Frontotemporal Dementia (FTD)

Monica K. Crane, MD
Associate Director
Cole Neuroscience Center, UTMCK
Clinical Assistant Professor, Dept. of Medicine
Frontotemporal dementia (FTD) Overview

- Background and clinical definition
- Prevalence
- Anatomy
- FTD clinical subtypes
- Neuropathology and genetics of Frontotemporal lobe dementia (FTLD)
- Historical cases
FTD = a clinical neurodegenerative disease affecting frontal & temporal lobes

- Personality changes
- Loss of socially acceptable behavior & emotions
- Bizarre and compulsive behaviors
- Language dysfunction
- Movement disorder
FTD International Research Criteria:

Three of the following: OR

1. Early disinhibition
2. Early apathy, loss of motivation
3. Loss of emotional recognition
4. Perseverative, compulsive, ritualistic behavior
5. Hyperorality/dietary changes
6. FTD neuropsychological profile

Either #7 or #8 one symptom from #1-6

7. Frontal and/or anterior temporal atrophy; other radiologic findings
8. Presence of a known mutation

B. L. Miller, C. Ikonte, M. Ponton, et al. *Neurology* 1997;48;937
“Dementia That's Neither Alzheimer's Nor Easy”

FDG-PET images of metabolic activity: healthy controls, AD, and FTD. Scale red (high FDG uptake)-yellow-green-blue (low FDG uptake).

Photo Credit: Dr. Janet Miller, Dr. Suzanna Lee, MGH/ Harvard, Radiology Rounds April 2006
FTD syndromes ~ 10-15%
Alzheimer’s Disease (AD) ~ 50-70%
Vascular dementia ~ 5-10%
Dementia with Lewy Bodies & Parkinson’s disease dementia ~ 10%

Boxer AL, Miller BL. Alzheimer Dis Assoc Disord. 2005;19 S1:S3-6
FTD Prevalence

FTD: Alzheimer’s disease (AD) ratio is 1:1 in those aged 45-65.

FTD is more common that AD below age 60.

FTD spectrum comprises near 15% or more of the total FTD dementia cases.
Pick’s disease ≠ FTD
Pick’s is an autopsy finding only so do not use this term. The clinical disease is FTD.

In 1892, Dr. Pick reported a case of a 71 year-old man with focal atrophy and aphasia, & concluded that “progressive brain atrophy can lead to symptoms of local disturbance through local accentuation of the diffuse process.”

Dr. Arnold Pick (1851-1924) Prof. of Psychiatry, Prague
Frontotemporal lobar degeneration (FTLD) = Neuropathology of clinical FTD
Pick’s is a small subset of FTLD

Heterogeneity of FTD subtypes: Anatomy and Clinical presentation
What areas of the brain are affected in FTD?
FTD damages 3 major networks:
Dorosolateral prefrontal cortex (DLPFC)
Anterior cingulate cortex (ACC)
Orbitofrontal cortex (OFC)
Areas affected in FTD versus AD

Clinical Presentation: FTD Subtypes
Frontotemporal dementia subtypes

- Behavior variant (bvFTD)
- Semantic dementia (SD)
- Progressive nonfluent aphasia (PNFA)
- Progressive Supranuclear Palsy (PSP)
- Corticobasal degeneration (CBD)
- FTD with motor neuron disease (FTD-MND)
- ALS/CTE (Chronic Traumatic Encephalopathy)

Boxer AL, Miller BL. Clinical features of frontotemporal dementia. Alzheimer Dis Assoc Disord. 2005;19 S1:S3-6
Approximately 60% of patients with any form of FTD have bvFTD.

Figure 1. Coronal pathology section showing asymmetric right-sided atrophy (R temporal cortices with widening of the inferior horn of the lateral ventral).
Clinical Features of bv-FTD

- Gradual onset
- Impaired judgment and planning
- Apathy
- Impaired insight (anosognosia)
- Loss of empathy and emotion recognition (alexithymia)

- Disinhibition
- Abnormal eating behavior
- Stereotypical or ritualistic behavior
- Personal neglect
Profanity use during letter fluency tasks can differentiate FTD from AD. Ringman JM et al. Cogn Behav Neurol 2010;23:159-64

