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

Frontotemporal dementia
Behavioral variant of frontotemporal dementia (bvFTD)
3 traditional clinical variants of FTLD

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

Also:
- "Frontal variant" FTD
- "FTD"

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 fidgety, irrevocable, 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."
3 traditional clinical variants of FTLD

Behavioral variant

Language variants

Semantic variant

Nonfluent variant

Also:

“Frontal variant” 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

svPPA

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

nfvPPA
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
• Two main pathologies (intracellular inclusions)
  - Tau
  - TDP-43
  - Neurodegeneration with brain iron accumulation (NBIA)
  - Amyotrophic lateral sclerosis (ALS)
  - Amyotrophic lateral sclerosis (ALS)

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%
  - Charge multivesicular body protein 2B (CHMP2B) — 2%
  - Tar DNA binding protein 43 (TDP-43) — 2%
  - Tank Binding Kinease 1 (TBK1) — 2%
  - Likely more to be discovered
  - ~ 30% familial cases without identified mutation

Variable links between clinical features and pathology

• Tau
  - (Almost) Always tau
    - PSP
    - MAPT mutations
    - CTE
    - Pick’s disease*
  - Commonly tau (more than 50%)
    - CBD
  - Sometimes tau
    - bvFTD (50%)
    - svPPA (20%)
• TDP-43
  - (Almost) Always TDP
    - ALS
    - GRN mutations
    - C9orf72
  - Sometimes TDP
    - bvFTD (25%)
    - svPPA (30%)
• Mutation-clinical
  - C9orf72
    - ALS
    - FTD common
    - Any of other syndromes
    - GRN
    - Language disorders common
    - Any syndrome other than ALS
    - MAPT
    - Any syndrome other than ALS
    - svPPA rare in any mutation

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 FTLD 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 svPPA)

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

FTLD and immune diseases share genetic risk in HLA regions

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
  - lvPPA

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

Misdiagnosis of FTLD: psychiatric illness
- Rates Psychiatric Diagnosis within each Neurodegenerative Disease
  - Men
  - Women
  - Total

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

Regions atrophy Bipolar disorder (meta-analysis Bogg et al, Biol Psych, 2016)

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

Plasma measures of AD-related proteins are on the horizon (currently experimental)

Plasma abeta-42

Plasma p-tau

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

Nfl separates bvFTD from psychiatric disorders
Symptoms of FTLD represent end of a long process

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

Non-carriers → Presymptomatic Carriers → Symptomatic Carriers

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
    - >500 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

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

### Table 1. Potential FTLD Therapeutics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mode of Action</th>
<th>Status</th>
<th>Notes</th>
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<tbody>
<tr>
<td>GRN-067</td>
<td>Targeted therapeutics</td>
<td>Phase 2 (negative)</td>
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<tr>
<td>FRM-0334</td>
<td>HDAC inhibitor</td>
<td>Phase 2 (negative)</td>
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<tr>
<td>Chloroquine</td>
<td>Vesicular pH modulator</td>
<td>Repurposed; phase 1 (negative)</td>
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<td>Nimodipine</td>
<td>Increased progranulin secretion</td>
<td>Repurposed; phase 1</td>
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<td>AL-001</td>
<td>Anti-sortilin mAb</td>
<td>Phase 1</td>
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<tr>
<td>Proprietary A</td>
<td>HDAC inhibitor</td>
<td>Preclinical</td>
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<tr>
<td>Proprietary B</td>
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<td>Preclinical</td>
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<tr>
<td>Proprietary C</td>
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<td>C9orf72</td>
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<td>Repurposed</td>
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<td>Proprietary A</td>
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<tr>
<td>Proprietary B</td>
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<tr>
<td>Proprietary C</td>
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<td>Tau-targeted therapeutics:</td>
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<td>LMTX (Methylene Blue)</td>
<td>Protein clearance activator</td>
<td>Phase 3 (negative) for bvFTD</td>
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<tr>
<td>Lithium carbonate</td>
<td>GSK inhibitor</td>
<td>Phase 2</td>
<td>FTD</td>
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<tr>
<td>Abeotaxane (TPI-287)</td>
<td>Microtubule stabilizer</td>
<td>Phase I (negative) for CBD, PSP</td>
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<td>Salsalate</td>
<td>Tau acetylation inhibitor</td>
<td>Phase 1</td>
<td>PSP; abandoned</td>
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<td>E12N-terminal anti-tau mAb</td>
<td>Phase 2</td>
<td>PSP</td>
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<td>BIIB092</td>
<td>N-terminal anti-tau mAb</td>
<td>Phase 2</td>
<td>PSP</td>
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<td>BIIB092</td>
<td>N-terminal anti-tau mAb</td>
<td>Phase 1</td>
<td>nfvPPA; planned</td>
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<td>AADvac1</td>
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<td>DLZ</td>
<td>Kinase inhibitor</td>
<td>Neuroprotective agent</td>
<td>Phase 1</td>
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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

ISS-N1 makes the First FDA-approved Drug for Spinal Muscular Atrophy

Wisconsin Alzheimer's Institute

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