Biomarkers for Alzheimer’s Disease

Henrik Zetterberg, MD, PhD
Professor of Neurochemistry
The Sahlgrenska Academy, University of Gothenburg

Alzheimer’s disease

Neuropathological criteria for Alzheimer’s disease

Modified from: Blennow et al., Lancet 2006
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Distribution of brain changes in Alzheimer’s disease

Mild cognitive impairment
Mild dementia
Moderate dementia
Severe dementia

Molecular pathology

- Senile plaques are composed of a 42 amino acid long aggregation-prone protein called amyloid b42 (Aβ42)
- Neurofibrillary tangles are composed of hyperphosphorylated isoforms of the intraneuronal protein tau (P-tau)
- Neuroaxonal degeneration is reflected by release of intraneuronal tau proteins (all isoforms, total-tau; T-tau) into the brain interstitial fluid that communicates freely with CSF

Choosing the sample for biomarker analysis

Brain
CSF
Blood

Proximity to disease
Accessibility
Concentration of analyte
Proteolytic degradation
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Cerebrospinal fluid

Total volume: 150 mL, production rate: 20 mL per hour
Standard volume of sampling: 10-12 mL

Is lumbar puncture dangerous?

Consecutive studies on complications after LP

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of cases</th>
<th>Post LP headache</th>
<th>Meningitis / hematoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blennow et al., 1993</td>
<td>395</td>
<td>2.1%</td>
<td>0</td>
</tr>
<tr>
<td>Andreasen et al., 2001</td>
<td>241</td>
<td>4.1%</td>
<td>0</td>
</tr>
<tr>
<td>Peskind et al., 2005</td>
<td>342 (428 LP)</td>
<td>0.9%</td>
<td>0</td>
</tr>
<tr>
<td>Zetterberg et al., Eur Neurol, 2010</td>
<td>1089</td>
<td>0.9%</td>
<td>0</td>
</tr>
</tbody>
</table>

Core CSF biomarkers for Alzheimer’s pathology
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CSF biomarkers for Alzheimer’s pathology - candidates

- Neurofibrillary tangles (P-tau)
- Axonal injury (T-tau)
- Inflammation (IgG/IgM production)
- Oxidative stress (F2-isoprostanes)
- Blood-brain barrier damage (CSF/serum albumin ratio)

Amyloid pathology
- Aβ42 / Aβ40
- β-secretase / α-secretase
- BACE1 activity

Neurofibrillary tangles
- P-tau
- T-tau

Axonal injury
- T-tau

Different uses of biomarkers in the evaluation of patients with memory problems

1. To diagnose neuroinflammatory and neuroinfectious conditions
   - CSF cell count
   - Albumin ratio
   - Intrathecal IgG and IgM production
   - Specific inflammatory markers

2. Specific markers of AD neuropathology
   - T-tau, P-tau and Aβ42 as supporting diagnostic markers in the clinic
   - T-tau, P-tau and Aβ42 as additional inclusion criteria in studies of anti-AD drugs

3. Specific markers for drug effect monitoring
   - Reduced levels of T-tau after treatment indicate less intense axonal degeneration

CSF biomarkers for AD: Ab1-42

- β-secretase / α-secretase
- Plasma membrane
- BACE1
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Study design:
• Consecutive AD cases from a community-based sample
• AD (n=53), healthy controls (n=21)

CSF biomarkers for AD: Ab42

Andreasen et al., Arch Neurol 56:673, 1999

Study design:
• 155 autopsy cases
• Plaque counts - Bielschowsky stain of neocortex and hippocampus
• Post-mortem CSF samples

Data adjusted for:
• Age at death
• Education
• Dementia severity
• ApoE4
• Time from diagnosis until death
• PM interval
• Time until Ab42 analysis
• CAA severity

CSF Ab42 reflects plaque pathology

Stroop et al., Neurology 60:652-656, 2003

CSF Ab42 reflects plaque pathology (2)

General idea verified in PIB-PET studies:
• Negative correlation between CSF-Ab42 and PIB retention in the brain

Fagan AM et al., Ann Neurol 2006
Forsberg A et al., Neurobiol Aging 2008

Posterior cingulum

Fagan AM et al., Ann Neurol 2006
Forsberg A et al., Neurobiol Aging 2008

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Diagnostic value

High total-tau and phospho-tau and low Ab1-42 in CSF
= 85-95% sensitive and specific for AD in AD-control
and longitudinal MCI studies

>100 papers

Prediction of incipient AD
in MCI cases using CSF biomarkers

Study design:
- Follow-up study on MCI (>4 years)
- Lumbar puncture and analysis of Ab42 and variants of tau in CSF
- MCI n=134
  57 MCI → AD
  56 MCI → MCI
  21 MCI → other dementias

Comb. of Ab42/P-tau and T-tau:
- Sens. for MCI-AD 95%
- Spec. against other MCI 87%

