Clinical Update and Overview of FTD Disorders

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Johns Hopkins SOM
Disclosures:

- PI/CI of NIH and ADDF studies of dementia treatments
  - Low-dose lithium for behavioral disorder in FTD
- PI/CI of industry sponsored clinical trials for AD and FTD
  - TRx237-007 (NCT01626378) for FTD

Outline:

- The clinical spectrum of FTD
- Diagnosis and clinical care
- Treatment development
Dementia

Loss of thinking/behavioral skills:
- Memory
- Reasoning
- Social awareness
- Judgment
- Orientation
- Speech/language, etc.

Alzheimer disease
- Forgetting
- Confusion
- Disorientation
- Anxiety

FTD
- Misbehavior
- Aloofness/indifference
- Loss of communication skills
- Motor problems

Vascular
- Irritability
- Anxiety, depression
- Inattention
- Forgetting
- Problems speaking
- Problems walking

Lewy body dementia
- Forgetting
- Confusion
- Inattention
- Hallucinations
- Paranoia
- Parkinsonism
- Unsteadiness and falls

Others
- CJD
- Autoimmune
- Parkinson disease
- Huntington disease
- Etc.
Classical definition of frontotemporal dementia (FTD)
Onyike et al., 2011; Onyike & Diehl-Schmid, 2013

“...hallmarks are progressive decline in [conduct]: coarsening of temperament, dispositions, judgment, and comportment; dysregulation of emotions, drives and self-control; and disintegration of language and communication...”

“Thus results a behavioral phenotype beginning with combinations of indifference, impatience, carelessness, jocularity, insensitivity, distractibility, impulsiveness, stereotyped behaviors, compulsions and rigid routines; or language phenotypes featuring either effortful, dysfluent, agrammatical speech, plus impaired comprehension of sentences, or fluent, vacuous speech, with anomia and word (and object) agnosia”.
Other clinical types

- FTD with amyotrophic lateral sclerosis, FTD-ALS
  - Aberrant conduct
  - Executive dysfunction
  - Aphasia
  - Progressive spastic paralysis

- Corticobasal degeneration, CBD
  - Executive dysfunction
  - Apraxias
  - Aphasia
  - Parkinsonism

- Progressive supranuclear palsy, PSP
  - Executive dysfunction
  - Psychiatric states
  - Imbalance
  - Parkinsonism

- Amnestic FTD
  - Pronounced amnesia
  - Aberrant conduct
Histopathology in FTD  Bang et al., 2015

FTLD-tau:  (A) Pick bodies in Pick’s disease;  (B) a tufted astrocyte in PSP;  (C) an astrocytic plaque in CBD.

FTLD-TDP:  (E) small compact or crescentic cytoplasmic inclusions and short neuropil threads in FTLD-TDP type A;  (F) diffuse or granular cytoplasmic inclusions in FTLD-TDP type B; and  (G) long, tortuous dystrophic neurites in FTLD-TDP type C. TDP is seen in the nucleus in neurons lacking inclusions and localized to the cytoplasm as inclusion bodies in FTLD-TDP.

Other FTLD types are characterized by FUS-immunoreactive inclusions that stain negatively for tau and TDP-43; a vermiform neuronal nuclear inclusion in a dentate gyrus granule cell is shown (D); this neuron contains an ovoid cytoplasmic inclusion.

Small juxtanuclear ubiquitin-positive, TDP-negative inclusions (H) are pathognomonic of C9orf72 FTLD and contain dipeptide repeat proteins.  

Methods: Immunostains are 3-repeat tau (A), phospho-tau (B and C), FUS (D), TDP-43 (E–G) and ubiquitin (H). Sections are counterstained with haematoxylin.
## Genetic basis of hereditary FTD

