Frontotemporal lobar degeneration

Clinical Approaches and Preparation for Clinical Trials

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51 year old man with four years of personality change
Disclosures

• Consultant
  – Ionis pharmaceuticals
  – Wave neuroscience

• Investigator
  – Biogen pharmaceuticals

• Feel like a consultant for Mars, Heshey’s Inc.
Frontotemporal dementia
Behavioral variant of frontotemporal dementia (bvFTD)

- Clinical Features
  - Disinhibition/antisocial behavior
  - Loss of concern for others
  - Exceedingly poor judgment
  - Overeating
  - Compulsive behaviors (collecting)
  - Loss of executive control
  - Apathy
Overview

• Brief review of FTLD
  – Clinical
  – Pathological
  – Genetic

• Ongoing studies to prepare for clinical trials
  – ALLFTD
Frontotemporal lobar degeneration (FTLD)

• **Group of disorders**
  – Overarching term

• **Original term**
  – Neary et al, 1998
  – Circumscribed progressive deterioration of the frontal and/or temporal lobes
  – Three clinical syndromes
3 traditional clinical variants of FTLD

- Behavioral variant
  - Also: “Frontal variant” FTD “FTD”

- Language variants
  - Semantic variant
  - Nonfluent variant
Orbitofrontal cortex (inhibition)

Anterior cingulate cortex (drive)

Dorsolateral PFC (Executive control)
Traditional Frontal Neuropsychology: Mostly dorsolateral frontal

- Working memory (BA46) – digit back
- Generation – letters, animals, shapes
- Inhibition – Stroop, antisaccade, flanker task
- Alternate sequence – dorsolateral – Trails B
- Combination – Card sorts
- Abstraction – proverbs
The frontal lobes are important for regulation of social behavior

Phineas Gage, 1823 - 1860
Gage had a dramatic change in personality after the accident

...because his personality had changed so much, the contractors who had employed him would not give him his place again. Before the accident he had been their most capable and efficient foreman, one with a well-balanced mind, and who was looked on as a shrewd smart business man. He was now fitful, irreverent, and grossly profane, showing little deference for his fellows. He was also impatient and obstinate, yet capricious and vacillating, unable to settle on any of the plans he devised for future action. His friends said he was “No longer Gage.”
FTD is associated with bizarre socioemotional changes because of its specific neuroanatomy

Regions of gray matter atrophy in FTD and AD

FTD vs. Controls
AD vs. Controls

• p<0.05, corrected for multiple comparisons
3 traditional clinical variants of FTLD

- Behavioral variant
- Language variants
  - Semantic variant
  - Nonfluent variant

Also:
“Frontal variant” FTD
“FTD”
Semantic variant of Primary Progressive Aphasia (svPPA)

- Profound anomia
- Problems with word comprehension
- Fluent, empty speech
- Trouble with object recognition (agnosia)
- Trouble with recognition of familiar/famous faces
3 traditional clinical variants of FTLD

- **Behavioral variant**
- **Language variants**
  - Semantic variant
  - Nonfluent variant

Also:
- “Frontal variant” FTD
- “FTD”
Nonfluent variant of Primary Progressive Aphasia (nfvPPA)

- Hesitant, non-fluent, Broca-like speech
- Agrammatism
  - Decreased use of function words
  - Sometimes “telegraphic” speech
- Articulation difficulties
  - Difficulty with individual words
  - Speech apraxia
Common feature across these syndromes is pathology

- **Nomenclature**
  - Frontotemporal lobar degeneration (FTLD)

- **Two main pathologies (intracellular inclusions)**
  - Tau – ~48%
  - TDP-43 – ~50%
  - Fused in sarcoma (FUS) – ~2%

- **Other disorders previously not linked to FTLD have same pathology**
  - Tau
    - Movement disorders (Parkinson’s plus)
      - Progressive supranuclear palsy (PSP)
      - Corticobasal degeneration (CBD)
    - Chronic Traumatic Encephalopathy (CTE)
    - Argyrophilic grain disease (AGD)
  - Tar DNA binding protein 43 (TDP-43) pathology
    - Amyotrophic lateral sclerosis
Etiology of FTLD is unknown