Prediction of AD within 10 years
in patients with MCI

Combination of Ab42/P-tau and T-tau:
- T-tau > 350 pg/mL
- Ab42 / P-tau ratio < 6.5
- Sens. for MCI-AD 88%
- Spec. non MCI-AD 94%
- PPV - 94%
- NPV - 89%
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CSF biomarkers for Alzheimer’s disease – diagnostic performance in a homogeneous mono-center population, 2010

- AD patients: n=32
- Stable MCI: n=13
- Other dementias: n=15
- Controls: n=20


Sensitivity 83% Specificity 88%

Prediction of incipient AD in MCI cases using CSF biomarkers in a multi-center study

MCI-AD vs. controls
MCI-AD vs. stable MCI + MCI-other

CSF T-tau (ng/L)

Sensitivity 83% Specificity 72%

Mattsson et al., JAMA 2009

The Alzheimer’s Association QC program for CSF biomarkers

- Goal 1 - Establish a standardized protocol for lumbar puncture and CSF processing
- Goal 2 - Monitor analytical variability
- Goal 3 - Establish a detailed protocol for laboratory procedures for AD CSF biomarkers
- Goal 4 - Improved quality and stability of assays

Please sign up if you perform Alzheimer biomarker analyses:
Neurochem@neuro.gu.se

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Can CSF markers predict development of AD in pre-symptomatic individuals?

Study design:
- Population-based study, 55 healthy individuals
- LP at baseline, mean age 72
- Follow-up 8 years later: 45 remained normal, 10 AD with dementia or drop in MMSE > -5

Gustafson et al., JNNP 2007

Can CSF markers predict development of AD in pre-symptomatic individuals? (2)

Study design:
- Clinical study on 57 healthy elderly individuals
- LP at baseline
- Follow-up during 3 years

Storrued et al., Dement Geriatr Cogn Disord 2007; 24: 118-124

Can we measure Ab oligomers in CSF?

Abeta = ß-Amyloid
○ = biotin
□ = avidin-HRP
Y = 82E1, N-terminus-specific MAb
K = chemiluminescent substrate

Xia W et al., Arch Neurol. 2009 Feb; 66(2): 190-9
Fukumoto H et al., FASEB J. 2010 Aug; 24(8): 2716-26

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Can we measure Ab oligomers in CSF? (2)

Are CSF biomarkers dynamic?

Are CSF biomarkers dynamic? (2)
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AD drug development

If you are interested in details of this, please read:


Biomarkers in studies of inhibition of Ab aggregation

Change from Baseline at Week 12

Trial design:
- Randomized, double-blind,
- placebo-controlled, parallel study
- 12 weeks oral treatment with 0 mg (placebo), 50mg and 250mg of PBT-2
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CSF biomarkers in active Ab immunotherapy trials
CSF substudy in the AN1792 trial (active β-amyloid immunization)
• Paired CSF samples (baseline and 1 year) from AD cases:
  antibody responders n=11, placebo n=10
  Reduction with treatment (in antibody responders) on the downstream biomarker T-tau
  No clear effect on β-amyloid (Aβ42)

CSF biomarkers in passive Ab immunotherapy trials
Phase II bapineuzumab trials:
• CSF samples from 27 bapineuzumab and 19 placebo cases
• CSF samples taken at baseline and 1 year
  CSF T-Tau
  Change at Week 54 (pg/ml)
  Bapineuzumab        Placebo
  -150                -100
  -50                 0
  50                 100
  p=0.0013
  CSF P-Tau
  Change at Week 54 (pg/ml)
  Bapineuzumab        Placebo
  -15                 -10
  -5                 0
  5                 10
  p=0.027
  p=0.0305

Phase III clinical trials on bapineuzumab
Phase III bapineuzumab APOE ε4 trial:
• Multicenter, randomized, double-blind, placebo-controlled trial
• Mild-moderate AD (MMSE 16-26)
• Bapineuzumab  n=658
• Placebo             n=432
Main outcome: change in ADAS-Cog over 18 months
Sperling R, presented at EFNS 2012
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**CSF biomarkers in the Phase III bapineuzumab trial**

- Phase III bapineuzumab APOE ε trial:
  - Multicenter, randomized, double-blind, placebo-controlled trial
  - Mild-moderate AD (MMSE 16-26)
  - Bapineuzumab: n=658
  - Placebo: n=432

*Secondary outcome:* change in CSF phospho-tau over 18 months

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**The current situation in AD drug development:**

- Promising biomarker changes but no clinical benefit
- Too little, too late?
- Studies on preclinical AD needed
- Are we missing something?

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**Summary**

- CSF biomarkers can monitor the neuropathology of AD:
  - T-tau is a marker of cortical axonal degeneration
  - P-tau is a marker of neurofibrillary tangle pathology
  - Ab1-42 is a marker of plaque pathology
- These markers have high diagnostic accuracy and have been implemented in the recently revised clinical criteria for Alzheimer’s disease (http://www.alz.org/research/diagnostic_criteria/)
- Current research is aiming at establishing biomarkers for microglial activation and synapse loss

Biochemical markers together with neuroimaging and clinical evaluation allow for making a pre-dementia diagnosis of AD and can be used to detect biochemical treatment effects in clinical trials of anti-AD drug candidates