ALS and Frontotemporal Dementia

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Objectives

• Discuss Frontotemporal lobar dementia (FTLD): clinical presentation, radiographic evidence, and genetics

• Discuss ALS and FTLD: clinical presentation, epidemiology, demographics, pathology, and genetics

• Discuss cognitive testing in ALS/FTLD

• Discuss management
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
Cognitive Abnormalities in ALS

• As patients with motor neuron disease associated with dementia were published in increasing numbers and the clinical features of frontotemporal dementia were better described including consensus criteria first published in 1998, it became clear that the dementia seen in ALS patients is best characterized as FTD
Over 100 Years of Cognitive Abnormalities in ALS

- Raymond 1889
- Marie 1892
- Ziegler 1930
- Weshsler 1932
- Hudson 1981
- Caselli 1993
- Strong 1996
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  – Withdrawn due to depression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 dysphagia

• FTLD behaviors
  – Apathetic
  – Disinhibited
  – Poor judgement
  – Easily frustrated
  – Quick to anger
  – Lack of insight
  – Language difficulty
    • Word finding
    • Spelling
    • aphasia
Case Study

• 56 year old, right handed male, onset late 2010
  – Progressive difficulty communicating
    • Slurred speech
    • Sentences grammatically incorrect
    • Transposition of words
  – Progressive behavioral changes
    • Disinhibition (language, removing clothing)
    • Apathy
    • Stereotypical and compulsive behaviors
    • Withdrawn
    • Impairment in regulation of personal conduct
    • Lack of insight
Case Study

– Progressive behavioral changes
  • Decline in personal hygiene
  • Mental rigidity and inflexibility
  • Distractability and impersistence

– Executive dysfunction
  • Problem in planning, organizing, abstracting, and prioritizing
  • Impaired verbal fluency
  • Lack of insight

– Emotionally labile
Case Study

- sensory and motor examination in upper and lower extremities normal
- DTRs 2+
- Negative jaw jerk
- Cranial nerve examination normal
Case Study

- Work-up
  - MRI-atrophy in frontal and temporal lobes, frontal horns of lateral ventricles mildly enlarged
  - EEG-Normal
  - EMG/NCS-normal
  - PET Scan-glucose hypometabolism in frontal lobes
Case Study

• Initial impression: Frontotemporal Dementia
• Genetics requested but no insurance coverage and never completed
Case Study

• 2011
  – Clinical features
    • Progressive dysphagia/choking
    • Right > left upper extremity hand intrinsic weakness and atrophy, fasciculations in FDIH
    • DTRs 3+, Positive Babinski on right
    • Facial/palate/tongue weakness
    • Dysarthric/nasal speech
    • Positive jaw jerk
Case Study

• 2011
  – Behavioral worsening
    • Inability to adjust to new routines and change in environment (increased agitation)
    • Word finding and naming more difficult
    • Verbal output decreased
    • Worsening of all original behavioral and executive dysfunction
Case Study

• 2011
  – MRI-increased atrophy in frontal and anterior temporal regions, increasing enlargement of frontal horns of the lateral ventricles
  – EMG/NCS-diffuse denervation in 3 limbs/cranial innervated musculature, defect in neuromuscular transmission (RNS), increased jitter on SFEMG; consistent with motor neuron disease of the ALS type
Case Study

– PET scan
  • Glucose hypometabolism in frontal and temporal lobes
Case Study

• 2012
  – Generalized weakness/atrophy
  – DTRs 3+
  – PEG tube/BiPAP
  – Severe cognitive impairment and behavior
  – Hospice
  – Death
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<th>2010</th>
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<th>2012</th>
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<td>Letter (F, A, S)</td>
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<td>Animal</td>
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<td>Trial A (most in 90 sec)</td>
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<td>Trial B (most in 3 minutes)</td>
<td>200 sec (average 75; &gt;273 deficient)</td>
<td>350 sec</td>
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</table>
Clinical Impression:
Frontotemporal Lobar Dementia and ALS

Brain and spinal cord submitted to UCSF for confirmation
What is Frontotemporal Lobar Dementia?