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>%</th>
<th>Pathologic type</th>
<th>Clinical type</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAPT</td>
<td>17q21</td>
<td>20-25</td>
<td>Tau +</td>
<td>FTD ± parkinsonism; PNFA; CBD; PSP</td>
</tr>
<tr>
<td>PGRN</td>
<td>17q21</td>
<td>20-30</td>
<td>TDP43 +</td>
<td>FTD; SD</td>
</tr>
<tr>
<td>C9ORF72</td>
<td>9p21</td>
<td>25-40</td>
<td>TDP43 +</td>
<td>FTD; FTD-ALS; ALS; amnesic; psychiatric</td>
</tr>
<tr>
<td>CHMP2B</td>
<td>3p11.2</td>
<td>&lt;1</td>
<td>Ubiquitin +, Tau −, TDP43 −</td>
<td>FTD</td>
</tr>
<tr>
<td>VCP</td>
<td>9p13</td>
<td>&lt;1</td>
<td>TDP43 +</td>
<td>IBMPFD</td>
</tr>
<tr>
<td>TBK1</td>
<td>12q14.1</td>
<td>&lt;1</td>
<td>TDP43 +</td>
<td>FTD; FTD-ALS; ALS</td>
</tr>
</tbody>
</table>
Spectrum of FTD

**CLINICAL**
- PSP
- CBD
- PNFA
- bvFTD
- SD
- FTD-ALS

**PATHOLOGICAL**
- MAPT
- PGRN
- C9ORF72
- TARDBP
- TBK1

**GENETIC**
- CHMP2B

Legend:
- Movement
- Language
- Behavior
Penetrance for PGRN, MAPT and C9ORF72 mutations show larger similar profiles and time course.

TMEM106B variants influence disease penetrance in carriers of PGRN and C9ORF72 mutations. van Deerlin et al., 2010; Finch et al., 2011; van Blitterswijk et al., 2014.

C9ORF72 repeat length has not been shown to influence penetrance or phenotype. Rutherford et al., 2012.
Progression of FTD
Karageorgiou & Miller, 2014, slide courtesy of V. Kamath, PhD

- **EARLY**
  - Aberrant conduct
- **INTERMEDIATE**
  - Poor hygiene
  - Stereotypies
- **ADVANCED**
  - Poor memory
  - and orientation

- Behavior
- Executive
- Language
- Memory
- Visuospatial

STAGE

IMPARIEMT
### Summary of mean survival in FTD

**Kansal et al., 2016**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Onset</th>
<th>Sample</th>
<th>N</th>
<th>Died</th>
<th>Mean survival [95% CI]</th>
</tr>
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<tbody>
<tr>
<td>AD</td>
<td>70</td>
<td>C</td>
<td>479</td>
<td>98</td>
<td>6.86 [5.56, 8.15]</td>
</tr>
<tr>
<td>bvFTD</td>
<td>59</td>
<td>C</td>
<td>73</td>
<td>15</td>
<td>8.17 [7.52, 8.83]</td>
</tr>
<tr>
<td>bvFTD</td>
<td>60</td>
<td>C</td>
<td>81</td>
<td>42</td>
<td></td>
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<tr>
<td>bvFTD</td>
<td>60</td>
<td>C</td>
<td>48</td>
<td>12</td>
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<tr>
<td>bvFTD</td>
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<td>C</td>
<td>354</td>
<td>242</td>
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<tr>
<td>bvFTD</td>
<td>60</td>
<td>C</td>
<td>61</td>
<td>20</td>
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<tr>
<td>bvFTD</td>
<td>57</td>
<td>C</td>
<td>120</td>
<td>47</td>
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<tr>
<td>bvFTD</td>
<td>56</td>
<td>A</td>
<td>26</td>
<td>26</td>
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</tr>
<tr>
<td>PNFA</td>
<td>65</td>
<td>C</td>
<td>22</td>
<td>7</td>
<td>8.11 [6.81, 9.41]</td>
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<tr>
<td>PNFA</td>
<td>64</td>
<td>C</td>
<td>101</td>
<td>36</td>
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<tr>
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<tr>
<td>SD</td>
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<td>C</td>
<td>21</td>
<td>3</td>
<td>7.45 [5.40, 9.50]</td>
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<tr>
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<td>59</td>
<td>A</td>
<td>9</td>
<td>9</td>
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<tr>
<td>PPA</td>
<td>63</td>
<td>C</td>
<td>49</td>
<td>34</td>
<td>6.50 [4.82, 8.18]</td>
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<tr>
<td>FTD-ALS</td>
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<td>C</td>
<td>56</td>
<td>53</td>
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<tr>
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<td>15</td>
<td>2.50 [1.63, 3.37]</td>
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<tr>
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<td>A</td>
<td>9</td>
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<tr>
<td>PSP</td>
<td>63</td>
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<tr>
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<td>C</td>
<td>162</td>
<td>98</td>
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<tr>
<td>PSP</td>
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<td>C</td>
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<tr>
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<td>C</td>
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<tr>
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<td>A</td>
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<tr>
<td>PSP</td>
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<td>A</td>
<td>11</td>
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</tr>
<tr>
<td>CBD</td>
<td>64</td>
<td>C</td>
<td>18</td>
<td>8</td>
<td>6.40 [5.12, 7.67]</td>
</tr>
<tr>
<td>CBD</td>
<td>61</td>
<td>A</td>
<td>9</td>
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</tr>
<tr>
<td>CBD</td>
<td>67</td>
<td>A</td>
<td>10</td>
<td>10</td>
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</tr>
</tbody>
</table>

