
  • Hoffman’s or Babinski signs

• Lower motor neuron findings
  • Atrophy
  • Fasciculations
  • weakness
ALS is not just a disease of the motor system

- Parkinsonism
- UMN degeneration
- Sensory abnormalities
- Cerebellar degeneration
- LMN degeneration
- Ocular abnormalities
- Dementia
- Autonomic dysfunction
Over 100 years of cognitive abnormalities in ALS

- Raymond 1889
- Marie 1892
- Ziegler 1930
- Wechsler 1932
- Hudson 1981
- Caselli 1993
- Strong 1996
Case Study

- 52 year old right-handed woman onset 2001
- Progressive difficulty communicating
  - Slurred speech
  - Sentences grammatically incorrect
  - Words and sentences transposed
- Progressive behavioral changes
  - Withdrawn
  - Tactless
  - Preoccupied with locking doors and windows
- Emotional lability
Case study (continued)

- By 2002 swallowing difficulty started and arm weakness was noticed on examination.
- Behavior worsened with inability to adjust to new routines and anger outbursts.
- Word finding and naming difficulty became more obvious and verbal output decreased.
Examination

- Impaired comprehension and repetition
- Dysarthric, nasal speech
- Face, palate, and tongue weakness
- Brisk jaw jerk
- Fasciculations in left arm
- Normal tone
- Mild weakness right > left hands
- Brisk reflexes and upgoing toe on the right
<table>
<thead>
<tr>
<th>Test</th>
<th>Aug 2002</th>
<th>Jan 2003</th>
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<tbody>
<tr>
<td>MMSE</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>CVLT-10 min recall (9)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Rey – 10 min recall (17)</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Modified Trails</td>
<td>61” (14/14)</td>
<td>120” (5/14)</td>
</tr>
<tr>
<td>D words</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Designs</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Animals</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>BNT (15)</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Rey copy (17)</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Facial Recog (6)</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Calculations (5)</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
MRI (Aug 2002)
Mild cortical atrophy
Rostral > caudal
Spinal cord
Moderate atrophy of anterior roots
Neocortex (frontotemporal) & Entorhinal cortex
Mild superficial spongiosis, gliosis, and neuron loss
Spinal cord
Severe neuron loss throughout spinal cord

Thoracic SC
Cervical SC
Ubiquitin positive, tau/α-syn/neurofilament negative inclusions in neocortex and entorhinal cortex
Ubiquitin-positive inclusions in hypoglossal nucleus and anterior horn of spinal cord
Pathology of ALS-FTD

- Ubiquitin-positive, tau- and alpha-synuclein-negative inclusions in spinal cord and frontal and temporal lobes
- TDP-43 was recently discovered to be the major disease protein in both ALS and one form of FTLD
- The protein was recovered only from affected central nervous system regions, including hippocampus, neocortex, and spinal cord and represents the common pathologic substrate linking these neurodegenerative disorders.

What is Frontotemporal Lobar Dementia?

- FTLD
  - Selective degeneration and atrophy of frontal and anterior temporal lobes of brain
  - Presents with personality changes, language difficulty, or behavioral disturbance
  - Progressive, irreversible
  - Not a higher risk in pseudobulbar patients
  - Clear criteria established (Neary, 1998)
  - Clearly distinguished from Alzheimer’s disease
Major FTLD variants
Three prototypical presentations

Frontotemporal dementia (FTD)  
‘Frontal’
- Apathy, disinhibition
- Decreased speech output
- Disorganization
- Poor insight

Semantic Dementia (SD)  
‘Temporal’
- Loss of semantic knowledge
- Poor word comprehension
- Word finding problems
- Good insight

Progressive non-fluent aphasia (PA)  
Left perisylvian
- Non-fluent, effortful speech
- Agrammatism
- Good comprehension
Genetic overlap of ALS and FTLD

- Familial: 10% of ALS, 40% of FTLD
- Affected family members may have only ALS, only FTLD, or both in familial cases
- Suggests a relationship in the pathogenesis of these 2 disorders
ALS
FTLD
FTLD/ALS
ALS
FTLD
Possible FTLD
Evaluated by UCSF

B.M. 60
D.E. 32
L.E. 56
E.E. 54
C.L. 52

D.E. 32

L.E. 56
E.E. 54
C.L. 52
New Gene found for ALS-FTD

- Most common gene for ALS-FTD found in 2011 (hexanucleotide repeat)
- 12% of familial FTD and 23% of familial ALS
- 3% of sporadic FTD and 4% of sporadic ALS
ALS in FTLD

- 36 patients with sporadic FTLD and no known motor neuron disease
  - 14% definite ALS
  - 36% possible ALS
  - 14% fasciculations (1 pt = definite ALS after 1 yr)
  - 17% swallowing trouble
  - 5% other abnormalities

Methods for current study

- 107 patients with dementia and 11 healthy controls studied prospectively
- EMG of all four limbs and tongue muscle performed every 2 years
- Speech pathology assessment
- Neuroimaging and neuropsychological testing
- Autopsy program for all patients
ALS in other degenerative diseases

![Bar chart showing prevalence of ALS in various conditions]