• Progressive neurodegenerative syndrome occurring between 45 and 65 years of age
  – FTD occurs in 5-15% of patients with dementia and it is the third most common degenerative dementia
  – FTD occurs with equal frequency in both sexes
  – The usual course is one of progressive clinicopathological deterioration with mortality within 6-8 years
What is Frontotemporal Lobar Dementia?

– Relative preservation of memory, praxis, and visuospatial skills with impairment of behavior, language, and/or personality

– Patients characteristically lack insight into their problems
What is Frontotemporal Lobar Dementia?

– Initial features at presentation may include changes in behavior (behavioral variant, bvFTD), difficulty with expression of language but with relative preservation of comprehension (primary progressive aphasia or non-fluent progressive aphasia, PFNA), or impaired language characterized by anomia in conjunction with impaired semantic dementia (SD)
What is Frontotemporal Lobar Dementia?

- Patients with bvFTD may be disinhibited, apathetic, or manifest stereotypical behaviors.
- Features associated with non-fluent progressive aphasia may include anomia, phonemic paraphrasia, grammatical errors, stuttering, oral apraxia, alexia, or agraphia.
- Semantic dementia, the least common of FTLD, is characterized by speech that is fluent and grammatically correct but empty of content.
What is Frontotemporal Lobar Dementia?

- Naming of people, both familiar and famous, is frequently impaired, and while confrontational naming is very poor, repetition is generally preserved.
- Executive dysfunction is common early in FTD, when seen in Alzheimer’s disease it typically occurs later.
- Executive dysfunction is reflected in problems with planning, organizing, abstracting and prioritizing, along with verbal fluency.
MRI Imaging in FTLD

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,

Genetics in FTLD

- The most prevalent genes involved are for PGRN (progranulin) and MAPT (microtubule-associated protein tau), both located on chromosome 17q21
Pathology in FTLD

• More than 15 different pathologies can underlie FTD and related disorders and it has four major types of pathological features:
  (1) microvacuolation without neuronal inclusions,
  (2) microvacuolation with ubiquinated rounded interneuronal inclusions and dystrophic neurites
  FTD-ubiquinated (FTLD-U),
  (3) transcortical gliosis with tau-reactive rounded interneuronal inclusions,
  (4) microvacuolation and tau-positive neurofibrillary tangles
What is Frontotemporal Lobar Dementia?

• Behavior changes are the most common initial symptom of FTD, whereas speech and language problems are most common in NFPA and SD

• Clear criteria established (Neary, 1998)

• Clearly distinguished from Alzheimer’s disease
Neary Criteria

• Decline in personal hygiene and grooming
• Mental rigidity and inflexibility
• Distractibility and impersistance
• Hyperorality and dietary changes
• Perseverative and stereotyped behavior
• Utilization behavior
ALS and Frontotemporal Dementia
ALS and FTD

• Patients with ALS-FTD typically have onset of symptoms in their 50s
  – Like ALS without dementia, it is slightly more common in men than women
  – The ALS symptoms may precede, occur simultaneously, or follow the signs and symptoms of FTD, although, the most common finding is to have cognitive changes first followed by weakness
ALS and FTD

– Interval between cognitive symptoms and weakness may be few months up to 7 years, with a mean of 2 years

– Some but not all studies found bulbar onset disease more often in patients with ALS-FTD compared to those with ALS alone

– At least some patients have significant upper extremity weakness while lower extremities are relatively preserved, with maintained ambulation even at time of death
ALS and FTD

- Behavioral changes may include euphoria, indifference, and personality changes, while language impairment includes paucity of speech, ecolalia, impaired comprehension, and even mutism
ALS and FTD

• Survival in patients with ALS-FTD is worse compared to those with ALS alone or FTD alone
  – In those who are cognitively impaired but not frankly demented, the type of frontotemporal dysfunction may influence survival
  – ALS patients with executive dysfunction may have worse survival but those with abnormalities limited to language or visuospatial skills have similar survival compared to the cognitively normal ALS patients
ALS and FTD