“I'm not going to say the word I'm thinking of.”
<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>FTD</th>
<th>AD</th>
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<tbody>
<tr>
<td>Age of onset</td>
<td>Rarely &gt;75</td>
<td>Increases w age</td>
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<tr>
<td>Behavior &amp; Social problems</td>
<td>Early disinhibition, + socially inappropriate</td>
<td>Moderate-severe, increases with severity</td>
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<tr>
<td>Language</td>
<td>Isolated language problem</td>
<td>Language + memory</td>
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<tr>
<td>Visuospatial deficit</td>
<td>Rare in mild-moderate</td>
<td>Common</td>
</tr>
<tr>
<td>Motor signs</td>
<td>Common</td>
<td>Unusual</td>
</tr>
<tr>
<td>Mood</td>
<td>Alexithymia, withdrawal, verbal irritability, labile</td>
<td>Sadness, anhedonia</td>
</tr>
<tr>
<td>Psychotic features</td>
<td>Somatic, religious, bizarre delusions</td>
<td>Delusions increase with disease severity</td>
</tr>
<tr>
<td>Appetite/hunger/diet</td>
<td>Overeating, weight ↑↑; carbohydrate craving</td>
<td>Weight loss, anorexia; misses meals</td>
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>50% of FTD subtypes misdiagnosed as primary psychiatric disease


Figure. % of patients initially misdiagnosed prior to ND diagnosis

CST Cognitive pattern differentiates AD from FTD

Domain Specific Cognitive Patterns (DSCP) for MCI, EARLY AD, Mild to Moderate AD and FTD groups

- MCI
- Early AD
- Mild to Mod AD
- FTD

Crane, MK et al. Neurology. 2011 Suppl(March) 76;
VIDEO example of bvFTD alexithymia
VIDEO example of a bvFTD patient with a palmar grasp reflex
Frontotemporal dementia subtypes

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• Semantic dementia (SD)
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Boxer AL, Miller BL. Alzheimer Dis Assoc Disord. 2005;19 S1:S3-6
Semantic dementia (SD) or temporal variant

**LEFT predominance**
- Language features: fluent speech but loss of semantics (word choice)
- Reading declines, numbers intact

**RIGHT predominance**
- Severe deficits in understanding emotions; loss of empathy
- Difficulty recognizing faces and facial expression
- Eventually R-sided disease progresses to L with language features, and visa versa
- SD patients develop bvFTD behaviors
VIDEO example of semantic deficits
VIDEO example of bvFTD with phonetic fluency deficits
Frontotemporal dementia subtypes

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Boxer AL, Miller BL. *Alzheimer Dis Assoc Disord*. 2005;19 S1:S3-6
Progressive nonfluent aphasia (PNFA)

• 20% of FTD cases

• Hesitant, effortful speech; stutter or return of childhood stutter

• Anomia, agrammatism, sound errors (“gat” for “cat”)

• Eventually develop severe movement disorder that overlaps with PSP and CBD

Marcel Ravel, (1875-1937) French composer.
- in the early stages of PNFA/FTD when composing the orchestral work *Boléro* (1928).
Progressive nonfluent aphasia (PNFA)

Fig. Coronal T1 weighted MRI of mild and moderate PNFA
Case 1: mild PNFA, atrophy of temporal lobe & pars triangularis.
Case 2: moderate PNFA, global atrophy with L-sided and perisylvian predominance.
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Progressive supranuclear palsy (PSP)

- Progressive supranuclear palsy
  Deterioration of cells in the brainstem, frontal cortex and basal ganglia

Dudley Moore 1935-2002
Progressive supranuclear palsy (PSP) key features

- Postural instability and falls within first year of diagnosis
- Vertical supranuclear opthalmoparesis
  - Upward gaze paresis with abnormal saccadic eye movements
- Axial rigidity
- Cognitive decline
- Early stage difficult to distinguish from multiple system atrophy, Parkinson disease, and small vessel disease.
- Most patients with PNFA have PSP or CBD postmortem
PSP radiologic features

- Hypometabolism on FDG-PET in basal ganglia, brainstem, and frontal lobes
Midbrain atrophy in PSP

(A) Normal: convex upper border of the midbrain
(B) Severe atrophy of the midbrain with
• (C) concave upper border of midbrain “humming bird sign”.
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Boxer AL, Miller BL. *Alzheimer Dis Assoc Disord.* 2005;19 S1:S3-6
### Corticobasal Degeneration (CBD) Criteria

<table>
<thead>
<tr>
<th>Core Features</th>
<th>Supportive Features</th>
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<tr>
<td><strong>Cortical Dysfunction</strong></td>
<td>• Lateralized cognitive dysfunction with preserved memory and learning</td>
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<tr>
<td>– Asymmetric ideomotor apraxia</td>
<td>• MRI with asymmetric atrophy in parietal and frontal cortex</td>
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<tr>
<td>– Alien limb phenomenon</td>
<td>• FDG-PET decreased glucose uptake in parietal and frontal cortex, basal ganglia and thalamus.</td>
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<td>– Visual or sensory hemineglect</td>
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<td>– Focal or asymmetric myoclonus</td>
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<tr>
<td>– Non-fluent aphasia (overlap with PNFA)</td>
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<tr>
<td><strong>Extrapyramidal Dysfunction</strong></td>
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<tr>
<td>– Asymmetric rigidity lacking</td>
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<tr>
<td>sustained levodopa response, and focal dystonia</td>
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Pt1: Mild, focal atrophy of corpus callosum with mild hypometabolism in L frontoparietal cortex (arrow).

