The Spectrum of Frontotemporal Degeneration

Organization of Talk
1. What is frontotemporal degeneration (FTD)?
2. What are the clinical syndromes of FTD?
3. Principles of Management
4. Resources and Referral

Brief History of FTD Syndromes
1892 Arnold Pick described 6 patients with FTD
1911 Alzheimer describes the neuropathology
1993+ Renaissance: Epidemiology, Clinical Criteria
1997 Age of Tauopathy: FTDP-17, abnormal tau
2006 Age of TDP43 protein and progranulin gene
2009+ NEW AGES OF EXPLORATION, THERAPY

Epidemiology of FTD Syndromes
1. 5-8% of dementias; 13.5-15% if onset<65
2. Prevalence/Incidence in 45-64 yr age grp: 15/100,000 and 1-2/100,000
3. Usual onset in 50’s (mean onset 57-58)
4. Slightly more men than women
5. Duration shorter than AD (mean 8yrs)

Key Points on FTD
1. Common early-onset neurodegenerations
2. Variable phenotypes and syndromes involving social behavior and language
3. 10-15% autosomal dominant genetic mutations in MAPT, PRGN, VCP, CHMP2B
4. Management is primarily symptomatic and behavioral with special attention to caregivers
FTD-Common Syndromes

1. bvFTD: behavioral variant ~ 50%
   A. apathy-abulia-detachment
   B. Disinhibition-impulsivity
   C. FTD-MND (motor neuron disease)

2. Language predominant variants
   A. PNFA: Prog. non-fluent aphasia ~ 25%
   B. SD: Semantic dementia ~ 25%

3. CBS or PSP: parkinsonism symptoms

Frontotemporal Degenerations

<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>Age at Onset</th>
<th>Male</th>
<th>Initial MMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontotemporal Dementia</td>
<td>56.7</td>
<td>57.5 (9.7)</td>
<td>63.5</td>
<td>22.7 (6.6)</td>
</tr>
<tr>
<td>Progressive Nonfluent Aphasia</td>
<td>18.7</td>
<td>59.3 (8.2)</td>
<td>66.7</td>
<td>21.5 (7.8)</td>
</tr>
<tr>
<td>Semantic Dementia</td>
<td>24.6</td>
<td>63.0 (9.7)</td>
<td>39.1</td>
<td>22.5 (7.0)</td>
</tr>
</tbody>
</table>

bvFTD

Core diagnostic features
A. Insidious onset and gradual progression
B. Early decline in social interpersonal conduct
C. Early impairment regulation of personal conduct
D. Early emotional blunting
E. Early loss of insight

Neary et al. Neurology 1998;51:1546-51;
SE 85%, SP 99% among 34 patients in Knopman et al, 2005
### Symptoms in 53 bvFTD Pts

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Onset</th>
<th>2 yrs</th>
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<tbody>
<tr>
<td>Decline in social conduct</td>
<td>39.6%</td>
<td>83%</td>
</tr>
<tr>
<td>Impaired personal regulation</td>
<td>69.8%</td>
<td>88.7%</td>
</tr>
<tr>
<td>Emotional blunting</td>
<td>35.8%</td>
<td>94.3%</td>
</tr>
<tr>
<td>Lack of insight</td>
<td>58.5%</td>
<td>100%</td>
</tr>
<tr>
<td>Compulsive-like behaviors</td>
<td>45.3%</td>
<td>88.7%</td>
</tr>
<tr>
<td>Logopenia and anomia</td>
<td>41.5%</td>
<td>96.2%</td>
</tr>
<tr>
<td>Hyperorality (other KBS)</td>
<td>0</td>
<td>20.8%</td>
</tr>
</tbody>
</table>

- Mendez & Perryman, 2002

### UCLA FTD & Neurobehavior Clinic

- Results of 134 referrals for possible bvFTD
  1. 23 (17.2%) initially met criteria for bvFTD
  2. 40 converted to bvFTD by two year f/up
  3. 36 had psychiatric disorder
  4. 17 had Alzheimer’s disease
  5. 9 had another neurological disorder
     - Anoxic encephalopathy (2), prion disease (2), Hashimoto’s encephalopathy, neurosarcoidosis, NPH, paraneoplastic syndrome, sleep apnea syndrome
  6. 9 without final diagnosis