- ALS patients with dementia primarily characterized by poor memory such as seen in Alzheimer’s disease, did not have further shortening of survival
ALS and FTD

– Clinical studies

• Hodges et al 2003: 8.2 yrs FTD vs 2.4 yrs ALS-FTD
• Roberson et al 2005: 10-20 yrs FTD vs 2.0 yrs 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
ALS and FTD

– Clinical studies
  • Olney et al 2005 showed a survival difference of more than one year between patients with co-morbid disease versus ALS alone
Effect of FTLD on survival

[Graph showing the effect of FTLD on survival over months, with two lines representing ALS only and ALS + FTLD.]
ALS and FTD

EEGs are frequently normal though may show background or focal slowing
ALS and FTD-Imaging

In a voxel-based morphometry study, MRIs of both ALS and ALS-FTD patients had atrophy in the frontotemporal regions compared to controls, though frontal atrophy was greater in ALS-FTD patients.

- Atrophy in 10 patients with ALS and 10 patients with ALS-FTD vs 22 controls found in bilateral motor/premotor cortices, left middle and inferior frontal gyri, anterior portion of the superior frontal gyri, superior temporal gyri, temporal poles, and left posterior thalamus.
ALS and FTD-Imaging

- Lomen Hearth described grey-white abnormalities on DTI MRI predicting neuropsychological testing
  - Measurements on DTI MRI included grey matter volume (GV), white matter mean diffusivity (MD), and fractional anisotrophy (FA)
DTI reveals brain structure

Vector plot of primary eigenvector

Photo of cadaver brain from Visible Human Project, NLM

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:

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

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<tr>
<th>Test</th>
<th>R Frontal</th>
<th>L Frontal</th>
<th>R Temporal</th>
<th>L Temporal</th>
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<tr>
<td>MMSE</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>CVLT-SF</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
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<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>
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<tr>
<td>DKEFS-Trail</td>
<td>MD(0.52)**</td>
<td>MD(0.45)**</td>
<td>GV(0.67)**</td>
<td>MD(0.36)**</td>
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<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>
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</tbody>
</table>

*p<0.05; **p<0.008; ***p<0.001; RSQ in parenthesis

ALS and FTD-Classification

• Strong and colleagues proposed the following classification system for the frontotemporal syndromes in ALS
## 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>
</tr>
<tr>
<td>ALSbi</td>
<td>Evidence of cognitive impairment at or below the 5th percentile on at least two distinct tests of cognition that are sensitive to executive functioning</td>
</tr>
</tbody>
</table>

*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>
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<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>
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<tr>
<td>Utilization behavior</td>
<td>Social withdrawal</td>
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<td></td>
<td>Reduced verbal output</td>
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<td></td>
<td>Poor self-care</td>
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<td>Gluttony</td>
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<td></td>
<td>Apathy/loss of spontaneity</td>
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<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>
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<tr>
<td></td>
<td>Verbal or motor perseveration</td>
</tr>
</tbody>
</table>

ALS and FTD-Classification

– ALSci may have impaired verbal fluency or executive dysfunction, and those with ALSbi have the behavioral features associated with frontotemporal dysfunction, but do not meet Neary criteria for FTD

– Patients with behaviorally predominant form of ALS-FTD may also have impaired language, with reduced verbal fluency as the most common language deficit found
ALS and FTD

– Overall, memory is relatively preserved in patients with ALS-FTD, and the memory problems reported are believed to be frontal dysfunction

• Patients may have difficulty with retrieving memories and have poor learning strategies
• Lack of concentration and poor attention may also play a role in a patient’s performance
• In keeping with the dementia of ALS not fitting an Alzheimer’s like pattern, the MMSE is typically normal in ALS patients
Epidemiology

• U.S.
  – Frontal lobe dementia second or third most common type of degenerative dementia in autopsy series
  – The precise frequency with which FTD with ALS occurs in autopsy studies is unknown (but low)
Epidemiology

• International
  – In a Scandinavian autopsy series, dementia was 2-6% of patients with MND
  – The relative frequency of FTD/MND in all patients with dementia appears similar in U.S. and Japan
  – Certain populations (i.e. Charmorro Indians of Guam, indigenous residents of Kii Peninsula) have disproportionately higher incidence and prevalence of overlap syndromes (MND, dementia, parkinsonism)
Race, Sex, and Age-Related Demographics

• FTD/MND described in Asian, European, and African descent

• No data available about incidence and prevalence among racial groups
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%).