- FTD
- PA
- SD
- AD
- CBD/PSP

Categories:
- Normal
- Possible ALS
- Definite ALS
Survival in FTD with co-morbid ALS

- Hodges et al 2003 8.2yrs FTD vs. 2.4yrs ALS-FTD
- Roberson et al 2005 10-12yrs FTD vs. 2yrs ALS-FTD
- Hu et al 2009 87 patients with ALS-FTD
  - 67 months survival if FTD symptoms first
  - 28 months survival if ALS symptoms first
  - 19 months if simultaneous ALS-FTD onset
FTLD is not new in ALS

- Old descriptions
  - Withdrawn due to depression
  - Stubborn
  - Seeking control in some area of life
  - Anger outbursts due to frustration of ALS
  - Denial
  - Language problems due to dysarthria

- FTLD behaviors
  - Apathetic
  - Dis-inhibited
  - Poor judgement
  - Easily frustrated
  - Quick to anger
  - Lack of insight
  - Language difficulty
    - Word finding
    - Spelling
    - Aphasia
FTLD in ALS

- 31 abnormal on word generation tests
  - 17 underwent further evaluation
    - 15 confirmed FTLD
    - 2 low normal on language testing
- 69 normal on word generation tests
  - 27 underwent further evaluation
    - 8 confirmed FTLD
    - 19 normal

Lomen-Hoerth et al, Neurology, 2003
# Defining cognitive sub-types in ALS*

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Clinical Characteristics</th>
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<tbody>
<tr>
<td>ALS – FTD</td>
<td>ALS patient meeting either the Neary criteria or Hodge’s criteria for FTD</td>
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<tr>
<td>ALS-bvFTD</td>
<td>ALS patient meeting Neary criteria for PNFA</td>
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<tr>
<td>ALS-PNFA</td>
<td>ALS patient meeting Neary criteria for SD</td>
</tr>
<tr>
<td>ALS-SD</td>
<td>ALS patient meeting at least 2 non-overlapping supportive diagnostic features from either the Neary criteria or Hodge’s criteria for FTD</td>
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<tr>
<td>ALSbi</td>
<td>Evidence of cognitive impairment at or below the 5(^{th}) percentile on at least two distinct tests of cognition that are sensitive to executive functioning</td>
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*Table from Strong et al., 2009*
# Behavioral Criteria (ALSbi)

<table>
<thead>
<tr>
<th>Neary Criteria</th>
<th>Hodges Criteria</th>
</tr>
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<tbody>
<tr>
<td>Decline in personal hygiene and grooming</td>
<td>Loss of insight</td>
</tr>
<tr>
<td>Mental rigidity and inflexibility</td>
<td>Disinhibition</td>
</tr>
<tr>
<td>Distractibility and impersistence</td>
<td>Restlessness</td>
</tr>
<tr>
<td>Hyperorality and dietary changes</td>
<td>Distractibility</td>
</tr>
<tr>
<td>Perseverative and stereotyped behavior</td>
<td>Impulsiveness</td>
</tr>
<tr>
<td>Utilization behavior</td>
<td>Social withdrawal</td>
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<tr>
<td></td>
<td>Reduced verbal output</td>
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<tr>
<td></td>
<td>Poor self-care</td>
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<td></td>
<td>Gluttony</td>
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<td></td>
<td>Apathy/loss of spontaneity</td>
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<td></td>
<td>Sexual hyperactivity</td>
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<td></td>
<td>Lack of foresight/planning</td>
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<td></td>
<td>Reduced empathy or unconcern for others</td>
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<td></td>
<td>Verbal stereotypes or echolalia</td>
</tr>
<tr>
<td></td>
<td>Verbal or motor perseveration</td>
</tr>
</tbody>
</table>
Incidence of FTLD in ALS

The 26% that is not normal but also not FTD is being redefined as Executive Dysfunction (9%), Behavior Abnormalities (17%)
Prevalence of Cog/Beh Impairment Among ALS Patients

- 22% Lomen-Hoerth et al 2003
- 45% Ringholz et al 2005
- 27% Robinson et al 2006
- 30% Rippon et al 2006
- 48% Murphy et al 2007
- 25% Rusina et al 2010
Mimics of cognitive and behavioral impairment in ALS

- Depression or other underlying psych disorder
- Pseudobulbar affect
- Hypoxia or hypercapnea
- Educational level/baseline intellectual functioning
- Presence of bulbar palsy or paralysis limiting testing
- Advanced disease
NINDS ALS Cognitive Subgroup Instrument Recommendations

- **Cognitive-Behavioral Screens**
  - ALS Cognitive Behavioral Screen
  - Penn State Screen
  - UCSF Screen Battery

- **Cognitive Measure**
  - Abrahams Written Verbal Fluency
  - Behavioral Measures
  - Frontal Behavior Inventory (FBI)
  - FBI-ALS Version
  - FBI- Modified by Heidler-Gary
  - Neuropsychiatric Inventory (NPI)
  - NPI-Clinician Version
  - NPI-Q
  - Frontal Systems Behavior Scale
  - Cambridge Behavioral Inventory-Revised

