Frontotemporal Degeneration: Translating Research Into Practice

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Objectives

• Review evolving construct of FTD:
  - Compare / contrast with AD
  - FTD is not a single disease entity

• Diagnosis: Phenotype → Biomarker

• Treatment: Symptomatic → Path.subtype specific
FTD Overview

- 5% of adult dementia cases, est. 20,000 affected individuals in US (similar to ALS)
- 50% of cases with onset <65 years old
- Multiple different clinical syndromes
- Multiple different pathological substrates
Fundamentals of FTD

- Frontotemporal *dementia* = clinical syndrome
- Frontotemporal (Lobar) *degeneration* = disease entity
- Clinical onset is variable: behavioral change, language disturbance, motor signs
- Clinical syndrome evolves over time e.g. language change initially, later motor and/or behavioral changes
- Useful to think of as a *dynamic process*
Pick’s Disease

• 1892: Pick described case of lobar atrophy affecting frontal and/or ant. temporal lobe

• 1911: Alzheimer describes pathological association to silver-staining “Pick bodies”
FTD Clinical Criteria

• 1970-80s: Pick’s disease
  Frontal Lobe Dementia w/o Pick bodies

• 1994: Lund-Manchester FTD Criteria
  - Pick’s disease
  - Frontal Lobe Degeneration type (e.g. DLDHF)
  - Motor Neuron Disease type

• 1998: Neary Criteria for Frontotemporal Lobar Degeneration (FTLD):
  - Frontotemporal Dementia (bvFTD)
  - Primary Progressive Aphasias (language)
• 2011 FDTC Criteria (Rascovksy et al, 2011):
  - Multicenter validation study in 176 autopsy-proven bvFTD subjects

  - **Possible**: 3/6 of: disinhibition / apathy / loss of empathy/ compulsions / hyperorality/ dysexecutive syndrome

  - **Probable**: above + functional disability or characteristic brain imaging
FTLD – Clinical Syndromes

- **Frontotemporal dementia** (bv FTD) – prominent behavior and personality changes (*right temporal-insular region*)

- **Progressive nonfluent aphasia** (PNFA) – early speech and language dysfunction (*left prefrontal cortical region*)

- **Semantic dementia** (SD) – loss of word and object meaning (*L>R anterior temporal region*)
FTD – Treatment

- No proven therapies, empiric symptomatic Rx
- Cholinesterase-inhibitors? (? AD or FTD)
- Trazadone for agitation (Lebert et al, 2004)
- SSRIs for obsessive-compulsive behaviors (sweet craving, ritualistic behavior, etc.)
- Open-label trial of memantine suggests possible therapeutic benefit on behavior; multicenter placebo-controlled trial underway
Clinical Assessment of Behavior

- Neuropsychiatric Inventory (NPI) (Cummings et al, 1994): caregiver interview of 12-behavioral symptoms in dementia

- NPI Distress Scale (Kaufer et al, 1998): measure of caregiver distress for each behavioral symptom present

- NPI-Questionnaire (NPI-Q): (Kaufer et al, 2000): short-form of NPI designed for clinical practice
Apathy / Disinhibition / Irritability most prominent and most distressing

Average Reported Caregiver Ratings

Behavioral Categories

Severity
Distress
Delusions
Hallucinations
Agitation
Depression
Anxiety
Elation
Apathy
Disinhibition
Irritability
Motor Disturbance
Nighttime Behaviors
Appetite
Social Cognition

- “Emotional intelligence”
  - Empathy / Sympathy vs Sociopathy
  - Self / social awareness
- Perceiving other’s emotional state:
  SD and bvFTD subjects have difficulty recognizing sarcasm (Rankin, 2009)
- Social affiliation / bonding: oxytocin as a possible treatment for bvFTD
MRI Features of FTD Subtypes

MRI features are suggestive but are not standardized for diagnosis

bv FTD  SD  PNFA  bv FTD

J Neurol Neurosurg Psychiatry 2011;82:476-486.
Brain Imaging in FTD

“R/O FTD” is the only approved indication for brain PET in dementia.
Midline cerebral morphometry distinguishes frontotemporal dementia and Alzheimer’s disease

