CSF biomarkers in aging and the transition to Alzheimer’s Disease

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Biomarkers, key AD lesions and symptoms

Jack et al, 2009
CSF biomarkers and AD

- Low CSF Aβ42, and high levels of tau and P-tau181 are a core **biomarker signature** related to AD pathology.
- Many studies have defined cutoffs to diagnose AD vs controls, or for differential diagnosis.
- CSF biomarkers can clarify:
  - timing of the onset of pathology
  - the relationship to brain structural changes and to symptoms
  - pathological mechanisms that may contribute to AD
What does the ‘concentration’ of a biomarker in CSF mean?

- CSF biomarkers turn over, and reflect recent brain events
- Markers reach ISF space through
  - secretion e.g. Aβ
  - leakage or damage e.g. tau
- They then undergo clearance:
  - Uptake by cells in the brain
  - Degradation by enzymes
  - Binding to plaques e.g. Aβ42
  - Passage into blood
- Levels of biomarkers in CSF represent an equilibrium between these processes
secretases

APP

Aβ

Aβ clearance into blood vessels

AD

Aggregation: oligomers, fibrils and amyloid plaques

Enzymes break down Aβ

Microglia clear Aβ
Low CSF Aβ42 in AD is related to amyloid deposition

Lower CSF Aβ42 is associated with higher fibrillar amyloid amyloid burden (PIB)
- Fagan et al, 2006; 2008, Rabinovici et al, 2009

About 14% of normal subjects are PIB neg, but have low CSF Aβ42
- variability of CSF, or pre-fibrillar Aβ e.g. diffuse deposits
- Fagan et al, 2010
Tau and tangles

kinase

phosphatase

Phosphate

Microtubule-binding region

Soluble tau

Paired helical filament

Total tau assay

P-tau assay
CSF total tau and P-tau

- 2-3 fold ↑ in AD vs controls; sensitivity 75-85%
- Levels not related to APO-E genotype or dementia severity
- Remains stably ↑ in AD
- Acute damage e.g. stroke, or neuronal death e.g. CJD, leads to marked ↑ total tau, not P-tau

CSF Tau increases after stroke, P-tau181 does not

Hesse, 2001
A CSF study across the adult lifespan

- Funded as NACC Collaborative project: UCSD, UWA, OHSU, U Penn

  - I/E criteria for normals:
    - Age 20 – 100, recruited to fill age strata
    - Generally healthy, CDR 0, MMSE > 27/30, normal on NYU story learning and recall
    - BMI: non-obese
    - No recent infectious or inflammatory illnesses
    - No neurological illness affecting CNS
    - No chronic inflammatory illness, major organ failure, normal CBC, chem 12, glucose and platelet count
    - Normal neurological exam
### Demographics and biomarker levels

<table>
<thead>
<tr>
<th></th>
<th>Controls &lt; 60</th>
<th>Controls ≥ 60</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>155</td>
<td>145</td>
<td>104</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>41 ± 3.0</td>
<td>72 ± 7.2</td>
<td>72 ± 9.2</td>
</tr>
<tr>
<td><strong>Sex (% F)</strong></td>
<td>54</td>
<td>54</td>
<td>46</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>16 ± 2.7</td>
<td>16 ± 2.7</td>
<td>16 ± 3.2</td>
</tr>
<tr>
<td><strong>APO-E e4+ (%)</strong></td>
<td>38</td>
<td>28</td>
<td>69</td>
</tr>
<tr>
<td><strong>Body Mass Index</strong></td>
<td>24 ± 3.2</td>
<td>26 ± 3.4</td>
<td>26 ± 3.3</td>
</tr>
<tr>
<td><strong>CSF Aβ42</strong></td>
<td>274 ± 41</td>
<td>236 ± 67</td>
<td>157 ± 54</td>
</tr>
<tr>
<td><strong>CSF Tau</strong></td>
<td>54 ± 14</td>
<td>71 ± 24</td>
<td>105 ± 37</td>
</tr>
<tr>
<td><strong>CSF P-tau181</strong></td>
<td>26 ± 8</td>
<td>33 ± 14</td>
<td>51 ± 18</td>
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</table>
Comparisons between AD and controls

**ADNI BASELINE CSF**

- **Tau / Aβ42:** AUC = 0.90, sens = 87%, spec 85%
  - Shaw et al, 2009

- **Tau / Aβ42:** AUC = 0.84, Sens = 86%, spec 75%
  - Galasko et al, ICAD 2008
MCI, CSF biomarkers and the Alzheimer’s Disease Neuroimaging initiative (ADNI)

Cutoffs for Aβ42, tau and P-tau181 came from a cohort of autopsy-proven AD and elderly controls.

CSF Aβ42 and tau/ Aβ42 predicted which MCI subjects progressed to AD in 12 months.