- **Pseudobulbar Affect Scales**
  - CNS- Lability Scale
  - Emotional Lability Questionnaire

- **Depression Scales**
  - Beck Depression Scale
  - Geriatric Depression Scale
  - Hospital Anxiety and Depression Scale
  - ALS Depression Inventory
  - Hamilton Depression Rating Scale

- **Summary Statement**
  - Minimum: Cognition and Behavior
  - Strongly consider: Depression
  - Consider: Pseudobulbar Affect

- **Summary Table**
  - CDE classification, construct measure, ALS specific, administration time

*Chairs: Cathy Lomen-Hoerth & Zachary Simmons. Members: Sharon Abrahams, Richard Buchsbaum, Lora Clawson, Laura Goldstein, Murray Grossman, Robert Miller, Dan Moore, Jennifer Murphy, Seamus Thompson, Susan Woolley

**Funded by the NINDS/NIH via a contract to KAI Research, Inc (N01-NS-7-2372)
Voxel-based morphometry study

- Atrophy in 10 patients with ALS and 10 patients with ALS-FTD vs. 22 controls
  - Bilateral motor/premotor cortices
  - Left middle and inferior frontal gyri
  - Anterior portion of the superior frontal gyri
  - Superior temporal gyri
  - Temporal poles
  - Left posterior thalamus
Continuum of Abnormalities
Chang et al, Neurology 2005
MRI analysis

- Templates of lobar grey matter and white matter (determined from DTI connectivity) were registered to the patients’ T1-weighted volumes (1x1x1.5mm³) and DTI data (2.2x2.2x2.2mm³) to determine grey matter volume (GV) and white matter mean diffusivity (MD) and fractional anisotropy (FA), respectively.

- Anova (p < 0.05) were used for cross-sectional comparisons of MRI metrics between ALS and ALS-FTD cohorts after removing age and gender effects.

- Stepwise regression models of cognitive variables as functions of lobar GV, FA, and MD with age and gender as covariates were performed.
DTI reveals brain structure

Photo of cadaver brain from Visible Human Project, NLM

Vector plot of **primary eigenvector**

DTI color map of axonal fiber orientation
Whole brain connectivity from DTI fiber tracking
Lobar white matter defined by DTI connectivity to lobar grey matter
Grey & white matter abnormalities predict neuropsychological testing

Statistical Model:

Neuropsyc Result = lobar GM volume + lobar WM FA + lobar WM MD

<table>
<thead>
<tr>
<th></th>
<th>R Frontal</th>
<th>L Frontal</th>
<th>R Temporal</th>
<th>L Temporal</th>
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</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>CVLT-SF</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Verbal-Fluency</td>
<td>GV(0.31)*</td>
<td>FA(0.41)**</td>
<td>GV+FA(0.46)**</td>
<td>GV+FA(0.45)**</td>
</tr>
<tr>
<td>DKEFS-Trails</td>
<td>MD(0.52)**</td>
<td>MD(0.45)**</td>
<td>GV(0.67)**</td>
<td>MD(0.36)**</td>
</tr>
<tr>
<td>Boston-Naming</td>
<td>MD(0.18)*</td>
<td>GV(0.17)*</td>
<td>GV(0.32)**</td>
<td>GV(0.35)**</td>
</tr>
<tr>
<td>DKEFS-Stroop</td>
<td>MD(0.45)**</td>
<td>GV(0.33)*</td>
<td>GV(0.43)**</td>
<td>GV(0.40)**</td>
</tr>
</tbody>
</table>

*p<0.05; **p<0.008; ***p<0.001; RSQ in parenthesis
Does this milder form of FTLD have clinical significance?

- Two hypothesis:
  - Survival is shorter in patients with ALS-FTLD than ALS alone
  - Compliance with treatment recommendations is significantly less in patients with ALS-FTLD than ALS alone

Effect of FTLD on survival

Chi sq = 5.14
P < 0.02
Survival in ALS with co-morbid FTD

- Olney et al 2005 showed a survival difference of more than a year between patients with co-morbid disease versus ALS alone.

- Since the Olney publication, subsequent authors have demonstrated similar findings with a shortened survival in ALS patients with co-morbid disease for both mildly impaired and moderately impaired patients, Gordon et al 2010
## NPPV and PEG Compliance

<table>
<thead>
<tr>
<th></th>
<th>NPPV</th>
<th>PEG</th>
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<tbody>
<tr>
<td>ALS-FTLD</td>
<td>25%</td>
<td>28%</td>
</tr>
<tr>
<td>ALS only</td>
<td>62%</td>
<td>69%</td>
</tr>
<tr>
<td>z</td>
<td>2.22</td>
<td>2.01</td>
</tr>
<tr>
<td>p (one-tail)</td>
<td>&lt; 0.02</td>
<td>&lt; 0.03</td>
</tr>
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</table>
Important Clinical Issues for ALSci and ALSbi

- Reduced survival rate
- Poor compliance (poor use of PEG, BiPap)
- Caregiver distress
- Poor safety awareness (falls, choking)
- Inability to manage important decisions
- Implications for stem cell therapy
Richard K. Olney, MD
Founding Director ALS Treatment and Research Center at UCSF