Clinicopathologic complexities – the multi-proteinopathy problem

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The Diagnostic Process

1. Detailed history including family history, neuro exam, cognitive screen
2. Laboratory assessments
3. Structural imaging (MRI preferred)
4. Detailed neuropsychology testing if needed
5. Additional work-up if indicated (CSF, PET, etc.)
HPI + Cognitive Data + Neurologic Exam

- Formulate the differential diagnosis on the basis of published criteria
  - NIA-AA criteria for MCI and dementia / Dubois criteria
  - AD variants – Crutch criteria for PCA; Gorno -Tempini IvPPA criteria
  - FTD – Lund-Manchester or Neary criteria
  - McKeith DLB criteria
  - Etc.
Rule Out Etiologies

- Depression
- Hypothyroidism
- Vit. B12 deficiency
- End organ failure
- NPH
- Subdural hematoma
- Toxic encephalopathy
- HIV/Syphilis as appropriate
Eckman, Nature Sci Report 2018

<table>
<thead>
<tr>
<th>Healthy controls</th>
<th>Typical AD</th>
<th>Limbic-predominant</th>
<th>Hippocampal-sparing</th>
<th>Minimal atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTA = Right 0 Left 0 PA = 0 GCA-F = 0</td>
<td>MTA = Right 4 Left 4 PA = 1 GCA-F = 1</td>
<td>MTA = Right 4 Left 4 PA = 0 GCA-F = 0</td>
<td>MTA = Right 0 Left 0 PA = 2 GCA-F = 1</td>
<td>MTA = Right 0 Left 0 PA = 0 GCA-F = 0</td>
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</tbody>
</table>
Tau PET – LEADS data
And it is getting more complicated...

(a) With AD pathology

- Probable AD Mixed AD and Vascular
  - Inf
  - Inf + Vess
  - Vess

- Probable AD Mixed AD and Other Degenerative
  - TDP
  - TDP + HS
  - LB
  - LB + HS
  - LB + TDP

(b) No AD pathology

- Probable AD Vascular
  - Inf
  - Inf + Vess
  - Vess

- Probable AD Other Degenerative
  - TDP
  - TDP + HS
  - LB
  - LB + TDP
  - LB + HS

Kapasi, Acta Neuropath 2017
Prevalence and Clinical Phenotype of Quadruple Misfolded Proteins in Older Adults

Shama Karanth, MDS; Peter T. Nelson, MD, PhD; Yuriko Katsumata, PhD; Richard J. Kryscio, PhD; Frederick A. Schmitt, PhD; David W. Fardo, PhD; Matthew D. Cykowski, MD; Gregory A. Jicha, MD, PhD; Linda J. Van Eldik, PhD; Erin L. Abner, PhD, MPH

Dementia Prevalence
- QMP: 89.1%
- Tau + Aβ + TDP-43: 81.7%
- Tau + Aβ + αSyn: 61.1%
- Tau Braak stage V-VI + Aβ: 71.9%
- Tau Braak stage I-IV + Aβ: 71.9%
- Tau + TDP-43: 71.9%
- Tau: 71.9%

Proportion, %
- Participants with dementia: 100%
- 19.2%
- 27.1%
- 20.6%
- 19.2%
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- 14/83 (16.9%) of cognitively normal participants had quadruple proteinopathy

- MCI with quadruple proteinopathy showed faster conversion to dementia (more aggressive disease)

- PURE AD was rare (19.2%)
**LATE** (Nelson, Brain 2019)

- LATE is 100x more common than FTD due to TDP-43
- Clinically: older patients (LATE-20% in 80+ years old), more gradual cognitive decline and more agitation than pure AD but the combination – accelerated cognitive decline > pure AD
- Imaging: asymmetric, more severe hippocampal atrophy (anterior hippocampus), hypometabolism/atrophy in the medial temporal lobe and inferior frontal gyrus

- 64% of autopsy cases (N=83) showed ARTAG
  - 67% of amnestic predominant
  - 43% of CBD
  - 57% of IvPPA
  - 57% of very mild dementia
  - 50% of PCA
  - All CN (N=3)
LBD spectrum  (Ferman et al, Neurology 2020)

- In the presence of **tau NFTs** the diagnostic accuracy of clinical Dx of probable DLB (2+ of VH, fluctuations, parkinsonism, RBD) and DLB syndrome (1 sx) declined
  - w/o NFT - 96% sensitivity for prob DLB with diffuse LB
  - w NFT – 70% sensitivity for prob DLB with diffuse LB (+ onset of DLB clin syndrome later in the disease course)

- Among those with pure AD pathology 16% had 2+ and 22% 1 feature c/w clinical Dx of probable DLB or DLB syndrome
LBD + NFT affect both the clinical presentation and prognosis

Figure 1 Cumulative incidence model for the latency of probable dementia with Lewy bodies (DLB) across pathologic subgroups

- L - NFT-
- H - NFT+
Causative Pathology

- Can clinicians accurately predict all concomitant proteinopathies in the absence of biomarkers?

**WE CAN’T**

- In cases with multiple proteinopathies, a formal clinicopathologic consensus conference might be warranted to determine the primary etiology via interpretation of the pathology data in the context of the observed clinical syndrome