Incidences of FTLD in ALS-MDA/MIND

- Normal, 52%
- FTLD, 19%
- AD, 3%
- Not Normal, Not FTLD, 26%

Executive Dysfunction: 8%
Behavior Abnormal: 18%

N=1152 patients (1992-2012)
Prevalence of Cognitive/Behavioral Impairment Among ALS Patient

• 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 psychiatric disorder
- Pseudobulbar affect
- Hypoxia or hypercapnia
- Educational level/baseline intellectual functioning
- Presence of bulbar palsy or paralysis limiting testing
- Advanced disease
Screening for Cognitive Impairment in the Clinic
Cognitive Testing

• Extensive neuropsychological testing is impractical, expensive, time consuming for patients with marked weakness and dysarthria

• A screening battery is extremely important to develop

• When testing ALS patients, one also needs to take into account respiratory status, pseudobulbar affect, medications, depression, and pain
Cognitive Testing

– In the 2009 practice parameter from AAN, authors acknowledged lack of consensus on how best to study cognitive changes in patients with ALS
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)
Cognitive Testing

• ALS Cognitive Behavioral Screen (Wooley et al)
  – 15 item ALS specific behavioral questionnaire filled out by caregiver, and an 8 item cognitive assessment of patient that is estimated to take only 5 minutes

• Penn State Screen Battery of Frontal and Temporal Dysfunction Syndromes takes approximately 20 minutes
  – Currently being evaluated across the country

• UCSF screen battery takes approximately 45 minutes
  – Includes ALS specific version of the FBI, written verbal fluency, the ALS Cognitive Behavioral Screen, an emotional lability scale, and the Beck Depression Inventory

• University of Arkansas-category fluency, the CBI, and anti-saccade testing (looking in opposite direction to your wiggling finger-measure of frontal lobe inhibition)
Cognitive Testing-MDA/MIND

- MMSE not of much help
- Trail Making A and B
- Word and letter naming
- Penn State Battery of Frontal and Temporal Dysfunction
Cognitive Testing in FTLD/ALS

• Naming tests (phonemic fluency [letter, word] and semantic fluency [animal] associated with left triangularis in frontal lobe and superior temporal lobe region (including planum temporale)

• Sequencing tests (Trail Making A and B) also associated with frontal lobe function
Measures of Verbal Fluency: FAS (phonemic) and Animal Naming (semantic fluency)

• Phonemic fluency can be assessed by the number of words generated in one minute for the letters F, A, and S
  – Normative data has been generated for age, and years of education
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Measures of Semantic Fluency: Animal Naming

- Semantic fluency can be assessed by the number of animals named in one minute
  - Normative data has been generate for age and years of education
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<td>92</td>
<td>17.6</td>
<td>(4.7)</td>
</tr>
<tr>
<td>70–79</td>
<td>228</td>
<td>16.1</td>
<td>(4.0)</td>
</tr>
<tr>
<td>80–89</td>
<td>200</td>
<td>14.3</td>
<td>(3.9)</td>
</tr>
<tr>
<td>90–95</td>
<td>24</td>
<td>13.0</td>
<td>(3.8)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>310</td>
<td>17.4</td>
<td>(5.1)</td>
</tr>
<tr>
<td>Female</td>
<td>425</td>
<td>16.5</td>
<td>(5.0)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>735</td>
<td>16.9</td>
<td>(5.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age 16-59 Years</th>
<th>Age 60-79 Years</th>
<th>Age 80-95 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education (Years)</td>
<td>Education (Years)</td>
<td>Education (Years)</td>
</tr>
<tr>
<td>0-8 (n = 4)</td>
<td>0-8 (n = 75)</td>
<td>0-8 (n = 75)</td>
</tr>
<tr>
<td>9-12 (n = 109)</td>
<td>9-12 (n = 165)</td>
<td>9-12 (n = 103)</td>
</tr>
<tr>
<td>13-21 (n = 78)</td>
<td>13-21 (n = 94)</td>
<td>13-21 (n = 46)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percentile Score</th>
<th>Age 16-59 Years</th>
<th>Age 60-79 Years</th>
<th>Age 80-95 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>26</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>75</td>
<td>23</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>50</td>
<td>20</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>25</td>
<td>17</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td>11</td>
<td>9</td>
</tr>
</tbody>
</table>