- ~ 70% sporadic (sFTLD)
- ~ 30% familial (fFTLD)
  - family history suggesting autosomal dominant inheritance

Multiple mutations have been identified
- Chromosome 9 open reading frame 72 (C9orf72) – 25%
- Progranulin protein (GRN) – 5-20%
- Microtubule associated protein tau (MAPT) – 10-20% – <2%
- Valosin Containing Protein (VCP) – <2%
- Charged multivesicular body protein 2B (CHMP-2B) – <2%
- Tar DNA binding protein 43 (TDP-43) – <2%
- Fused in Sarcoma (FUS) – <2%
- Tank Binding Kinease 1 (TBK1) – <2%

Likely more to be discovered
- ? 50% of familial cases without identified mutation
Variable links between clinical features and pathology

<table>
<thead>
<tr>
<th>Tau</th>
<th>TDP-43</th>
<th>Mutation-clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Almost) Always tau</td>
<td>(Almost) Always TDP</td>
<td>C9orf72</td>
</tr>
<tr>
<td>PSP</td>
<td>ALS</td>
<td>ALS</td>
</tr>
<tr>
<td>MAPT mutations</td>
<td>svPPA</td>
<td>bvFTD common</td>
</tr>
<tr>
<td>CTE*</td>
<td>GRN mutations</td>
<td>Any of other syndromes</td>
</tr>
<tr>
<td>Pick’s disease*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commonly tau (more than 50%)</td>
<td>Sometimes TDP</td>
<td>GRN</td>
</tr>
<tr>
<td>CBD</td>
<td></td>
<td>Language disorders common</td>
</tr>
<tr>
<td>Sometimes tau</td>
<td></td>
<td>Any syndrome other than ALS</td>
</tr>
<tr>
<td>bvFTD (50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nfvPPA (50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C9orf72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>svPPA rare in any mutation</td>
</tr>
</tbody>
</table>

* Pathologically defined disease, specific clinical features not established
FTLD is not uncommon

- **Common cause pre-senile dementia**
  - 1:1 with AD 45-64 years (Ratnavalli, Hodges 2002)
  - More common than AD below 60 yrs (Knopman 2004)

- **Rare after 70?**
  - 3% clinical prevalence of FTD 80-90 (2003 Skoog)
  - Include diseases with similar molecules: PSP, CBD, ALS even more common
  - Association TDP-43 & cognition independent of plaque, hippocampal sclerosis (Nelson 2008)
  - Tau and TDP-43 major proteins in “chronic traumatic encephalopathy” NFL football players’ dementia (also found following war trauma)
New mechanisms in FTLD: development

Increased likelihood of left-handedness in svPPA (and lvPPA)
New mechanisms in FTLD: development

Association between FTLD and STEM professions

- Nearly 1 in 5 FTD STEM occupation
- STEM careers in FTD are nearly 3x that of AD & PSP and population estimates (p<0.001)
New mechanisms in FTLD: immune activation

- Autoimmune diseases 3x more likely in TDP-43 FTLD than expected
  - Inc TNF-alpha in svPPA and GRN

Z Miller et al, JNNP, 2013
FTLD and immune diseases share genetic risk in HLA regions

Broce et al, PLoS Medicine, 2018
Misdiagnosis of FTLD: Alzheimer’s disease

- Executive function ➔ Frontal disorder ➔ FTD
  - Disorganization
  - Distraction
  - Poor planning
  - Poor performance on cog testing (executive fxn)

- Progressive aphasia ➔ FTLD
  - IvPPA
Logopenic variant of primary progressive aphasia (lvPPA)

- Hesitant, nonfluent speech
  - Particularly due to word finding
- Islands of preserved speech/phrases
- Relatively good articulation
- Relatively poor comprehension
- Pathology is usually Alzheimer’s disease
IpvPPA
Rates Psychiatric Diagnosis within each Neurodegenerative Disease

- bvFTD (n=69)
- AD (n=65)
- svPPA (n=41)
- nfvPPA (n=17)
- CBD (n=25)
- PSP (n=15)
- ALS (n=20)