Shaw et al, 2009
CSF biomarkers and structural MRI in MCI

ADNI MCI subjects with an AD CSF profile showed greater atrophy at baseline and on follow-up

Fjell et al, 2010
Detecting an AD signature in normals

- Amyloid pathology is a likely initiating event in AD
- Deposition is followed by a long preclinical buildup of structural changes before symptoms emerge
- A signature of pathology in cognitively normal subjects should meet the following predictions:
  - Resembles the signature in AD-dementia
  - Increased frequency with age
  - Increased in genetically predisposed subjects
  - Predicts cognitive decline and progression to MCI and AD
### Age, APO-E e4 and amyloid biomarkers

#### Table 1: Age of normal subjects and % with AD CSF

<table>
<thead>
<tr>
<th></th>
<th>Age of normal subjects</th>
<th>% with AD CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADNI</td>
<td>76 ± 5</td>
<td>31 - 38</td>
</tr>
<tr>
<td>DESCRIPA normal complaints</td>
<td>67 ± 6</td>
<td>31</td>
</tr>
<tr>
<td>Galasko et al</td>
<td>67 ± 10</td>
<td>25</td>
</tr>
</tbody>
</table>

#### Graph A: PIB PET +

- 40-59
- 60-69
- 70-79
- 80-89

**Age**

- Morris et al, 2010
CSF Aβ42 in controls vs age and APO-E e4

Mean − 2SD, young NC

Aβ42 pg/mL

Age (years)
CSF T-tau in controls vs age and APO-E e4

Mean ± 2SD, young NC
CSF P-tau181 in controls vs age and APO-E e4

![Graph showing CSF P-tau181 levels in controls vs age and APO-E e4](image)

- **P-tau181 pg/mL**
- **Age (years)**
- **Mean ± 2SD, young NC**
Young NC cutoff

Tau / Aβ42 in controls vs age and APO-E e4
Do CSF biomarkers predict decline in normals?

61 subjects, initially CDR 0, mean age 75
HR for progression = 2.4 for tau/Aβ42 and
1.8 for Ptau181/Aβ42
Fagan et al, 2007

109 controls, mean age 70
HR for progression = 1.6 for tau/Aβ42
Galasko et al, unpublished
CSF biomarkers in control subjects who progressed

Aβ42

PTau181

Tau

Tau/ Aβ42
Proteomic adventures  2D-DIGE  Craig-Shapiro et al

CSF discovery samples:
  AD         NC
  ↓
Immunodeplete 6 highly abundant proteins
  ↓
Differential dye labels for:
  AD   NC   Pool
  Cy5   Cy3   Cy2
  ↓
2D gel electrophoresis
  ↓
Fluorescence image analysis
Excise differentially expressed spots
Digest, sequence with MS
  ↓
Compare levels in AD vs controls in Discovery and Validation cohorts
YKL40

A secreted 40 kD glycoprotein

In AD, YKL i.r. is in the vicinity of fibrillar amyloid plaques (A, B, C).

Present within a subset of GFAP-positive astrocytes (D) and not in LN-3-positive microglia (E, F).

YKL-40 is also seen in swollen cell processes associated with plaques (G); these lack reactivity for dystrophic neurite marker PHF-1 (H, I) and microglial marker LN-3 (J, K, L), and may represent astrocytic processes.

YKL-40 i.r. is also observed in occasional neurons in the superficial white matter (M, N, O), some of which contain neurofibrillary tangles.
YKL40 levels were increased in CDR 1 vs 0 subjects in the discovery cohort, and in a larger independent sample in CDR 0.5 and 1.

YKL40 levels correlated with tau and P-tau181 levels.
CSF YKL-40/Aβ42 and tau/Aβ42 as predictors of
A. conversion from CDR 0 to CDR>0 and
B. progression from CDR 0.5 to CDR>0.5.
Kaplan-Meier estimates of rates of conversion and progression are shown; red curves represent the upper tertile and black curves the lower two tertiles.
BDNF, aging and AD

• Identified in a proteomic CSF study using iTRAQ: ↓ in AD (Zhang et al, 2008)
• BDNF is an activity-dependent secreted protein
• Present at synapses; roles in synaptic plasticity, hippocampal neuronal circuits
• Can promote neurogenesis in dentate gyrus
• Enhances aspects of spatial memory in rodents
• BDNF knockout mouse shows impaired LTP
• An allelic variant (Val66Met) may be associated with poorer memory performance and smaller hippocampal volume in humans
CSF BDNF in aging and AD

CSF BDNF levels are decreased in AD vs controls
(202 ± 31 vs 242 ± 33 pg/mL)

In NC, levels decrease with age and
Lower BDNF was associated with worse performance and greater 12 month decline in immediate and delayed recall and category fluency.

Independent of APOE e4, and CSF Aβ42 and tau.

Li et al, 2009
Can CSF biomarkers help to map a cascade in AD?

<table>
<thead>
<tr>
<th>Parts of the cascade</th>
<th>Potential biomarkers</th>
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<tbody>
<tr>
<td>Damage to neurons and axons, tangle formation</td>
<td>Tau, P-tau neurofilaments</td>
</tr>
<tr>
<td>Glial reaction</td>
<td>GFAP, YKL40</td>
</tr>
<tr>
<td>Inflammation</td>
<td>S100b, cytokines</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>F2-isoprostanes</td>
</tr>
<tr>
<td>Synaptic damage</td>
<td>?</td>
</tr>
<tr>
<td>Synaptic function and plasticity</td>
<td>Neurotransmitters, sAPPα, sAPPβ, BDNF</td>
</tr>
<tr>
<td>Trafficking</td>
<td>SORLA/LR11</td>
</tr>
<tr>
<td>Lipids, cholesterol</td>
<td>24-OH-cholesterol</td>
</tr>
<tr>
<td>Neurogenesis</td>
<td>? BDNF</td>
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</tbody>
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