2018 AANP Diagnostic Slide Session
Case 4a

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Disclosures

• No relevant financial relationships to disclose
Clinical History

- 37 year old lawyer, no family history of dementia
  - At age 33, started to have performance issues at work
  - Progressively abulic and socially withdrawn
  - By age 34, he began to choke frequently on food and developed a nasal voice and bilateral ptosis
  - Unable to care for his children

- Physical exam:
  - No fasciculations, normal strength
  - Brisk reflexes, no Babinski sign or sustained clonus
  - Ptosis
Clinical History

- Imaging studies:
  - Initial MRI and CT were normal
  - PET scan - bilateral frontal diminution of glucose utilization, worse on the right than the left, with extension to the right caudate
Gross Findings

- Brain weight: 1160 grams (fresh)
- Moderate atrophy of the frontal lobe and caudate
- Mild atrophy of the temporal and parietal lobes
H&E: Frontal Cortex
H&E: Pre-central Gyrus
H&E: Thalamus
2018 AANP DSS Case 4b

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DISCLOSURES: I have no relevant financial relationships to disclose
Clinical History

72-year-old RH female with incoordination and frequent falls

- Increasing forgetfulness, anosmia, micrographia
- Clinical diagnosis of possible Parkinson’s disease
- Trial of carbidopa/levodopa → no improvement
- Died after 5 years of severe parkinsonism and dementia
Autopsy Gross Findings

- Brain weight 1147 grams
- Diffuse cerebral atrophy
- Ex-vacuo hydrocephalus
- Depigmentation of substantia nigra
H&E, 5x
Hippocampus
Differential Diagnosis?
# Frontotemporal Lobar Degeneration (FTLD)

<table>
<thead>
<tr>
<th>Major molecular class</th>
<th>Recognized subtypes</th>
<th>Associated genes</th>
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<tbody>
<tr>
<td>FTLD-tau</td>
<td>PiD, CBD, PSP, AGD, MSTD, NFT-dementia, WMT-GGI, Unclassifiable</td>
<td>MAPT</td>
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<tr>
<td>FTLD-TDP</td>
<td>Types 1-4, Unclassifiable</td>
<td>GRN, VCP, 9p (TARDBP)</td>
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<td>FTLD-UPS</td>
<td>FTD, 3</td>
<td>CHMP2B</td>
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<td>FTLD-FUS</td>
<td>aFTLD-U, NIFID, BIBD</td>
<td>(FUS)</td>
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FTLD-FUS (FET)

- FTLD subtypes that are immunoreactive for the *fused in sarcoma* protein (FUS)
  - Mostly sporadic without underlying FUS gene mutations
- 3 FTLD-FUS subtypes:
  - Basophilic Inclusion Body Disease (BIBD)
  - Neuronal Intermediate Filament Inclusion Disease (NIFID)
  - Atypical Frontotemporal Lobar Degeneration with Ubiquitinated Inclusions (aFTLD-U)
### Pathologic Features of FTLD-FUS Subtypes

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Case</th>
<th>ub-ir NCI cerebral cortex</th>
<th>IF-ir NCI cerebral cortex</th>
<th>BI subcortical</th>
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**Semi-quantitative grading:**
- none, + rare, ++ occasional, +++ moderate, ++++ numerous

Case 4a Final Diagnosis

Basophilic Inclusion Body Disease (BIBD)
BIBD

- Histologic hallmark is the FUS-positive basophilic inclusion body
  - Mimics Pick bodies, but are tau-negative
- Basophilic inclusion bodies preferentially affect the superficial laminae of the neocortex and are also in the subcortical nuclei
- Clinically may present as behavioral-variant frontotemporal dementia or juvenile or adult-onset ALS
- Early age of onset, but no genetic cause identified
Additional stains for Case 4b

- Neocortical amyloid plaques (mild)
- Negative for TDP-43, FUS, $\alpha$-synuclein
Case 4b

Frontal lobe
Substantia Nigra
Cerebellar
White matter

Tau (PHF1)
Tau (PHF1), 5x
Hippocampus
3R-Tau (RD3), 40x Hippocampus

4R-Tau (RD4), 40x Hippocampus

Biochemistry (Immunoblot)
Pick's Disease (PiD)  
FTDP-17 (MAPT)

Progressive supranuclear palsy (PSP)  
Corticobasal degeneration (CBD)  
Globular glial tauopathy (GGT)  
Argyrophilic grain disease (AGD)  
Aging-related tau astrogliopathy (ARTAG)  
FTDP-17 (MAPT)

Alzheimer’s disease (AD)  
Primary age-related tauopathy (PART)  
Chronic traumatic encephalopathy (CTE)  
FTDP-17 (MAPT)  
Anti-IgLON5-related tauopathy

3R Tau

4R Tau

3R + 4R Tau
Case 4b Final Diagnosis

Progressive supranuclear palsy (PSP) with 4R-tau positive Pick body-like inclusions
Acknowledgements for Case 4b

Dr. Gabor G. Kovacs, MD PhD
Dr. John Q. Trojanowski, MD PhD
References (Case 4a)

References (Case 4b)

  - *This DSS case is one of the three cases described in this paper*