Frontotemporal degeneration (FTD)

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Overview

- Case reports
- Normal function of affected brain areas
- FTD spectrum disorders
- Differential diagnosis
- Treatment
- Future directions
Cognitive syndromes of frontotemporal degeneration*

*not including ALS, PSP-like and CBD-like presentations

From David Knopman
FTLD background

- 2nd most common cause of dementia in patients < 65 y.o.
- ~ 5-10% of all dementias
Comparison of FTLD & AD Incidence

Logarithmic Incidence /100,000

US | UK | Spain

- FTLD
- AD

50-59 | 60-69
45-64 | 45-64
What do these brain areas do normally?
Normal functions of brain areas

- Frontal lobe
  - Important for personality, higher cognitive functions, language production, how to perform complex activities, attention, motivation, emotional response, empathy, theory of mind

- Temporal lobe
  - Important for language comprehension, storage of knowledge about the attributes and characteristics of things
Symptoms of bv-FTD (Rascovksy et al. Brain 2011)

- Progressive deterioration of behavior and cognition
  - Behavioral disinhibition
  - Apathy
  - Loss of empathy
  - Perseverative or compulsive behaviors
  - Hyperorality and dietary changes
  - Neuropsychological profile c/w FTD
Primary Progressive Aphasias (language variant FTD)

* Nonfluent / agrammatic variant PPA
  * Non-fluent (halting, effortful speech), poor grammar, drop-out of words

* Semantic variant PPA
  * Fluent speech, impaired naming and comprehension

* Logopenic PPA
  * Word-finding difficulty, poor repetition, impaired “buffer” system
Semantic dementia and PNFA

Rohrer et al, *Neurology* 2009
Related syndromes

- **CBS**
  - Cortical:
    - asymmetric apraxia and rigidity
    - alien limb, cortical sensory loss, myoclonus
  - Basal ganglia:
    - bradykinesia
    - increased resistance to passive movement

- **PSP**
  - vertical gaze palsy, axial dystonia, bradykinesia, rigidity, and falls
Kertesz et al., *Brain* 2005
Kertesz et al., *Brain* 2005
Kertesz et al., *Brain* 2005
From University of Utah, Dept. of Pathology
Three major FTLD neuropathologies

Tau pathology

Ubiquitinated inclusions (FTLD-U)
The Neuropathologic Syndromes

FTLD

- Tauopathies
  - Pick’s Disease
  - PSD
  - CBD
  - Multisystem tauopathy
  - Others

- TDP-43 proteinopathies
  - FTLD-U
    - Including PGRN & Valosin-containing protein gene mutations
  - FTLD-MND

- FUS inclusions
  - MND
  - FTLD-MND

Adapted from: Josephs KA. Ann Neurol. 2008 Jul;64(1):4-14
Differential diagnosis

- Patients with FTLD are often initially diagnosed with a different illness
  - Psychiatric disorder
  - Alzheimer’s disease
Distinguishing FTD from AD

- **Bv-FTD**
  - Early changes in personality, behavior, social cognition, and executive function with relatively intact memory and visuospatial ability
  - Motor symptoms

- **Nonfluent/aagrammatic variant PPA**
  - Relatively isolated to expressive aphasia
  - Aphasia and not word-finding difficulty

- **Semantic variant primary progressive aphasia**
  - Episodic memory relatively intact
  - Loss of semantic representation and not word-finding difficulty
  - Frontal behavioral syndrome
Distinguishing FTLD from a psychiatric disorder

