Movement Disorders and Frontotemporal Dementia

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Movement Disorders and FTD

• FTD can present with various hyperkinetic or hypokinetic movements
  – Abnormal movements can precede, coincide or follow cognitive impairments
• Clinical overlap → diagnostic challenges
• No clear clinical-pathological correlations

Classification of FTLD by Clinical Manifestations

[Diagram of FTLD classification]

Park et al 2013
Movement Disorders and FTD

MD and FTD: Pathophysiology

- Loss of afferent input from frontal cortex to subcortical gray matter
  - Dorsolateral and dorsomedial frontal cortices project to central band in striatum
  - Anterior cingulate, orbitofrontal and temporal polar cortices project to medial striatum and nucleus accumbens

MD and FTD: Pathophysiology

- Basal ganglia volume loss in FTLD
  - bvFTD: 25% loss
  - nFPA: 21% loss
  - svPPA: 8% loss
**MD and FTD: Clinical Phenotypes**

**Hypokinetic:**
- Parkinsonism
- Primary freezing of gait
- Progressive supranuclear palsy
- Corticobasal syndrome
- Multiple system atrophy
- Dementia with Lewy bodies

**Hyperkinetic:**
- Stereotypies
- Chorea
- Dystonia
- Myoclonus

**MD and FTD: Genetics**

- Various genetic mutations underlie mixed presentations
  - No direct genotype-phenotype correlations

- FTD and parkinsonism linked to chromosome 17 (FTDP-17)
  - Term introduced at international consensus conference in 1996

**FTDP-17**

- By 1996, 13 families described with autosomal dominant inheritance
- Mix of behavioral changes, dementia, parkinsonism, amyotrophy, dystonia, supranuclear gaze palsy
- Later determined to be MAPT or PGRN
MD and FTD: Genetics

- MAPT
- PGRN
- C9ORF72
- FUS
- CHMP2B
- TREM2
- VCP
- TARDBP

Known genes explain <50% of familial cases

MAPT

- Microtubule-associated protein tau gene
- Chromosome 17
- Described in 1998
- 80 identified pathogenic mutations
- Younger age of onset – 46-49 years old
  - About 10 years younger than PGRN

MAPT

- 36% present with movement disorder first
- Symmetric, akinetic-rigid parkinsonism most common
  - Usually no resting tremor
  - May respond to levodopa
- PSP + bvFTD phenotype
  - Younger age at onset
  - No falls in first year
PGRN
- Progranulin gene
- Chromosome 17
- Described in 2006
- 172 described pathogenic mutations
- Involved in cleavage of TDP-43
- Age of onset: 59-60 years
- Wide clinical variability

10% present with movement disorder first
- Parkinsonism in 41%
  - Usually later in disease course
  - Gait trouble 33%, bradykinesia 25%, tremor < 5%
- Hallucinations more common
  - Can look like DLB

More language involvement
- Non-fluent PPA without apraxia of speech
- More parieto-occipital atrophy, more asymmetric
  - Side of predominance runs in families
  - CBS phenotype
C9ORF72

- Described in 2011
- Age of onset: 55 years old
- >30 GGGGCC repeats
  - Intermediate expansions (20-30 repeats) may be associated with increased risk of PD and ET
  - Present in 1.6% with these conditions

C9ORF72

- Parkinsonism in up to 91% during disease course
  - Symmetric, akinetic-rigid
  - Positive DaTscans
- Can look like MSA – dysautonomia and ataxia
  - MSA-P, MSA-C, and MSA-FTD categories?
FUS

- Fused-in sarcoma gene
- Chromosome 16
- Younger age at onset
- Usually no family history
- Parkinsonism is rare, looks more like essential tremor
- Striking caudate atrophy

Josephs et al. 2010
FUS-FTLD

- Head and body of caudate nucleus show more atrophy than the tail
  - Opposite in Huntington's disease
- Nucleus accumbens severely degenerated
  - Preserved in HD

MD and FTD: Genetic Testing

- Only if strong family history or age of onset <50
- Start with MAPT
  - Especially if PSP phenotype
- If CBS or nfPPA phenotype, start with PGRN
  - Especially if asymmetric parietal atrophy present
- If MND present, don’t order MAPT or PGRN

Hypokinesia in FTD

- Parkinsonism is most common manifestation
  - Present in 20-30% of FTD cases
- Can be seen in all FTLD subtypes
- Ranges from mild to prominent severity
- Akinetic-rigid phenotype most common
  - Resting tremor rare, but possible
Parkinsonism in FTD

Park et al 2013

- Degree of parkinsonism correlated with age and age of onset of FTD
- Degree of global cognitive deficits similar

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Parkinsonism</th>
<th>Clinica classification</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ridge et al. 2013</td>
<td>30% (n=8/26)</td>
<td>Lifting or release</td>
<td>bvFTD (N=4), LBD (N=2)</td>
</tr>
<tr>
<td>Raj et al. 2014</td>
<td>&lt;2% (n=1)</td>
<td>Lifting or release</td>
<td>bvFTD (N=1)</td>
</tr>
<tr>
<td>Seedorf et al. 2016</td>
<td>1/5% (n=5/264)</td>
<td>Free of head positional rigidity, tremor, bradykinesia, and postural instability</td>
<td>bvFTD (N=6), LBD (N=3)</td>
</tr>
<tr>
<td>Gruet et al. 2017</td>
<td>12.5% (n=75/608)</td>
<td>Lifting or release</td>
<td>bvFTD (N=6)</td>
</tr>
<tr>
<td>Pekmez et al. 2018</td>
<td>5% (n=175)</td>
<td>Lifting or release</td>
<td>bvFTD (N=5)</td>
</tr>
</tbody>
</table>

• Degree of parkinsonism correlated with age and age of onset of FTD
• Degree of global cognitive deficits similar

191 FTLD patients
- Parkinsonism present in 38.7% overall
  - bvFTD: 46.5%
  - nPPA: 45.2% - Most severe, UPDRS Part III: 21.9
  - svPPA: 24.2% - Least severe, UPDRS Part III: 12.5
  - FTD-MND: 50%
Park et al 2017

- No difference in vascular risk factors between those with and without parkinsonism
- Presence of parkinsonism in FTLD associated with more:
  - Psychosis
  - Behavioral symptoms
  - Impaired iADLs
- Psychomotor speed and non-verbal memory more impaired in FTD + parkinsonism

Hyperkinesia in FTD

- Stereotypies: motor and vocal
- Choreaathetosis
- Orofacial dyskinesia
- Dystonia
  - Blepharospasm
- Myoclonus

Stereotypies in FTD

- FTD is most common cause of new-onset recurrent abnormal behaviors in middle/late life
  - Present in 78% of autopsy-proven FTD
- Presence of two or more domain stereotypies can reliably distinguish FTD from AD
  - Eating/COOKING
  - Roaming
  - Speaking
  - Movements
  - Daily rhythm
Chorea in FTD

- Used to be exclusion criteria for diagnosis of FTLD
- HD-like presentation in PGRN, C9ORF72, or TARDBP
- Caudate atrophy in FUS
  - Basophilic inclusion body disease subtype

Take-Home Points

- Significant clinical overlap between FTLD and atypical parkinsonian syndromes
- 27% of FTLD can present *initially* as movement disorder
- PSP + bvFTD → think MAPT
- CBS + nPPA → think PGRN
- Severe caudate atrophy → think FUS