**Summary:**
- Mean survival: 2.5 years in FTD-ALS to 8.2 in bvFTD
- Median survival: 2.8 in FTD-ALS to 12.2 in SD
- FTD-ALS aside, survival in FTD is comparable to that in AD

**Slow progression FTD:**
- bvFTD-like, minimal progression, no cortical atrophy and normal ADL scores – “FTD phenocopy”. *Kipps et al., 2007*
- Parent and child with 20+ years of bvFTD, autopsy-confirmed. *Brodtmann et al., 2013*
- Slow progression (C9ORF72+)
  - bvFTD pedigree of 30+ years *Gomez-Tortosa et al., 2013*
- 4 of 87 (with 2 C9ORF72+) in UCSF series: bvFTD for >5 years, no decline in ≥2 years since first visit, no atrophy on MRI at latest visit *Khan et al., 2012*
Evaluation schema

1. Presentation
2. Chronology
3. Tempo
4. Complications

Exam
Scales
Labs
CSF
EEG
MRI & FDG-PET
Genetics
Psychometry
Amyloid & tau
QEEG
Amyloid- & tau-PET
History illustration

Clinical timeline

Onset at age 70: abnormal conduct + distractibility

- Word searching
- Semantic paraphasia
- Preference for sweets
- Gorging
- Dysphagia

70

71

Diminished energy

Dysarthria

72

Reduced speech output

Mild left upper limb weakness

Anathria

Choking

FINIS

73

Gait apraxia, falls

Mild limb weakness

First visit

Low speech spontaneity

Dysfluent and vacuous

Verbal stereotypy

Impaired repetition

Impaired word and sentence comprehension

No spelling errors

Still ambulant

Wrote last email
<table>
<thead>
<tr>
<th>Test</th>
<th>Domain</th>
<th>Comments</th>
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<tbody>
<tr>
<td>MMSE</td>
<td>Cognition</td>
<td>Widely known and takes 5-10 minutes to administer.</td>
</tr>
<tr>
<td>MoCA</td>
<td>Cognition</td>
<td>Widely available; takes ~10 minutes. Very sensitive in the early stages</td>
</tr>
<tr>
<td>ACE</td>
<td>Cognition</td>
<td>Better known in Europe and Asia; Takes 15-20 minutes</td>
</tr>
<tr>
<td>FRS</td>
<td>Illness severity</td>
<td>Used in studies to measure severity; takes &gt;20 minutes</td>
</tr>
<tr>
<td>NPI; NPI-Q</td>
<td>Behavior</td>
<td>Widely used; measures many behaviors – but not that define FTD</td>
</tr>
<tr>
<td>FAB</td>
<td>Behavior</td>
<td>Developed for FTD; may help distinguish FTD from AD in the clinic</td>
</tr>
<tr>
<td>CDR; CDR7</td>
<td>Illness staging</td>
<td>Widely used; in-person and online training available; Modified version for FTD</td>
</tr>
</tbody>
</table>
Brain imaging patterns in FTD

Onyike CU, from the JH FTD-YOD Clinic archives
Quantitative MRI in FTD
Harper et al, 2015