Regions of Atrophy in FTD (Rosen et al, Neurology, 2002)

Regions atrophy Bipolar disorder (meta-analysis Bora et al, Biol Psych, 2010)
Diagnosis if primarily clinical

- Sensitivity and specificity above 80%
  - Autopsy-confirmed cases
Biomarkers in diagnosis: Amyloid Imaging

- Differentiate AD vs FTLD
- Not helpful for:
  - FTLD protein prediction
  - Early diagnosis/prediction

Rabinovici et al, Neurology, 2007
Rabinovici et al, Neurology, 2011
Plasma measures of AD-related proteins are on the horizon (currently experimental).

**Plasma abeta-42**

ROC curve:

- hPlasma Ab42:40 conc. ratio
- AUC = 0.8865
- P value <0.0001

**Plasma p-tau**

Ovod et al, Alz & Dem 2017

Thijssen et al, submitted, courtesy of Adam Boxer
Neurofilament light chain (NfL): a marker of neuronal injury

• Several diseases
  – Multiple sclerosis
  – Traumatic brain injury
  – Amyotrophic lateral sclerosis
  – HIV

Elevated in FTLD

Correlates with degree of brain atrophy

Plasma and CSF levels correlate

Scherling et al, Ann Neurol 2014

NfL separates bvFTD from psychiatric disorders

Figure 1. Serum neurofilament light chain (Nfl) differentiates bvFTD from primary psychiatric disorders. (A) Serum Nfl levels in CON (27), BI (11), SCZ (11), DP (28), bvFTD (20). (B) ROC curve showing the diagnostic performance of Nfl in bvFTD-CON, bvFTD-BI, bvFTD-SCZ, and bvFTD-DP. The AUC values and corresponding p-values are provided for each group.
Symptoms of FTLD represent end of a long process

Risk/Mutation → Biochemical Changes → Early pathological changes → Neural systems Dysfunction

Non-carriers
Presymptomatic Carriers
Symptomatic Carriers

Detectable change in cog/behavioral function

Presymptomatic Symptomatic
Familial FTLD (fFTLD) is becoming an important focus for studies of FTLD

• Recruit participants before symptoms develop
  – Identify predictive markers
  – Prepare for studies of prevention

• Specific/predictable mechanisms
  – Related to each mutation
New studies are addressing the full spectrum of FTLD

- ARTFL-LEFFTDS Longitudinal FTLD (ALLFTD)
  - 19 sites
  - Familial FTLD
    - >650 participants (symptomatic, asymptomatic)
  - Sporadic FTLD
    - >750 cases
Baseline atrophy predicts risk of conversion to dementia

Individualized atrophy maps (w-score)

Supervised classification algorithm (logistic regression)

Prospective prediction of conversion to dementia

Imaging based dementia classification

Imaging-based dementia prediction score

Baseline atrophy predicts risk of conversion to dementia
NfL is also elevated in fFTLD

Non-carriers  C9orf72  GRN  MAPT

Confidential—not for distribution
NfL also predicts higher rate of decline in fFTLD

Rojas et al, submitted
Current treatment of FTLD

- Symptomatic management
  - SSRIs (e.g. citalopram)
  - Trazadone
  - Atypical antipsychotics
  - AVOID cholinesterase inhibitors in bvFTD
    - May exacerbate symptoms/increase agitation
- Specific treatment
  - Trial of memantine failed
- Speech therapy for language disorders
  - Under investigation
# Variety of treatments being investigated

