Reconsidering BACE1 activity in CSF as biomarker candidate of biologically defined Alzheimer’s disease

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Alzheimer’s disease (AD)

AD Pathomechanism

Giacobini E et al. Nat Rev Neurol (2013); 9: 677-86
Established AD markers = ‘downstream’ markers

Upstream AD biomarkers are urgently needed!

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β-site APP cleaving enzyme 1: BACE1

Giacobini E et al. Nat Rev Neurol (2013); 9: 677-86
Can BACE1 activity serve as AD biomarker candidate?

Zetterberg H et al. 2008: Yes
Zhong Z et al. 2007: Yes
Wu G et al. 2008: Yes
Rosen C et al 2012: Yes
Mulder SD et al 2010: Yes

Ewers M et al 2008: No
Perneczky R & Alexopoulos P 2013: No
Savage MJ et al 2015: No
Origins of the discrepancies

Differences in methodology

Diagnostic uncertainties…
The multifactorial genesis of AD symptoms

Studies based on biomarker-underpinned diagnoses are needed!
ADNI

Alzheimer’s Disease Neuroimaging Initiative

Multicenter Study

50 academic institutions and private corporations in the USA and Canada

www.adni-info.org
# Study Groups

<table>
<thead>
<tr>
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<th>Control Group</th>
<th>Dementia due to AD</th>
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<tbody>
<tr>
<td>N</td>
<td>51</td>
<td>57</td>
</tr>
<tr>
<td>Age (years)</td>
<td>74.14 (4.65)</td>
<td>73.75 (7.93)</td>
</tr>
<tr>
<td>Sex (men:women)</td>
<td>25:26</td>
<td>27:30</td>
</tr>
<tr>
<td>MMSE (points)</td>
<td>29.08 (0.91)</td>
<td>23.51 (1.84)*</td>
</tr>
<tr>
<td>Aβ_{42} (ng/L)</td>
<td>244.20 (25.90)</td>
<td>134.04 (27.75)*</td>
</tr>
<tr>
<td>p-Tau (ng/L)</td>
<td>16.86 (3.52)</td>
<td>48.88 (19.20)*</td>
</tr>
<tr>
<td>t-Tau (ng/L)</td>
<td>53.46 (14.71)</td>
<td>152.84 (49.62)*</td>
</tr>
<tr>
<td>sAβPPβ (pM)</td>
<td>4269.08 (1447)</td>
<td>4360.53 (1249.10)</td>
</tr>
<tr>
<td>BACE1 activity (pM)</td>
<td>41.12 (14.71)</td>
<td>49.72 (16.62)*</td>
</tr>
</tbody>
</table>

AD: Alzheimer’s disease; APOE: Apolipoprotein E; MMSE: Mini mental state examination; Aβ_{42}: amyloid-β 1-42; p-Tau: tau phosphorylated at threonine 181; t- Tau: total tau; sAβPPβ: soluble amyloid-β protein precursor β; BACE1: β-site APP cleaving enzyme 1

Data presented as mean (standard deviation)

*statistically significant differences, P< 0.05

AD: Aβ_{42} < 192 ng/l, t-Tau > 93 ng/l and p-Tau > 23 ng/l
Controls: Aβ_{42} > 192 ng/l, t-Tau < 93 ng/l and p-Tau < 23 ng/l
BACE1 activity

*P=0.006
Outlook

Replication in larger cohorts

Imaging-underpinned diagnoses (especially amyloid imaging)

Oligosymptomatic AD
Thanks a lot!
Cerebrospinal fluid tau and amyloid-β1-42 in patients with dementia

Tobias Skillbäck, Bahman Y. Farahmand, Christoffer Rosén, Niklas Mattsson, Katarina Nägga, Lena Kilander, Dorota Religa, Anders Wimo, Bengt Winblad, Jonathan M. Schott, Kaj Blennow, Maria Eriksdotter, and Henrik Zetterberg
Hirnpathologien bei älteren Menschen

Genetic factors, age, education, diet and lifestyle factors, cognitive reserve...

- Cerebrovascular factors
- Amyloid accumulation
- Neurofibrillary tangles
- Further brain pathologies

→ Synaptic dysfunction
  - Axonal degeneration
  - Cell death

→ Cognitive dysfunction