Assessment & Biomarkers/Imaging Correlates of Dementia

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Impact of Alzheimer’s Disease: Most Common Cause of Dementia

- 5.5 million Americans have AD; 16 million by 2050
- 6th leading cause of death (5th over age of 65)
- Someone is diagnosed with AD every 66 seconds
- Mortality from AD has increased by 89% since 2000
- Over $259 billion in health care costs in 2017
- 1n 2016, 15 million Americans provided care valued at $230 billion

2017 Alzheimer’s Association Facts & Figures
Stages of Alzheimer’s Disease

Malignant Phase
- Neuritic plaques, tangles, neuron and synapse loss

Presymptomatic Phase
- Onset of disease pathology
- Promoting Factor *Age
- Clinical symptoms appear
- Diagnosis
- Loses independence

Diffuse plaques

Death
DIAN Study: Estimated Biomarker Changes Relative to Symptom Onset

Diagnostic Hallmark of AD: Amyloid Plaque
Diagnostic Hallmark of AD: Neurofibrillary Tangle
NIA/Alzheimer’s Association Diagnostic Criteria for Dementia

• Cognitive/behavioral symptoms that:
  • Interfere with functional ability
  • Represent a decline from previous function
  • Are not explained by delirium or major psychiatric disorder
  • Are detected through a combination of history taking & objective cognitive assessment
  • Affect at least 2 cognitive domains (memory, reasoning/judgment, visuospatial skills, language, personality)

McKhann et al. Alzheimer’s & Dementia 2011;7:263-269
NIA/Alzheimer’s Association Diagnostic Criteria for Probable AD

• Meets criteria for dementia
• Gradual onset
• Initial & most prominent cognitive deficits:
  • Amnestic (memory)
  • Non-amnestic (language, visuospatial, executive dysfunction)
• Probable AD with increased certainty:
  • documented decline
  • genetic mutation
  • Biomarker positivity

McKhann et al. Alzheimer’s & Dementia 2011;7:263-269
Stages of Alzheimer’s Disease

Stage 1
Asymptomatic amyloidosis
- High PET amyloid tracer retention
- Low CSF Aβ1-42

Stage 2
Amyloidosis + Neurodegeneration
- Neuronal dysfunction on FDG-PET/fMRI
- High CSF tau/p-tau
- Cortical thinning/Hippocampal atrophy on sMRI

Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for MCI

MCI ➔ AD dementia
# New ATN Classification of Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Biomarker Profile</th>
<th>Cognitively unimpaired</th>
<th>MCI</th>
<th>dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-T-N-</td>
<td>normal AD biomarkers, cognitively unimpaired</td>
<td>normal AD biomarkers with MCI</td>
<td>normal AD biomarkers with dementia</td>
</tr>
<tr>
<td>A+T-N-</td>
<td>Preclinical Alzheimer’s pathophysiology</td>
<td>Alzheimer’s pathophysiology contributing to MCI</td>
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Biomarkers of Alzheimer’s Disease

Neuroimaging Biomarkers of AD

Magnetic Resonance Imaging (MRI)

• Widespread atrophy of medial temporal lobe (MTL), hippocampus, parietal, temporal and frontal lobes
• DTI/DWI reveal white matter and axonal disintegration and atrophy
• Conflicting results on functional MRI, but reduced activation on memory encoding tasks in MTL, post. Cingulate, precuneus, etc.

Positron Emission Tomography (PET) Imaging

• Amyloid and tau imaging reveals deposition of these proteins in areas known to be afflicted by AD
• FDG PET reveals reduced metabolism in temporoparietal, posterior cingulate, MTL
• Neuroinflammation and receptor imaging
MRI and PET Imaging in Alzheimer’s Disease

## CSF Biomarkers of Alzheimer’s Disease

<table>
<thead>
<tr>
<th>AD Pathology-Related Mechanism</th>
<th>CSF Measure</th>
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<tbody>
<tr>
<td>Amyloid Deposition</td>
<td>Aβ40, Aβ42, sAPPα, sAPPβ, Aβ oligomers, BACE1 levels/activity, ratios e.g., Aβ42/p-Tau, Aβ40/Aβ42, N-terminal truncated Aβ42 APLP-1</td>
</tr>
<tr>
<td>Neurodegeneration</td>
<td>Total Tau, p-Tau, oligomeric forms of Tau</td>
</tr>
<tr>
<td>Neuronal/Axonal Damage and White Matter Integrity</td>
<td>Neurofilament L (NFL),</td>
</tr>
<tr>
<td>Synaptic Function/Damage</td>
<td>Neurogranin, SNAP25, Visinin-like-protein 1 (VLP1),</td>
</tr>
<tr>
<td>Neuroinflammation</td>
<td>YKL-40, MCP1, Soluble form of TREM2, cytokines, chemokines, com3, S-100</td>
</tr>
</tbody>
</table>
Meta-analysis of CSF Biomarkers of AD