- Development aspects
  - Select ROI
  - Display ROI
  - Define increments
  - Set up training
  - Validate method

- Rater reliability:
  - Inter: 0.62-0.91
  - Intra: 0.71-0.83
PET-ligand imaging in FTD

Ghetti et al., 2015

[F18]-T807 ligand PET in a 56 year-old affected carrier or the P301L MAPT mutation
Clinical decision tree

Devineni and Onyike, 2015; Onyike, 2016
## Basics of dementia care

*Onyike & Huey 2013; Wylie et al., 2013*

<table>
<thead>
<tr>
<th>Problem</th>
<th>Role</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease/disorder</td>
<td>Diagnose</td>
<td>Provide evaluation, direct investigation, make referrals</td>
</tr>
<tr>
<td>Disability, crisis</td>
<td>Solve problems</td>
<td>Crisis interventions and psychosocial/rehabilitative care</td>
</tr>
<tr>
<td>Distress</td>
<td>Provide relief</td>
<td>Make prescriptions</td>
</tr>
<tr>
<td>Demoralization, stress</td>
<td>Guidance</td>
<td>Provide clarification, support and direction</td>
</tr>
</tbody>
</table>
Tailored care

Curative
- Preventive care
  - Target ligands
  - Pluripotent cells

Ameliorative
- Neuromodulators
- Psychotropics
- Psychotherapies

Rehabilitative
- Psychotherapies
- Psychosocial programs
- Physiotherapies
- Carer skills programs

Palliative
- Dietary interventions
- Home services and equipments
Social/behavioral interventions

Belle et al., 2006; Gitlin et al., 2010; Nichols et al., 2011; McKinnon et al., 2013; Mioshi et al., 2013; Wylie et al., 2013; O’Connor et al., 2014; Samus et al., 2014; Bier et al., 2015; Morhardt et al., 2015; Onyike, 2016

- Psychotherapeutic methods
  - Social engagement, structured and unstructured activities, use of distractors
  - Behavior remodeling
  - TAP: Tailored Activities Program
  - DICE: Describe, Investigate, Create, Evaluate
  - Problem-Solving Therapy approaches

- Care support programs
  - Clinic-based case management
  - ACT: Advancing Caregiver Training
  - REACH: Resources for Enhancing Alzheimer’s Caregiver Health
  - COPE: Care of Persons with Dementia in their Environment

- Rehabilitative devices and programs
  - Alarms, trackers, and smartphone and tablet apps
  - MIND@Home: Maximizing Independence in the Home
  - CARE-D: Care Pathway Model for Dementia
The DICE (Describe, Investigate, Create, Evaluate) Method
Onyike 2016, adapted from Kales et al., 2015

The care triad:
- Person
- Carers
- Environment

**Describe**
- Characterize the behavior and its context in interviews
- Check for imminent dangers and serious health problems or risks
  - High danger/risk
  - Increase supervision/observation
  - Prescribe psychotropic for agitation
  - Arrange urgent physician examination
  - Psychiatrist, neurologist or internist
  - Emergency department or hospital referral

**Investigate**
- Search for explanations
- Specify the factors - in the patient, caregiver and environment
  - High danger/risk
  - Increase supervision/observation
  - Prescribe psychotropic for agitation
  - Arrange urgent physician examination
  - Emergency department or hospital referral

**Create**
- Develop a collaborative plan of care
- Aim for a multifaceted plan of care to address all pertinent factors
  - High severity
  - Increase observation/supervision
  - Prescribe psychotropic, analgesic, antibiotic, etc.
  - Maintain hands-on physician participation

**Evaluate**
- Assess effectiveness of intervention
- Manage any adverse effects
- Revise plan of care as needed
- Monitor progress of recovery and for complications or new problems
# Pharmacologic (medication) interventions

Lebert et al., 1999; Moretti et al., 2002; Ikeda et al., 2004; Lebert et al., 2004; Huey et al., 2006; Cruz et al., 2008; Singam et al., 2013