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Article abstract—We investigated and contrasted midline cerebral structures in frontotemporal dementia (FTD) and Alzheimer’s disease (AD). FTD and AD may be difficult to distinguish clinically. FTD typically affects frontal and anterior temporal regions, whereas AD tends to involve more posterior temporal and parietal areas. We hypothesized that disease-specific cerebral alterations would be differentially reflected in corresponding regions of the corpus callosum (CC), pericallosal CSF space (PCS), or their ratio (CC:PCS). Regions-of-interest (ROIs) from midsagittal MRIs in 17 AD, 16 FTD, and 12 elderly control (EC) subjects were analyzed. ROIs were divided into four regions using an anatomic landmark-based computer algorithm and were adjusted for head size variation. FTD subjects had a much smaller anterior CC region and significantly larger PCS area, particularly in anterior regions. AD and EC subjects did not differ significantly in any total or regional ROI measure. Total and anterior CC:PCS ratios were markedly lower in FTD patients. Across groups, total CC:PCS correlated significantly with midsagittal cerebral area and was similarly associated with Mini-Mental State Examination score. Anterior CC (AD) and PCS (FTD) regions exhibited disease-specific relationships to these variables. A discriminant model using two ROI variables correctly classified 91% of AD and FTD patients, comparing favorably with blind clinical MRI diagnostic ratings. Midline cerebral structural alterations reflect differential patterns of cerebral degeneration in AD and FTD, yielding morphometric indices that may facilitate the study of brain-behavior relationships and differential diagnosis of dementia.

NEUROLOGY 1997;48:978–985

Brain imaging research in FTD has come a long way in the last 15 years but hasn’t been translated into clinical diagnostic tools (yet)
FTLD – Neuroimaging State-of-the-Art

• Clinical MRI and PET imaging currently provide data that is helpful, but not definitive
• Need quantitative structural and functional imaging data that is diagnostically robust
• MRI:  - Voxel-based morphometry (atrophy)
  - Diffusion Tensor Imaging (connectivity)
  - FTD Neuroimaging Initiative
• PET: Tau–imaging tracers (similar to PIB)
FTLD – Genetics

• About 10-20% of FTD cases are autosomal dominantly inherited:
  • 1997: Familial FTD-parkinsonism linked to chrom. 17 → microtubule assoc. protein tau (MAPT) mutations
  • 2006: Progranulin mutations linked to chrom. 17 and TDP-43 – motor neuron disease
• Chromosome 16 – Fused in sarcoma (FUS)
FTLD – Pathology

- Two major pathological subtypes:
  - FTLD-tau: tau protein inclusions (40%)
  - FTLD-TDP-43: (ubiquitin inclusions) (55%)
  - FTLD-FUS (5%)
  - Other rare forms (VCP, CHMP2B)
FTLD – TDP-43

• TDP-43 (DNA-binding protein) is primary constituent of ubiquitin inclusions (formerly FTLD-U); growth factor

• 55% of FTLD

• Associated with progranulin gene mutations (chrom. 17)
  - Semantic dementia
  - FTD-motor neuron disease
FTLD – Tau

• Tau-positive inclusions (40% of FTLD)
• Includes:
  - Pick’s disease (Pick bodies)
  - Microtubule-associated protein mutations (MAPT)
  - Progressive supranuclear palsy
  - Corticobasal degeneration
  - Argyrophilic grain disease
Progressive Supranuclear Palsy
(Steele-Olzewski-Richardson, 1964)

Key clinical features:
- Speech / swallowing difficulties
- Early postural instability / falls
- Vertical supranuclear gaze paresis
- Axial rigidity
- Subcortical dementia in most (later)
- Apathy, depression, anxiety
- Pseudobulbar affect
PSP: Pathology & Treatment

• Tau-positive neurofibrillary tangles
• Cholinergic drugs (e.g. donepezil) may help cognition, but worsen motor dysfunction
• Dopaminergic agents ± benefit
• SSRIs for mood & pseudobulbar signs
• Supportive care (PT & swallowing)
PSP Experimental Treatments

- Lithium, Valproic acid, NP031112 (GSK-3 inhibitors)
- Pyruvate / creatine / niacinamide
- Coenzyme Q
- AL-108 (davunetide)- neuroactive peptide microtubule stabilizer (Phase 2/3 trial)
Corticobasal Degeneration

- Limb dyspraxia, gait disturbance, myoclonus, “alien hand” (asymmetric)
- Corticobasal “syndrome”:
  - may begin with cognitive or motor signs, later develop the other
  - variable pathological substrates
FTLD-tau, CBD, and PSP form a spectrum of tauopathies:

- CBD may begin with PSP motor features and develop focal cortical atrophy, or vice versa

- 1/3 of bvFTD patients develop CBD

- 1/3 of PPA patients develop bvFTD or CBD
“Three Rivers” Model of FTLD-Tau

Relative cognitive / motor signs vary over time
“Three Rivers” Model of FTLD-U (TDP-43)