| M (SD) | 19.8 (4.2) | 14.4 (3.4) | 13.1 (3.8) |
|        | 21.9 (5.4) | 16.4 (4.3) | 13.9 (3.4) |

Note. M = mean; SD = standard deviation.
Trail Making Test (TMT) Parts A & B

Instructions:
Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Time the patient as he or she connects the "trail." If the patient makes an error, point it out immediately and allow the patient to correct it. Errors affect the patient’s score only in that the correction of errors is included in the completion time for the task. It is unnecessary to continue the test if the patient has not completed both parts after five minutes have elapsed.

Step 1: Give the patient a copy of the Trail Making Test Part A worksheet and a pen or pencil.
Step 2: Demonstrate the test to the patient using the sample sheet (Trail Making Part A – SAMPLE).
Step 3: Time the patient as he or she follows the "trail" made by the numbers on the test.
Step 4: Record the time.
Step 5: Repeat the procedure for Trail Making Test Part B.

Scoring:
Results for both TMT A and B are reported as the number of seconds required to complete the task; therefore, higher scores reveal greater impairment.

<table>
<thead>
<tr>
<th>Trail</th>
<th>Average</th>
<th>Deficient</th>
<th>Rule of Thumb</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>29 seconds</td>
<td>&gt; 78 seconds</td>
<td>Most in 90 seconds</td>
</tr>
<tr>
<td>B</td>
<td>75 seconds</td>
<td>&gt; 273 seconds</td>
<td>Most in 3 minutes</td>
</tr>
</tbody>
</table>

Sources:
Trail Making Test Part B

Patient's Name: ___________________________  Date: ______________________

Diagram:

Numbers: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12

Connect the numbers and letters in order as quickly as possible.
Penn State Brief Exam of Frontal and Temporal Dysfunction Syndromes

- 6 subscales
  - National Adult Reading Test (NART) to assess premorbid intelligence (IQ) or those with sufficient intelligibility of speech (http://www.commondateelements.ninds.nih.gov/CRFdetail.aspx?Formid=1031)
Penn State Brief Exam of Frontal and Temporal Dysfunction Syndromes

• Neurobehavioral Cognitive Status Examination (COGNISTAT) to assess reasoning (similarities, judgement, attention span, language (repetition auditory comprehension, naming), 2-D constructional skills, mental calculations, orientation, and verbal memory (http://www.cognistat.com/)

• Reading comprehension via the Boston Diagnostic Aphasia Exam (BDAE) Oral Reading and Reading Comprehension-Short Form for those with sufficient intelligibility of speech (5 items) (http://www.proedinc.com/customer/ProductView.aspx?ID=3399&sSearchWord=Boston++Diagnostic+Aphasia+Exam)
Penn State Brief Exam of Frontal and Temporal Dysfunction Syndromes

• Frontal Behavioral Inventory (FBI) is given concurrently to the caregiver to assess for behavioral changes
Pathology
Mild Frontal and Temporal Atrophy

Spinal Cord Moderate Atrophy of Anterior Roots

Neocortex (Frontotemporal) and Entorhinal Cortex
Mild Superficial Spongiosis, Gliosis, and Neuronal Loss

Spinal Cord
Severe Neuron Loss Throughout Spinal Cord

Ubiquitin Positive, Tau/α-Syn/Neurofilament Negative Inclusions in Neocortex and Entorhinal Cortex