<table>
<thead>
<tr>
<th>Treatment class</th>
<th>Pharmacologic type</th>
<th>Target</th>
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</thead>
<tbody>
<tr>
<td>Antidepressant</td>
<td>Bupropion</td>
<td>Inattention; depression</td>
</tr>
<tr>
<td></td>
<td>SSRI &amp; SNRI</td>
<td>Depression; anxiety; irritability; impulsions; compulsions</td>
</tr>
<tr>
<td></td>
<td>Mirtazapine</td>
<td>Dyssomnia/insomnia</td>
</tr>
<tr>
<td>Tranquilizers/sedatives</td>
<td>Benzodiazepines</td>
<td>Anxiety; agitation; aggression; myoclonus; REM sleep behaviors</td>
</tr>
<tr>
<td></td>
<td>Zolpidem</td>
<td></td>
</tr>
<tr>
<td>Stimulants</td>
<td>Amantadine</td>
<td>Inattention; perseveration</td>
</tr>
<tr>
<td></td>
<td>Methylphenidate</td>
<td>Inattention/distractibility</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Neuroleptics</td>
<td>Paranoia; hallucinations; irritability; agitation; aggression</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Topiramate</td>
<td>Hyperphagia; foraging</td>
</tr>
</tbody>
</table>
Brain stimulation protocols
Tsapkini et al., 2014; Cotelli et al., 2014; Manenti et al., 2015

• Transcranial direct current stimulation, tDCS
• Transcranial magnetic stimulation, TMS
• Electroconvulsive therapy, ECT

• Results:
  • tDCS + speech therapy $\rightarrow$ improved spelling in PPA + generalization of effects to untrained tasks (the latter not seen in placebo + therapy)
  • tDCS + speech therapy $\rightarrow$ improved naming in PPA compared to placebo + therapy
  • tDCS over left parietal cortex $\rightarrow$ shorter latency for naming actions in corticobasal syndrome (no effect with right-side stimulation or placebo)
Clinical trials on the horizon

Low-dose lithium
ClinicalTrials.gov ID#: NCT02862210
https://clinicaltrials.gov/ct2/show/NCT02862210

- Design:
  - RCT for agitation, aggression and disinhibited/compulsive behaviors
  - N = 60; 12 week Phase II trial
  - NPI ≥6; MMSE 5–26
  - Titration: 150, 300, 450 and 600 mg/day
  - Serum [Li] 0.2–0.6 mmol/L, sampling 12–14 h after last dose, blinded
  - Goals: change in agitation, aggression and restlessness scores

Intranasal oxytocin (FOXY)
ClinicalTrials.gov ID#: NCT01937013
https://clinicaltrials.gov/ct2/show/NCT01937013

- Design:
  - RCT for apathy/asocial states
  - N = TBD; 16 week Phase II trial
  - Entry based on diagnosis,
  - Dose finding phase (stage 1, weeks 1–6): placebo v. 24, 48 and 72 U
  - Stage 2 (weeks 11–16): placebo v. selected dose
  - Exclusion criteria relate to mimics of diagnosis or behaviors, and to compliance and safety
  - Goals: change in NPI apathy and IRI empathy scores.
Candidate mechanisms for drug targeting
Nalbandian et al., 2011; Cleary and Ranum, 2013; Ling et al., 2015; Mis et al., 2016

- Dysregulation of cellular repair → apoptosis
- Tau polymerization → disruption of axonal transport
- Dysfunction of endosomal trafficking and autophagy
- Mitochondrial dysfunction – in MSP
- Activation of microglia and cytokines/interleukins
- Repeat associated non-ATG (RAN) translation – in C9 FTD/ALS, SCA8, DM1 and FXTAS – toxic dipeptide repeat proteins
- Compromise of TDP43 repression of non-conserved cryptic exons
- Prion-like propagation of neuropathology vs. regional differences in proteinopathy expression
How you can participate

• ARTFL/LEFFTDS centers
  • Observational studies
  • Genetics


• FTD Registry: [https://ftdregistry.org](https://ftdregistry.org)

• Neuropathology: FTD centers, ADRCs

• At Johns Hopkins:
  • Clinic: +1-410-502-2981
  • ARTFL: +1-410-502-5816
  • Trials: +1-410-550-9020

• Support groups: [http://www.theaftd.org/get-involved/regions](http://www.theaftd.org/get-involved/regions)
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