Molecular Imaging Heterogeneity of Clinically Defined AD

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  – Eisai, Genentech, Lundbeck, Merck, Putnam, Roche
Outline

• Heterogeneity in causes of clinical AD dementia
  • Amyloid-negative MCI/AD
    • Prevalence
    • Demographics, clinical features
    • Biomarker signatures, relationship to SNAP

• Heterogeneity in clinical presentations of AD neuropathology
  • Molecular correlates of non-amnestic AD
  • Early age-of-onset AD (sporadic)
Rates of Aβ Biomarker Negativity in Clinical AD

Bapineuzumab: Mild-Mod AD

Liu et al. Neurology 2015

ADNI: Late MCI and AD

Landau et al. Neurology 2016
Prevalence of Aβ+ in Clinical AD Decreases with Age

Ossenkoppele et al. JAMA 2015
Characterization of Aβ- MCI/AD in ADNI

- **Demographics**
  - Older than Aβ+
  - M > F

- **Cognition and function**
  - Better at baseline (MCI)
  - Slower decline (MCI and AD)

- **Lower prevalence ApoE4**
  - MCI: Aβ- 16% vs. Aβ+ 71%
  - AD: Aβ- 4% vs. Aβ+ 75%

- **Less abnormal neurodegeneration biomarkers**
  - CSF t-tau, p-tau
  - Baseline MRI and FDG
  - Longitudinal MRI

Landau et al. Neurology 2016
Neurodegeneration in Aβ-negative Amnestic AD (N=21)

Chételat et al. Brain 2016
Suspected Non-Alzheimer Disease Pathology (SNAP)

- SNAP in MCI and AD dementia
  - 17%-35% of MCI
  - ~6%-15% of AD dementia
  - Older age-of-onset
  - Male > female
  - ApoE4 rates 11%-32%

- Rate of decline intermediate between A-/N- and A+/N+

- No clinical fingerprint of a single underlying disease
  - Increased WMH in some studies
  - No features of DLB
  - No increases (yet) in tau PET

Intermediate Risk of Cognitive Decline in MCI-SNAP

201 MCI from ADNI/EU
Followed up to 5 yrs (mean 2.5)
Decline:
Conversion to AD
MMSE decline ≥ 3 pts/yr
MMSE ≤ 24

<table>
<thead>
<tr>
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<th>Crude</th>
<th>Adjusted</th>
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<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>MCI A+N-</td>
<td>1.13 (0.49 - 2.62)</td>
<td>0.771</td>
</tr>
<tr>
<td>MCI SNAP</td>
<td>2.66 (1.20 - 5.93)</td>
<td>0.016</td>
</tr>
<tr>
<td>MCI A+N+</td>
<td>3.85 (1.91 - 7.78)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Carolí et al. Neurology 2015
Neuropathological Diagnoses in Low Amyloid Clinical AD (N=50)

Dementia onset late 70s, death mid 80s

ApoE4 – 26%

Most common diagnoses:
AD (8), VaD (8), DLB (5), HS (5), normal brain (5) FTLD (4)

PART not diagnosed but 44% had Braak III/IV

Monsell et al. JAMA Neurol 2015

Table 4. Primary NP Diagnosis for No to Sparse CERAD Neuritic Plaque Density in APOE4 Carriers and Noncarriers

<table>
<thead>
<tr>
<th>Primary NP Diagnosis</th>
<th>Braak Stages 0-II</th>
<th>Braak Stages III-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>APOE4 Noncarriers</td>
<td>APOE4 Carriers</td>
</tr>
<tr>
<td>Normal brain</td>
<td>3 (15.0)</td>
<td>0</td>
</tr>
<tr>
<td>AD</td>
<td>0</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>AD abnormality present but insufficient for diagnosis</td>
<td>2 (10.0)</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Lewy body disease</td>
<td>3 (15.0)</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>5 (25.0)</td>
<td>0</td>
</tr>
<tr>
<td>FTLD</td>
<td>2 (10.0)</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Hippocampal sclerosis</td>
<td>3 (15.0)</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Rosenthal fiber encephalopathy</td>
<td>1 (5.0)</td>
<td>0</td>
</tr>
<tr>
<td>Nigral degeneration with focal tauopathy</td>
<td>1 (5.0)</td>
<td>0</td>
</tr>
<tr>
<td>Tauopathy NOS</td>
<td>0</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>0</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Senile dementia with tangles (tangle-only dementia)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>FTD-NFT</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tauopathy/diffuse grain disease</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
CTE at Autopsy in Aβ-PET Negative AD

79 year-old retired NFL player with progressive memory loss
Heterogeneity of Aβ+ AD

FDG - PET

Controls > EOAD

Controls > LOAD

Lehmann et al. Brain 2013
Tau PET Patterns Correlate with AD Phenotype

LOAD (n=4)

EOAD (n=8)

PrPPA (n=7)

PCA (n=8)

Ossenkoppele et al. Brain 2016
Xia et al. JAMA Neurol 2017
Day et al. Alz Dis Assoc Disord 2017