Ubiquitin-Positive Inclusions in Hypoglossal Nucleus and Anterior Horn Cell of Spinal Cord

Pathology

• In 2006, 2 groups reported that the ubiquinated inclusions in FTD with ALS were TAR-DNA binding protein 43 or TDP-43
  – Patients with pure ALS have TDP-43 pathology primarily in the spinal cord, those with pure FTD have TDP-43 primarily in the cortex, while those with FTD-ALS have TDP in both areas
  – However, TDP43 in FTD-ALS found not only in typical areas but can also be seen in the cerebellum, parietal and even occipital lobes although to lesser degrees, suggesting TDP-43 is part of a multisystem degenerative process
Pathology

- TDP-43 levels in CSF are higher in patients with ALS or FTD
- In a patient with Parkinsonism, MND, and FTD, TDP-43 pathology was found not only in the motor system, hippocampus, and amygdala, but also in the globus pallidus, caudate, and putamen
Genetic Overlap of ALS and FTD
Genetic Overlap of ALS and FTLD

• Familial: 10% of ALS, and 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 two disorders
Genetic Overlap of ALS and FTLD

Genetic Overlap of ALS and FTLD

Pedigree From Case Study
Genetic Overlap of ALS and FTD

• In 2000, a genome-wide linkage analysis of two large data sets consisting of over seven hundred families, found a genetic locus between D9S301 and D9S167 on chromosome 9p21-q22 linked to ALS with FTD

• A second genome-wide linkage study in a large ALS/FTD showed linkage to chromosome 9 but at 9p13.3-21.2
New Gene Found for ALS-FTD

- Most common gene for ALS-FTD found in 2011 (expansion of a GGGGCC hexanucleotide repeat in the intron of protein *C90RF72* leading to an alternative splicing of this protein)
  - 30 repeats corresponded with individuals expressing the gene
  - In a U.S. based study found a prevalence of this expansion in 12% of familial FTD and 23% of familial ALS, 3% of sporadic FTD and 4% of sporadic ALS
  - In European population, higher prevalence rates: 46% in familial ALS, 21% in sporadic ALS, and 29% in familial FTD
Genetic Overlap of ALS and FTD

• A recent study in Nature involving 19 individuals within a five-generation family uncovered a new gene, UBQLN2 mutation underlying X-linked dominant inheritance of ALS/FTD
  – This mutation led to ubliquilin 3 protein pathology in the spinal cord and brain
  – Functional analysis showed an impaired degradation of ubiquinated proteins, a well known function of the ubiquilin-2 proteins
Genetic Testing on Case Study Patient

• From MDA grant, testing revealed 42 repeats of GGGGCC of protein **C90RF72** (blood was banked prior to death)

• Genetic testing in recently diagnosed daughter reveals 42 repeats of GGGGCC of protein **C90RF72**
Management
Management

• No specific pharmacological therapies approved for use
  – Pharmacological interventions for the behavioral disturbances seen in FTD have included antipsychotics, antidepressants, anticonvulsants, and dopamine agonists
  – Behavioral impairments, such as depression, irritability, and apathy with relative preservation of memory are compatible with serotonergic dysfunction
Management

– Majority of studies have shown deficiencies in the serotonergic system in FTD
– There is decreased 5HT2A receptor density in the orbitofrontal, frontomediaial, and cingulated cortices
– Early trials with selective serotonin reuptake inhibitors have been equivocal or have shown moderate benefit
– Recent study with trazadone promising for management of behavioral disturbance
Management

- Rivastigmine (Exelon) been reported to be more efficacious than galantamine (Razadyne) and donepezil (Aricept) in open label data and small randomized trials
Implications for Care

• People with ALS/FTD less likely to follow treatment recommendations
  – Caregiver should assume medical management
    • Creative approaches to implementing changes in care
    • Begin implementing changes before they are absolutely necessary
Implications for Care

– People with ALS/FTD have symptoms that will continue to change over time
  • Consider a combination of medication and behavior management interventions
  • Seek outside sources of support and information
  • Caregiver needs to take care of self and manage stress, remember that these changes are no one’s fault, and work to accept physical changes
Implications for Care