<table>
<thead>
<tr>
<th>Table 1. Potential FTLD Therapeutics</th>
<th>Mode of Action</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GRN-targeted therapeutics</strong></td>
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<td></td>
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<tr>
<td>FRM-0334</td>
<td>HDAC inhibitor</td>
<td>Phase 2 (negative)</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Vesicular pH modulator</td>
<td>Repurposed</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Increased progranulin secretion</td>
<td>Repurposed; phase 1b (neg)</td>
</tr>
<tr>
<td>AL-001</td>
<td>Anti-sortilin mAb</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Proprietary A, B</td>
<td>HDAC inhibitor</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Proprietary A-C</td>
<td>AAV gene therapy</td>
<td>Preclinical</td>
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<tr>
<td><strong>C9orf72 therapeutics:</strong></td>
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<tr>
<td>Proprietary A, B</td>
<td>C9orf72 antisense oligos</td>
<td>Phase 1 ALS; FTLD planned</td>
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<td><strong>Tau-targeted therapeutics:</strong></td>
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<td></td>
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<tr>
<td>LMTX (Methylene Blue)</td>
<td>Protein clearance activator</td>
<td>Phase 3 (neg. for bvFTD)</td>
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<tr>
<td>Lithium carbonate</td>
<td>GSK inhibitor</td>
<td>Phase 2 FTD</td>
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<tr>
<td>Abeotaxane (TPI-287)</td>
<td>microtubule stabilizer</td>
<td>Phase 1 (neg. for CBD, PSP)</td>
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<tr>
<td>Salsalate</td>
<td>Tau acetylation inhibitor</td>
<td>Phase 1 PSP; abandoned</td>
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<tr>
<td>ABV-8E12</td>
<td>N-terminal anti-tau mAb</td>
<td>Phase 2 PSP</td>
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<tr>
<td>BIIB092</td>
<td>N-terminal anti-tau mAb</td>
<td>Phase 2 PSP</td>
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<tr>
<td>BIIB092</td>
<td>N-terminal anti-tau mAb</td>
<td>Phase 2 PSP</td>
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<tr>
<td>BIIB092</td>
<td>Active anti-tau vaccine</td>
<td>Phase 1: nfvPPA</td>
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<tr>
<td>AADVac1</td>
<td>Mid-domain anti-tau mAb</td>
<td>Phase 1</td>
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<tr>
<td>UCB0107</td>
<td>0-GlcNAcase inhibitor</td>
<td>Phase 1 AD</td>
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<td>IONIS-MAPTrx</td>
<td>Antisense oligonucleotide</td>
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<td><strong>Other (Immunomodulatory, neuroprotective therapeutics):</strong></td>
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<tr>
<td>NP001</td>
<td>Macrophage activation inhibitor</td>
<td>Phase 2 ALS negative</td>
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<tr>
<td>DLZ Kinase inhibitor</td>
<td>Neuroprotective agent</td>
<td>Phase 1 ALS</td>
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<td><strong>Palliative Approaches:</strong></td>
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<tr>
<td>Oxytocin</td>
<td>Symptomatic improvement</td>
<td>Phase 2 bvFTD</td>
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<td>Rivastigmine</td>
<td>Cholinesterase inhibitor</td>
<td>Phase 2 PSP</td>
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<tr>
<td>Transcranial DC stim</td>
<td>Electric current stimulation</td>
<td>N/A (pilot) bvFTD, PPA</td>
</tr>
<tr>
<td>Transcranial magn. stim</td>
<td>Magnetic field stimulation</td>
<td>PPA</td>
</tr>
</tbody>
</table>

Boxer et al, Alz & Dem, in press
Antisense oligonucleotides (ASO’s) are a powerful new form of treatment

- Pipelines targeted at:
  - Cardiac disorders/HTN
  - Metabolic/renal disorders
  - Cancer
  - Infectious diseases
  - Rare inherited disorder
  - Neurological disorders
ASO’s reduce expression of tau

Reduced human tau mRNA, reduced tau deposition, hippocampal volume loss and increased survival, nesting behavior.

DeVos et al 2017
ASO’s provided the first disease modifying treatment for a neurodegenerative disease.
Guidance on diagnosis, management and resources
CADC dementia diagnosis toolkit

- Support diagnosis
- Multiple components
  - Instructions
  - Brief probe for complaints
  - Full assessment
- Differential diagnosis
  - Questions and interpretation
    - Scripts
    - Disclosure
    - Driving
    - Treatment
- Billing guidance
Conclusions

• FTLD includes a number of clinical syndromes
  – Linked by shared set of pathologies
• Diagnosis is primarily clinical
  – Support is available to facilitate
  – Biomarkers available, more coming
• Genetic causes are common
  – Helping to understand entire course of illness
The A/L/ALLFTD Consortium

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