The effect of ApoE phenotype on the association of plasma beta-amyloid and cortical amyloid accumulation

Amane Tateno,
Takeshi Sakayori, Woo-Chan Kim, Yoshiro Okubo
Department of Neuropsychiatry,
Nippon Medical School
Introduction

For the early diagnosis of Alzheimer’s disease (AD), researchers have been searching for biomarkers of AD in terms of accuracy.

At present, both amyloid positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) have been the most useful biomarkers in regard to good sensitivity and specificity (amyloid PET: 82% and 95%, CSF beta-amyloid (Aβ)_{1-42}: 96.4% and 76.9%). (Yang et al, 2012; Shaw et al, 2009)
Biomarkers of AD

Positron emission tomography (PET)
Clinical Imaging Center for Healthcare, Nippon Medical School

Cerebrospinal fluid (CSF)

Intravenous infusion

Positron emission tomography (PET)

Cyclotron
PET camera

Blood test
Biomarkers of AD: (evaluation of beta-amyloid)

- **PET & CSF**
  - **Advantage**
    - High sensitivity and specificity
    - High consistency
  - **Disadvantage**
    - Cost (PET device, cyclotron)
    - Technique (ligand synthesis)
    - Invasiveness (CSF, exposure)

- **Blood test**
  - **Advantage**
    - Low cost
    - Simple procedure
    - Less invasive
  - **Disadvantage**
    - Inconsistency of results from previous studies
Meta-analysis of plasma Aβ in AD

• Longitudinal study: Cognitively normal subjects who converted to AD had higher baseline Aβ_{1-40} and non-significantly increased Aβ_{1-42}/Aβ_{1-40} ratio.

• Cross-sectional study: AD patients had marginally but non-significantly lower Aβ_{1-42} levels than cognitively normal subjects. (Song et al, 2011)

• Lower Aβ_{1-42}: Aβ_{1-40} ratio was significantly associated with development of AD and dementia.

• Plasma levels of Aβ_{1-40} and Aβ_{1-42} alone were not significantly associated with outcome. (Koyama et al, 2012)
# Results from ADNI & AIBL

<table>
<thead>
<tr>
<th>ADNI</th>
<th>AIBL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Swaminathan et al, 2013</strong></td>
<td><strong>Rembach et al, 2014</strong></td>
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<tr>
<td><strong>U.S.A.</strong></td>
<td><strong>Australia</strong></td>
</tr>
<tr>
<td><strong>[\textsuperscript{11}C]PiB</strong></td>
<td><strong>[\textsuperscript{11}C]PiB</strong></td>
</tr>
<tr>
<td><strong>N=96</strong></td>
<td><strong>N=184</strong></td>
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<tr>
<td>Only ApoE $\varepsilon$4-group showed that $[\textsuperscript{11}C]$PiB uptake was positively correlated with plasma $A\beta_{1-40}/A\beta_{1-42}$.</td>
<td>Both at baseline and 18-month follow-up period, $[\textsuperscript{11}C]$PiB uptake was negatively correlated with plasma $A\beta_{1-42}/A\beta_{1-40}$</td>
</tr>
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</table>
Purpose

• In this study, we examined the correlation between plasma Aβ and the results of amyloid PET imaging with $^{18}$F-florbetapir in a Japanese population and a single-center study setting.

• We also tried to verify the effect of ApoE on the relationship with plasma Aβ and cortical Aβ accumulation.
## Subjects

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Age (mean ± S.D.)</th>
<th>MMSE (mean ± S.D.)</th>
<th>Clinical diagnosis of dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>35</td>
<td>76.2 ± 7.4</td>
<td>19.7 ± 6.5</td>
<td>AD (N=22) DLB (N=11) FTLD (N=1) Unspecified (N=1)</td>
</tr>
<tr>
<td></td>
<td>(M 10, F 25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>58</td>
<td>68.1 ± 14.8</td>
<td>25.1 ± 4.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(M 27, F 31)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Elderly healthy control</td>
<td>24</td>
<td>73.6 ± 5.3</td>
<td>28.8 ± 1.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(M 12, F 12)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

(MMSE; Mini-mental state exam)
Methods

• Amyloid PET imaging by $[^{18}\text{F}]$florbetapir
  • Mean cortical (6 regions: medial orbital frontal, temporal, anterior and posterior cingulate, parietal lobe, and precuneus) and whole cerebellar cortex
  • Calculated mean regional cerebral-to-cerebellar standard uptake value ratio (SUVR)
  • Threshold of SUVR greater than 1.099 was used to signify positive $\text{A}_\beta$.