– People with FTD may lose reasoning and decision making abilities
  • Assess driving ability
  • Limit use of power tools, equipment, etc.
  • Freeze financial accounts and run credit checks regularly

– Addressing legal issues
  • Because FTD will eventually interfere with one’s ability to participate in treatment planning..discuss early
    – Decision about feeding tube
    – Decision about ventilator
    – Other medical treatment decision
Implications for Care

– The patient should, **as early in disease process as possible:**
  
  • Appoint a healthcare Power of Attorney (POA)
  • Complete an Advanced Directive (Living Will)
  • The caregiver should develop an understanding of the patient’s goals for care while he/she can still verbalize
Implications for Care

- Manage difficult behaviors
  • Individualize management strategies
    - Consider the whole picture
    - Look for patterns in the person’s behavior or particular times of day
    - Keep log or record
    - Adjust strategies as behaviors change
Implications for Care

– Behavioral strategies
  • Use simple words, Yes/No questions
  • Praise desired behaviors
  • Find soothing rituals
    – Hand massage
    – Favorite music/movie
    – Time with a pet
  • Avoid arguing...change the subject
  • Finding a walking buddy for restless times during the day
Implications for Care

– Environmental strategies
  • Create a structured, predictable daily routine
    – Helps for apathy, disinhibition, sleep difficulty
    – Takes the pressure of making decisions off the patient
    – Tips
      » Match activities to ability level
      » Individualize routine to patient likes and interests
      » www.ftd-picks.org (support and resources, caregivers challenges)
Implications for Care

– Monitor patient’s contacts with the outside world
  • Disconnect land line
  • Use 1 cell phone with password
  • Child controls for TV, websites
  • Consider alarm or bell on door
  • Freeze credit card accounts
Implications for Care

– Keep out of sight/limit access to:
  • Car keys, car
  • Power tools
  • Guns and firearms
  • Medications
  • Unsafe foods (if choking, BINGING is a concern)
Implications for Care

– Physical interventions
  • Create picture board for communication
  • Use hand massage to encourage eating
  • Lock doors
  • Avoid physical restraint
  • Adjust sound, lighting to limit agitation
Implications for Care

– Concerns for ALS/FTD caregivers
  • Highest risk groups of all caregivers for stress!
    – Higher stress than Alzheimer’s disease
    – Higher stress than ALS caregivers
  • Depression, anxiety, anger, guilt, frustration, irritability, resentment
  • Physical illness
  • Impaired sleep
  • Isolation
  • Stigma
  • Caregiver burnout
Implications for Care

– Caregiver self-care techniques
  • Regular planned breaks
    – Even if just a few moments at a time
    – Have multiple friends/family members to help
    – Use in-home care, respite care
    – Adult day care
    – Long-term care placement
    – Hospice care
Implications for Care

• Relaxation and breathing techniques
• Prayer, meditation, reading, journaling
• Regular eating times
• Focus on improving own sleep
  – Use of baby monitor, alarm for bed
• Regular exercise (DVDs, videos, Wii, etc)
• Treatment for depression
• Stay connected to friends and family (phone, internet)
• Resource/support group
Implications for Care

– Problem solving
  • Tips
    – Pick your most challenging problem at the moment
    – Understand that the first option won’t always be the best solution
    – What you originally thought was the problem might not have been the problem!
    – Brainstorm all of the options, even if they don’t sound reasonable (need to think out of the box)
    – Seek options from other caregivers, family, friends, or ALS staff
    – What worked today may not work tomorrow
    – There’s always another option-persistence!
Implications for Care

– Other additional resources
  • AFTD hotline: phone 866-507-7222, email: info@ftd-picks.org
  • http://memory.ucsf.edu/ftd
  • www.caregiver.org
  • ALS Support Group
  • FTD Support Group
  • ALS Clinic Team
  • Bi-annual FTD Caregiver Conference, University of Pennsylvania; recordings of previous conferences available at www.ftd-picks.org