Covaried for age, p(FWE)<0.05
Age Moderates Tau Pattern in AD

A

AGE

Younger age, increased $^{18}$F-AV1451

Older age, increased $^{18}$F-AV1451

$\tau = 0.54 \ (P=0.001)$

Ossenkoppele et al. Brain 2016
Tau Burden in AD is Negatively Correlated with Age
Longitudinal Tau PET in EOAD

Visit 1
Nov. 2015

Visit 2
Conclusions

• Biomarkers identify patients with non-Aβ pathologies mimicking clinical AD
  • Consistently ~15% of AD dementia
  • Associated with ApoE4 neg, older age, male
  • Better prognosis than Aβ+ (but not benign)
  • Likely represents a mix of neuropathologies
    • PART, CARTS, AGD, vascular, DLB

• Biomarkers can identify AD pathology as cause of heterogeneous syndromes
  • Early-onset AD critical and under-studied cohort in which to investigate mechanisms that drive heterogeneity
  • Dedicated study will require multi-site collaborations
UCSF-MAC
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Cognitive Trajectories By Aβ Status

Landau et al., Neurology 2016
Characterization of Aβ- MCI/AD in ADNI

- Slightly older than Aβ+ (AD only)
  - Mean age 78 vs. 74
- Lower ApoE4
  - MCI: Aβ- 16% vs. Aβ+ 71%
  - AD: Aβ- 4% vs. Aβ+ 75%
- Better baseline cognition and function (MCI only)
- Slower cognitive decline (both groups)
- Higher prevalence of depression and hypertension
- Lower neurodegeneration biomarkers
  - CSF t-tau; p-tau, baseline MRI and FDG, longitudinal MRI
Atrophy in Aβ-Neg AD Dementia

Chételat et al, in revision
Conclusions

• SNAP is a biomarker-derived construct
  • Subject to limitations of biomarker distributions, thresholds and classifications
  • Current definition of “neurodegeneration” is cross-sectional, not longitudinal
• The biological substrate of SNAP is likely diverse
  • Non-degenerative: developmental differences, age, depression, hormonal (estrogen, cortisol), sleep, diabetes, genetics, etc.
  • Degenerative: vascular, DLB, PART, AGD, HS ± TDP-43, FTLD
Conclusions

• The prognosis of SNAP differs by baseline cognitive status
  • Healthy elderly: relatively benign (similar to A-N-)
  • MCI: intermediate between A-N- and A+N+
  • Dementia: majority show continued decline

• The substrate of SNAP likely differs by baseline cognitive status
  • Healthy elderly: greater contribution of non-degenerative factors (or very slow pathologies)
  • Dementia: primarily non-AD cortical/subcortical (non-amnestic) or limbic (amnestic) pathologies
  • MCI: mix of degenerative vs. non-degenerative
**Outcomes in Clinical AD Dementia with Negative Amyloid PET**

**Amnestic**: primary and predominant deficit in episodic memory

**Non-amnestic**: primary and predominant deficit in language, visuospatial, or executive functions

**Non-specific**: diffuse pattern of cognitive deficits

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<table>
<thead>
<tr>
<th>Diagram</th>
<th>Description</th>
<th>Probable AD</th>
<th>Non-amnestic Aβneg-AD</th>
<th>Non-specific Aβneg-AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>BEFORE the amyloid PET scan (n=40)</td>
<td>Amnestic Aβneg-AD (n=21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>AFTER the amyloid PET scan (n=37)</td>
<td>Probable AD (n=11)</td>
<td>FTD (5)</td>
<td>DLB (1)</td>
</tr>
<tr>
<td>C</td>
<td>Long-term diagnosis (n=29)</td>
<td>Probable AD (n=8)</td>
<td>MCI unk (1)</td>
<td>Psychotic (1)</td>
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<tr>
<td>D</td>
<td>Autopsy</td>
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Probable AD diagnosis: 
- Probable AD: Orange
- Probable AD diagnosis change: Orange

Missing information: Black

Diagnosis change from previous diagnosis: Light Orange

Chételat et al., Brain 2016
Agreement Between CSF Aβ$_{42}$ and Florbetapir PET

Landau et al., Neurology 2016
Early Tau PET Data Suggest SNAP ≠ PART

Mormino et al, JAMA Neurol 2016
Intermediate Risk of Cognitive Decline in MCI-SNAP

Caroli et al, Neurology 2015

Vos et al, Brain 2015
Intermediate Risk of Cognitive Decline in MCI-SNAP

Caroli et al, Neurology 2015
Vos et al, Brain 2015
Early-Onset AD (Age ≤ 65)

- 5% of all AD patients = ~250,000 in U.S.
  - Only ~5%-10% harbor APP/PSEN mutations
- Study mechanisms of heterogeneity and selective vulnerability in AD
  - Non-amnestic clinical presentations; focal cortical syndromes (lvPPA, PCA, fvAD)
- Identify novel genetic risk factors
  - Only ~50% carry ApoE4
  - Not represented in GWAS; will require targeted effort
- Employ biomarkers
  - Improve clinical diagnosis
  - Study mechanisms of “pure” AD: fewer co-pathologies
  - Under-represented in ADNI, not included in DIAN