- Olsson et al. analyzed CSF data from 231 studies involving over 15,600 patients with AD, and more than 13,000 healthy controls
- Four CSF biomarkers – total tau, p-tau, neurofilament light chain (NFL) and Aβ-42 emerged as the most robust measures differentiating AD from controls
- Moderate effect sizes were observed for VILIP-1, neuron-specific enolase (NSE), YKL-40 and heart fatty acid-binding protein (HF-ABP)
- AD and controls could not be differentiated on CSF levels of Aβ-38, Aβ-40, sAPP α or β, MCP-1, GFAP and CSF-plasma ratio of albumin

# Wisconsin Cohorts on Preclinical AD

<table>
<thead>
<tr>
<th>University of Wisconsin Alzheimer's Disease Program</th>
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<tbody>
<tr>
<td><strong>NIH Wisconsin ADRC</strong></td>
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<tr>
<td><strong>Cohort</strong></td>
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<tr>
<td><strong>Sample size</strong></td>
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<tr>
<td><strong>Year started</strong></td>
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<tr>
<td><strong>Visit frequency</strong></td>
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<tr>
<td><strong>Cognitive battery</strong></td>
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<td><strong>Computerized cognitive battery</strong></td>
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<td><strong>Questionnaires</strong></td>
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<tr>
<td><strong>Cerebrospinal fluid (CSF) samples</strong></td>
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<td><strong>Neuroimaging</strong></td>
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</table>
Wisconsin ADRC: CSF Biomarkers and Cognitive Function Trajectories in At Risk Study Participants

Fixed Effects:
- Biomarker Group
- Slope (Age at each visit)
- Gender
- Education
- Practice Effects
- Biomarker Group x Age at each visit

Random Effects:
- Intercept
- Slope

Mixed-effects regression models (R lme4)
Wisconsin ADRC: Clinical Utility of Multimodal Biomarker Data – AD Risk Prediction
What does resilience to dementia look like?

*Hypothesis: lower gliosis, less neural injury, and less synaptic degeneration*

Three groups compared:
- Dementia-AD (n=40): **YES dementia, YES amyloid/tau**
- Controls (n=25): **NO dementia, NO amyloid/tau**
- Mismatches (n=14): **NO dementia, YES amyloid/tau**

CSF Biomarkers of interest:
- p-Tau/Aβ42: Alzheimer’s pathology
- Aβ42/Aβ40: Amyloid pathology
- NFL: Axonal degeneration
- Neurogranin: Synaptic degeneration
- YKL-40: Activated microglia & astrocytes
- Total Tau: Neurodegeneration

Results:
- The “mismatch” group (normal cognition despite AD-level of plaques and tangles) had lower NFL (C), less gliosis (E) and lower total tau (F) than participants with dementia.

Merluzzi et al., Under Review
Wisconsin ADRC: Healthy Behaviors and CSF and Imaging Markers of AD

Health Behaviors and AD pathology / risk

**Sleep**

- Associations with sleep and AD pathology
  - Sprecher et al., *Neurology* (2017—In press)
  - Sprecher et al., *Neurobiology of Aging* (2015)

**Physical activity**

- Okonkwo et al., *Neurology*
  - Greater physical activity → lower amyloid burden with age

**Insulin Resistance**

- Insulin resistance is associated with FDG
  - Willette et al., *JAMA Neurol* (2015)
- Similar findings seen with amyloid
  - Willette et al., 2013
Multimodal Approach to the Diagnosis of AD

Patient presents to clinic with concern about AD risk

Alzheimer’s Risk Profile
- High risk
- Moderate risk
- Low risk
- Very low risk
Preclinical AD Consortium

Partnership between:
- UW-Madison
- Washington University
- Johns Hopkins University
- National Institute on Aging (BLSA)
- Several Australian universities (AIBL)
Conclusions

• Clinical diagnosis of Alzheimer’s disease can now be made reliably with comprehensive medical evaluation and the use of cognitive testing, neuroimaging and CSF assays
• An important caveat in interpretation of CSF biomarker data is variability in sample processing, storage, shipment and analytical techniques between studies and sites
• Better understanding of who is amyloid and tau positive and if they develop clinical symptoms will be key to understanding risk and resilience to AD
• Neuroimaging and CSF biomarkers will become important components of multimodal approaches to predict conversion from preclinical to clinical stages of AD
• Neuroimaging and CSF biomarkers can represent favorable effects of healthy behavior on AD pathology
• The validity and clinical utility of PET amyloid/tau imaging and CSF biomarkers has to evaluated in larger clinical studies before widespread applications for patient care