Relative cognitive / motor signs vary over time
Clinical-Pathological Overlap in Dementia

Textbook

- Alzheimer’s disease (AD) 60-70%
- Lewy Body Dementia (LBD) 15-25%
- Vascular dementia (VaD) 10-20%
- Frontotemporal dementia (FTD) 5%

“Real-world”
“Three Rivers” Model of AD-PD

Alzheimer’s and Parkinson’s also form a clinical-pathological spectrum

Relative cognitive / motor signs vary over time
Degenerative Dementia as a Dynamic Process

Abnormal proteins accumulate over time:

- amyloid AND tau (Alzheimer’s)
- alpha-synuclein (Parkinson’s)
- alpha-synuclein +/- amyloid (Lewy body dementia)
- tau OR TDP-43 (others) (FTD)

Producing clinical syndromes that change over time (cognitive / motor / behavioral)
Adapted from Kaufer & DeKosky, Dementia Classification: Relationship to the Neurobiology of Disease, *Neurobiology of Mental Illness, 2nd ed.*, 2009.
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Primary Progressive Aphasia

1982: Mesulam describes cases of progressive aphasia associated with degenerative brain diseases (fluent and nonfluent types)

Criteria:
- Progressive language disturbance is primary clinical manifestation in the first 2 years
- Not associated with stroke, tumor, etc.

Mesulam, Ann Neurol, 1982;11:592-598
Classification of Progressive Aphasia

Progressive Nonfluent Aphasia (PNFA)

Semantic Dementia (SD)

Logopenic Phonological Aphasia (LPA)

(Gorno-Tempini, 2010)
Progressive Nonfluent Aphasia

Mesulam, 1982

- Hesitant, effortful speech
- Speech 'apraxia'
- Stuttering
- Phonemic paraphasia
- Agrammatism
- Dec. letter > category fluency

Pathology: Tau 50%. “AD” 25%, TDP-43 20%
Semantic Dementia
(Snowden 1989, Hodges, 1992)

- Poor confrontation naming
- Impaired word comprehension
- Poor object / person knowledge
- Poor naming
- Surface dyslexia
- Dec. category > letter fluency

Pathology: TDP-43 70%, "AD" 25%, Tau 10%
Logopenic Phonological Aphasia

(M. Gorno-Tempini, 2004)

- Impaired single word retrieval
- Impaired repetition
- Slow speech with sound errors
- Grammatical, intact motor speech
- Spared single word comprehension
- Dec. category = letter fluency

Pathology: “AD” 50%. TDP-43 40%, Tau 10%
Amyloid PET Imaging in PPA

PIB +:

4/4 LPA
1/6 PNFA
1/5 SD

Rabinovici et al, Ann Neurol, 2008
Treatment of PPA

- Bromocriptine 15-week double-blind study – no effect (Reed et al Ann Neurol, 2004)

- Galantamine double-blind study in PPA and FTD showed trend effect favoring treatment (Kertesz et al, 2008)

- Memantine open-label 26 week study (N=43) showed benefit in bvFTD and SD, but not PNFA (Boxer et al, Alz Dis Assoc Disord 2009)

- Memantine double-blind crossover study (18->9) showed a trend for less decline on language tests (Johnson et al, Alz Dis Assoc Disord, 2010)
Clinical, genetic and pathological spectrum of frontotemporal lobar degeneration.

Seelaar H et al. J Neurol Neurosurg Psychiatry 2011;82:476-486
Chronic Traumatic Encephalopathy

- Associated with multiple concussions (notably in retired pro football players)
- Clinical signs: memory loss, behavioral changes, gait and speech problems, Parkinsonism
- Pathology: tau-positive tangles
- Variant of FTLD-tau?
- Research in CTE will help understanding of FTD disorders and vice versa
- 10-year NFL career with Baltimore Colts
- 2000: diagnosed with FTD
- 2007: Wife’s written appeal to NFL led to Mackey Plan-$88K for care of retired players
- Passed 7.7.11, autopsy pending
Importance of Diagnosis

• To obtain effective treatments, need placebo-controlled studies demonstrating efficacy AND safety

• To do treatment study, need subjects who have the disease

• Without valid diagnostic criteria, can’t do necessary treatment studies
Final Thoughts

- FTD is clinically & pathologically complex
- Defining robust clinical outcome measures for treatment studies is challenging
  - How do you measure “personhood?”
- No clear-cut transitional state (i.e. Mild Cognitive Impairment)
- Need subtype-specific biomarkers for tau and TDP-43 forms of FTD to advance diagnosis and treatment
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