###(Intl Consensus Criteria for bvFTD)

**I. Neurodegenerative Disease**
progressive deterioration behavior and/or cognition

**II. Possible bvFTD (3 of A-F present)**

A. Early behavioral disinhibition (1 or more)
   1. Socially inappropriate behavior
   2. Loss of manners or decorum
   3. Impulsive, rash or careless actions

B. Early apathy or inertia

C. Early loss of sympathy or empathy (1 or more)
   1. Diminished response to others people’s needs and feelings
   2. Diminished social interest, interrelatedness or personal warmth

D. Early perseverative, stereotyped or compulsive/ritualistic behavior
   1. Simple repetitive movements
   2. Complex, compulsive or ritualistic
   3. Stereotypy of speech

E. Hyperorality and dietary changes (1 or more)
   1. Altered food preferences
   2. Binge eating, increased consumption of alcohol or cigarettes
   3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile (all 3 present)
   1. Deficits in executive tasks
   2. Relative sparing of episodic memory
   3. Relative sparing of visuospatial skills
How does FTD affect Social Behavior?

1. Acquired sociopathy (Mendez et al, 2003; Miller et al, 1997)
2. ↓Understanding social concepts (Zahn et al, 2009)
3. ↓Self-referential emotions (Sturm et al, 2006)
4. ↓Recognition of facial emotions (Rosen et al, 2005)
5. ↓Empathy (cognitive-OF, emotional-TL; Rankin et al, 2005)
6. ↓Theory of Mind (Gregory et al, 2002; Lough et al, 2006)

Sociopathy in 16 FTD Patients

3 Unsolicited sexual approach or touching
3 Traffic violations including hit-and-run accidents
2 Physical assaults
1 Shoplifting
1 Deliberate non-payment of bills
1 Pedophilia
1 Indecent exposure in public
1 Urination in inappropriate public places
1 Stealing food
1 Eating food in grocery store stalls
1 Breaking and entering into others’ homes
Primary Progressive Aphasias

- PNFA – progressive non-fluent aphasia
  - Now nonfluent/agrammatic variant PPA
- SD – semantic dementia
  - Now semantic variant PPA
- PLA – progressive logopenic aphasia
  - Now logopenic variant PPA

Progressive NF Aphasia

- Grammatical difficulty in language production
- ↓ motor speech-effortful, hesitant, phonemic abnormality
- Apraxia of speech frequently present
- ↓ comprehension of syntactically complex sentences
- Spared word comprehension and object recognition
- Atrophy inferior left frontal-anterior insula region
Primary Progressive Aphasia

Inclusion criteria requires 1 through 3
1. Most prominent clinical feature is difficulty with language (word-finding, paraphasias, effortful speech, grammatical or comprehension deficits).
2. These deficits are the principal cause of impaired daily living activities
3. Aphasia should be most prominent deficit at symptom onset and for initial phases of the disease

NF/Agrammatic PPA (1)

- Difficulty with grammatical morphemes-
  - Function words (pronoun, preposition, auxiliary, conjunction, article); “Wh” questions
  - Inflections (number, case, gender, tense, aspect, comparison [comparative, superlative])
  - Difficulty with word order, e.g. usual SVO in English
  - Difficulty with complex sentences, e.g., involving movement of elements, passive sentences
  - Decreased syntactical comprehension

NF/Agrammatic PPA (2)

- Apraxia of Speech
  - Slow, halting, effortful trial and error groping with attempts at self-correction
  - Impaired sequential phonemes
  - Distorted phonemic substitutions, additions, repetitions, prolongations
  - Articulatory inconsistency
  - Abnormal prosody
  - Decreased words/min
  - ↓ phrase length and/or ↓ Mean Lexical Units
  - Decreased speech onset
  - Effortful or aproposodic speech

Semantic Dementia

- Multimodal semantic deficits (modality-specific)
- Semantic anomia ↓category fluency & ↓word comp.
- Abnormal person and object recognition
- Surface dyslexia & regularization, typORIZATION errors
- ↓specificity, general(superordinate) word preference
- Bizarre food choices or fads and rigidity
- Atrophy of temp polar, perirhinal “recognition” cortex