- Cognitive dysfunction, especially executive dysfunction
- Progressive course
- Motor symptoms
- Family history
- New onset of psychiatric disorder
- Distress and deficits in social cognition
<table>
<thead>
<tr>
<th>Aspect of multidisciplinary management</th>
<th>Early stage, mild impairment</th>
<th>Middle stage, moderate impairment</th>
<th>Advanced stage, severe impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physician responsibilities</strong></td>
<td>Diagnosis; Discussion of diagnosis and course of disease; Assessment of degree of assistance needed (e.g., home health aides); Assessment of burdensome symptoms and prescribing medications to manage them if necessary; Assessment for genetic testing and referral to a genetic counselor if warranted</td>
<td>Continued assessment of symptoms; Assessment of degree of assistance needed (e.g., possible out-of-home-placement); Discussion of medication efficacy, side effects, and dosing adjustments as needed</td>
<td>Assessment of degree of assistance needed (e.g., possible out-of-home-placement or hospice referral); Discussion of genetic implications of neuropathological findings after autopsy</td>
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<tr>
<td><strong>Programmatic patient support</strong></td>
<td>Consultations with cognitive rehabilitation professionals, physical therapists, speech therapists, and/or occupational therapists to enhance life participation and maintain functional abilities; Caregiver assistance and supervision to complete basic activities of daily living; Day programs for meaningful activity; Home health aides to help with patient self-care tasks and physical and safety needs; Referrals to residential facilities, palliative care and hospice when appropriate</td>
<td>Introduction to educational materials and supportive local, national, and online resources; Home health aide or companion to assist caregiver; Day programs to provide caregiver with respite; Meetings with support groups; Emotion-focused coping strategies for grief and loss and bereavement support</td>
<td></td>
</tr>
<tr>
<td><strong>Caregiver support</strong></td>
<td>Identification of health-care proxy; Completion of power-of-attorney; Consultation with social worker regarding benefit eligibility</td>
<td>Consultation with a social worker; Identification of suitable hospice and/or residential care facilities</td>
<td>Discussions to help family and patient plan for a peaceful death; Logistic and financial planning for death</td>
</tr>
<tr>
<td>Domain</td>
<td>Symptom</td>
<td>Pharmacologic tx</td>
<td>Non-pharmacologic tx</td>
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<td><strong>Language symptoms</strong></td>
<td>Expressive aphasia</td>
<td>None</td>
<td>Speech therapy; caregiver education; compensatory tools such as scripts and AACs</td>
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<tr>
<td></td>
<td>Naming and comprehension deficits</td>
<td>None</td>
<td>Speech therapy; caregiver education on communication methods</td>
</tr>
<tr>
<td><strong>Behavioral and neuropsychiatric symptoms</strong></td>
<td>Apathy and inertia</td>
<td>None</td>
<td>Caregiver education and support; supervision and direction</td>
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<tr>
<td></td>
<td>Agitation, aggression, and impulsive behaviors</td>
<td>Antidepressants, Atypical antipsychotics</td>
<td>Caregiver education; monitoring and removal of environmental triggers, caregiver oversight of physical and social environment</td>
</tr>
<tr>
<td></td>
<td>Lack of empathy and sympathy</td>
<td>None</td>
<td>Caregiver education; caregiver support groups</td>
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<tr>
<td></td>
<td>Perseverative and ritualistic behaviors</td>
<td>Antidepressants</td>
<td>Caregiver oversight; toleration of behavior; distraction</td>
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<tr>
<td></td>
<td>Compulsive eating and dietary abnormalities</td>
<td>Antidepressants</td>
<td>Caregiver oversight of diet; environmental and physical modifications; consultation with dietician</td>
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<tr>
<td><strong>Cognitive symptoms</strong></td>
<td>Executive dysfunction</td>
<td>Evaluation for medications that could impair cognition</td>
<td>Consultation with cognitive rehabilitation therapist; compensatory tools</td>
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<tr>
<td><strong>Motor symptoms</strong></td>
<td>Falls</td>
<td>Evaluation for medications that could contribute to parkinsonism, orthostasis, or balance impairment</td>
<td>Environmental modifications; physical therapy; consultation with occupational therapist; walkers and/or wheelchairs</td>
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<td>Dystonia</td>
<td>Botulinum toxin injections</td>
<td>Splinting; physical therapy</td>
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<td>Parkinsonism</td>
<td>Carbidopa/levodopa trial (in part, for diagnostic purposes)</td>
<td>Caregiver support</td>
</tr>
</tbody>
</table>
Future directions

- What is the course of FTD?

Jacks, CR Lancet Neurology 2013
Future directions, cont.

- Treatment development
  - Novel targets
    - Tau (TauRx)
    - Symptom clusters
      - Tolcapone
      - Oxytosin
  - Select groups of FTD patients
    - nimodipine for PGRN mutation carriers
From Weng et al, Neural Networks, 2012
Catechol O-methyltransferase (COMT)

- Inactivates released dopamine through enzymatic conversion to 3-methoxytyramine
- Selectively regulates dopamine in the PFC
  - The cortical dopamine transporter has a 1,000-fold higher affinity for dopamine than does COMT (Lewis et al, *J Comp Neurol* 2001).
  - However, in the PFC, the dopamine transporter is expressed at very low levels and does not appear to affect extracellular dopamine concentrations (Houtari et al, *J Pharm Ex Ther* 2002).
COMT cont.

- *COMT* has a common polymorphism that affects its function – a methionine (Met) for valine (Val) substitution at codon 158.
- The enzyme in individuals with the met/met genotype has 3-4 X lower activity than in individuals with the val/val genotype (Lotta et al, *Biochem* 1995)
Effects of COMT val158met polymorphism in general population (Barnett et al, Biol Psy, 2008)

- Mixed evidence of a small dose-dependent effect ($d=0.06$) on executive function and WM in healthy control populations
- Larger effect size in patient populations ($d=0.3-0.4$)
- Findings c/w inverted-U model of frontal dopaminergic function.
inverted-U model of frontal dopaminergic function
Huey et al, submitted

- Examined effect of COMT val158met polymorphism in 110 patients with FTD and 64 patients with CBS.

- Analyzed D-KEFS, MDRS2, WMS-III, NPI, Finger tapping, Grooved pegboard, TOLA, MRI volumetric analysis.

- We made a composite score for each of these domains to initially test as follows: the mean of the D-KEFS factor scores (executive), the mean of the WMS-III standardized scores (memory), and the mean of z-scores of the Finger Tapping, Grooved Pegboard, and TOLA scores.
COMT Imaging analysis

- VBM analysis in SPM 8
- Images segmented into gray matter, white matter, and CSF. GM images normalized and smoothed. Corrected for TIV.
- Whole brain ANOVA performed in SPM8 on the effects of COMT val allele dosage on grey matter volumes. Clusters surviving an uncorrected threshold of $p<0.001$ and a cluster size of 30 voxels were considered significant.
Results

- There was a significant effect of the COMT val allele on our composite executive function measure, $F(1, 76)=6.14$, $p=0.015$, but no significant effect of the COMT val allele on the memory or motor composite measures.
Figure 1. Difference between grey matter volume in patient with two compared to no val alleles at the COMT val158met polymorphism. Dark areas show regions of decreased grey matter volume in patients with two val alleles. Areas shown are significant at an uncorrected voxel-level threshold of $p < 0.001$. 
Why caudate?

- Included CBS patients
- Caudate receives extensive cortical afferent projections, esp. frontal association areas
- In animal models, head of caudate is especially vulnerable to dopamine depletion (J Neurol 2000)
Conclusions

- The *COMT* val158met polymorphism affects executive function and bilateral caudate volume in patients with FTD and CBS.

- $r = 0.22$ between sorting score and *COMT* val dosage. Comparable to other patient populations.
Figure 1. Study design