Pt2: Moderate atrophy of corpus callosum, moderate hypometabolism in L frontoparietal cortex (arrows).

Pt3: Severe, diffuse atrophy with bilateral hypometabolism accentuated in the right frontoparietal cortex (arrows).
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**FTD with motor neuron disease (FTD-MND)**

- ALS/CTE (Chronic Traumatic Encephalopathy)
  - Elevated levels of the TDP-43 protein have been found in CTE, and also been identified in patients with CTE, a condition that often mimics ALS and that has been associated with athletes who have experienced multiple concussions and head injury.
FTD with motor neuron disease (FTD-MND)

FTD-MND is a CLINICAL PHENOTYPE:
- 15% of FTD patients also have FTD-MND
- FTD-MND co-occurs in patients with bvFTD but rare in PNFA, CBD, PSP

- Early cognitive and behavioral changes with MND symptoms:
  - slurring of speech, difficulty swallowing, choking
  - Autonomic dysfunction
  - limb weakness or muscle wasting

- Patients live ≈ 1.4 years after diagnosis (respiratory complications of bulbar symptoms as cause of death)

- Most common MND is amyotrophic lateral sclerosis (ALS); older ALS patients may also have behavioral or cognitive problems similar to those seen in FTD (FTD-ALS syndrome)
Results of MRI voxel-based morphometry analyses: behavior & language dominant FTD-MND analysis compared to control.


Coon E et al. Neurology 2011;76:1886-1892
Neuropathology and Genetics
FTD inheritance

Genetic (40%)

- Approximately 20-50% of FTD patients have an affected 1st degree relative.

- Familial FTD is suspected when 2+ family members are affected in 2+ generations.

- Among individuals with FTD, approximately 10% have a single gene mutation (autosomal dominant inheritance).

Sporadic (60%)

- 50-80% of individuals appear to be the first person with FTD in the family, also called sporadic or nonfamilial FTD (family not at risk).
Frontotemporal Lobar Degeneration (FTLD) is the pathologic confirmation of clinical FTD

FTLDs are histopathologic diagnosis with neuronal loss & gliosis, spongiosis & ballooned neurons (image below).

Abnormal protein inclusions in neurons & glial cells.

- **Tauopathies**: FTLD with tau+ inclusions

- **TDP-43 proteinopathies**: FTLD with tau-, alpha-synuclein- inclusions which contain the protein TDP-43 + conjugated with ubiquitin+

- **FUS**: tau-, ubiquitin+, TDP-43-, with fused in sarcoma (FUS) inclusions
Tau immunopositive inclusions and neurofibrillary tangles (NFTs) in tauopathy family of FTLDs

Pick inclusion bodies: tau-positive spherical cytoplasmic neuronal inclusions, composed of straight filaments

NFTs and neuritic threads (arrow) in the gray matter of the frontal cortex.

Perinuclear inclusions of (asterisk) within the frontal cortex

BIGGEST ADVANCE in ALS and FTD

- Chromosome 9 open reading frame 72 (C9ORF72) gene mutation most common cause of familial ALS and FTD
  - Toxic buildup of RNA
  - Similar to other ALS genes but not SOD1
  - 40% of familial ALS of European descent
  - 15% of familiar ALS SOD1 mutation
  - Same expansion in 12% familial FTD and 3% sporadic FTD, 4% in sporadic ALS!


Trained in mathematics, chemistry and biology, Anne Adams, PhD decided to leave her career in science (1986) to care for a family member and to take up art.

In 1994, she became fascinated with the music of Ravel, and thus painted “Unravelling Boléro” a work that translated the famous musical score into visual form.

Ironically, Ravel was in early PNFA when composing Boléro. Both Adams and Ravel died from complications of PNFA/FTD.
Anne Adams, *Unravelling Boléro, 1994*
Each vertical figure represents a bar of music, with height corresponding to volume. The theme repeats & builds until a change to orange/pink, representing the key change preceding the dramatic conclusion.

At the time of this painting, Adams was nearly mute taking 10-15 seconds to initiate a word and was formally diagnosed with PNFA.

Adams then developed a shuffling gait, R limb apraxia and dystonia, and stopped all verbal communication. She died in 2007 from advanced FTD with motor and respiratory symptoms.

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Special recognition goes to my clinical mentor, Dr. John Dougherty, as well as to the neurologists and clinical team at Cole Neuroscience Center.