Semantic Variant PPA

- Degeneration of ability to understand word and object meaning (e.g. loss of semantics)
- Progressive semantic anomia (word-finding)
  - Does not take phonemic or contextual cues
  - Lost the meaning of words and word comprehension
  - Bidirectional deficits in confrontational naming
- Semantic Paraphasias (saying wrong word, or supraordinate e.g. animal for chipmunk)
- Generalized, amodal semantic deficits
Logopenic Variant PPA
- Word finding difficulty with gaps in fluency
- ↓ word retrieval with phonological errors
- ↓ repetition of sentences (hallmark)
- ↓ comp for long (not complex) sentences
- Decreased digit/word spans
- Probable decreased phonologic store
- Left post temp/inf parietal function

Evolution of FTD’s (2-5 yrs)
- FTDbv 1/2 → PNFA; 1/4 → CBS/PSP
- PNFA 1/2 → FTDbv; 1/3 → CBS/PSP
- CBS/PSP 1/2 → FTDbv; 1/2 → PNFA
- SD 3/4 → FTDbv

- Differences still persist at end of life

Kertesz et al, 2007; Snowden et al, 2007

FDDNP-PET Shows Different Distribution of Cortical Pathology in AD and FTD

Control Alzheimer’s Disease Frontotemporal Dementia

[Imagery of brain scans]
Frontotemporal Neuropathology

1. Neuronal loss, astrocytic gliosis, microvacuolar changes
2. Protein deposits (intraneuronal inclusions):
   A. 45% Tau+ intraneuronal inclusions
   B. 51% Ubiquitin+, tau- inclusions with TDP-43 protein
   C. 5% fused in sarcoma (FUS) deposits
3. Serotonergic>dopaminergic deficit (intact ACh and NE)

Types of TDP43 Proteinopathies

U1: dystrophic neurites in supfl cortical laminae
   - SD
   - ↓ confrontational naming and object naming
   - better survival

U2: intracytoplasmic inclusions - FTD-MND

U3: intraneuronal inclusions - FTD or PNFA
   - worse executive functions and social/behavior
   - Shorter survival and possible Progranulin mutation
MAPT, PRGN, VCP, CHMP2B

- 6% Microtubule-associated tau gene (C’17) mutations
  - Missense and deletions alter ability of tau to interact with microtubules
  - Disrupt alternate splicing of exon 10 changes ratio of 4R to 3R isoforms

- Programadin gene (C’17) mutations in 10%; TAR-DNA-binding protein-43 (TDP-43) in ui+ inclusions
- Valosin gene (C’9) mutation, for valosin containing protein, results in FTD, Paget’s, and IBM
- CHMP2B gene (C’3), for the charged multivesicular body protein 2B of endosomal sorting complex

Possible Biomarkers

- No relationship to ApoE ε4
- Increased ApoE ε2 allele
- Inconsistent CSF total tau (>normal; <AD)
- Tau/β42 amyloid ratio<AD;
- β42 amyloid > AD
- No CSF FTD-T vs FTD-U differences yet

Drugs Tested in FTLD

- Trozodone
- Galantamine
- Idazoxan
- Lithium plus fluoxetine
- Lithium plus paroxetine
- L-deprenyl
- Moclobemide
- Methylphenidate
- Piracetam
- Aripiprazole
- Rivastigmine
- Donepezil
- Olanzapine
- Risperidone
- Amanadine
- Guanfacine
- Allopurine
- Bromocryptine
- Calcium EDTA
- Memantine

Conclusions

- FTD is common in those younger than 65 and presents with social behavioral or language changes
- The clinical syndromes overlap and include bvFTD, PNFA, and SD as well as FTD-MND, CBS, PSP
- FTD are either tau+ or ub+/?TDP43 inclusions
- 10-15% auto dom mutations in MAPT, PRGN, other
- Management is primarily symptomatic and behavioral with special attention to caregivers

Caregiver Support

- Behavioral, functional, financial, and legal counseling
- Provide an “external executive”
- Use Alzheimer’s resources such as the Alzheimer’s Association
- Speech, occupational, physical therapy
- Establish dedicated support groups
- Daycare, respite care and nursing care

To refer a patient: Contact Jill Shapira, RN, PhD at 310-794-2550 or jshapira@mednet.ucla.edu

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