• Blood test
  • Plasma $\text{A}_\beta_{1-40}$, $\text{A}_\beta_{1-42}$, $\text{A}_\beta_{1-42}/\text{A}_\beta_{1-40}$, and ApoE phenotype
  • E4 group: subjects with ApoE4; non-E4 group: subjects without ApoE4

• Cognitive function
  • Mini-mental state exam (MMSE)
## Results

<table>
<thead>
<tr>
<th></th>
<th>E4 group</th>
<th>Non-E4 group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (M/F)</td>
<td>28 (10/18)</td>
<td>89 (39/50)</td>
<td>NS</td>
</tr>
<tr>
<td>Age, mean ± S.D.</td>
<td>71.6 ± 11.2</td>
<td>71.7 ± 12.2</td>
<td>NS</td>
</tr>
<tr>
<td>MMSE, mean ± S.D.</td>
<td>23.2 ± 6.6</td>
<td>24.6 ± 5.3</td>
<td>NS</td>
</tr>
<tr>
<td>Diagnosis, N(%)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Elderly healthy control</td>
<td>4 (14.3)</td>
<td>20 (22.5)</td>
<td></td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>11 (39.3)</td>
<td>47 (52.8)</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>13 (46.4)</td>
<td>22 (24.7)</td>
<td></td>
</tr>
<tr>
<td>Amyloid PET</td>
<td></td>
<td></td>
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<tr>
<td>SUVR, mean ± S.D.</td>
<td>1.18 ± 0.18</td>
<td>1.09 ± 0.17</td>
<td>0.03</td>
</tr>
<tr>
<td>Aβ positive, N(%)</td>
<td>17 (60.7)</td>
<td>28 (38.5)</td>
<td>0.006</td>
</tr>
<tr>
<td>Plasma (pmoL/L)</td>
<td></td>
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<tr>
<td>Aβ_{1-40}, mean ± S.D.</td>
<td>57.8 ± 77.7</td>
<td>37.0 ± 20.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Aβ_{1-42}, mean ± S.D.</td>
<td>9.6 ± 19.8</td>
<td>4.5 ± 3.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Aβ_{1-42}/Aβ_{1-40} ratio, mean ± S.D.</td>
<td>0.14 ± 0.06</td>
<td>0.13 ± 0.08</td>
<td>NS</td>
</tr>
</tbody>
</table>
Correlation between $\text{A}\beta_{1-42}/\text{A}\beta_{1-40}$ ratio and SUVR

**Whole group** There was no significant correlation between plasma $\text{A}\beta_{1-42}/\text{A}\beta_{1-40}$ and SUVR ($R^2=0.02$, $p=0.11$).  

$\text{E4 group}, R^2=0.04$, $p=0.34$  
$\text{Non-E4 group}, R^2=0.06$, $p=0.02$
Discussion (1)

• We reconfirmed that the correlation between $A\beta_{1-42}/A\beta_{1-40}$ and cortical $A\beta$ accumulation by amyloid PET differed according to ApoE phenotype.

• Our results support the hypothesis indicated by the ADNI study.
Discussion (2): Multi-center vs single-center

- **Multi-center study**
  - Standardization of methods to maintain examination quality is required.
  - Sometimes this is difficult due to disparities among various facilities.

- **Single-center study**
  - Compared to multi-center studies, single-center studies have reported to show larger intervention effects.

- Our findings from a Japanese population was important for allowing us to generalize the results that $\beta_{1-42}/\beta_{1-40}$ may be correlated with the accumulation of $\beta$ among non-E4 subjects.
Discussion (3)

• Extracellular concentration of Aβ might be a result of the balance between the synthesis and clearance rates of Aβ.

• ApoE allele might differentially regulate the clearance of Aβ from the brain, and the clearance of soluble Aβ from brain interstitial fluid could depend on the isoform of the human ApoE expressed (ApoE4 < ApoE3 < ApoE2).

(Koyama et al, 2012)
Correlation between $A\beta_{1-42}/A\beta_{1-40}$ ratio and SUVR

Most subjects were amyloid-negative

Cut-off 1.099

Adequate Cut-off?
Conclusions

• The relationship of $\text{A}\beta_{1-42}/\text{A}\beta_{1-40}$ and SUVR was affected by ApoE phenotype, however this correlation was very weak for a differential diagnosis.

• If we found adequate cut-off value of plasma $\text{A}\beta_{1-42}/\text{A}\beta_{1-40}$, especially among non-E4 subjects, blood test might be a useful screening modality for deciding whether subjects should be examined by amyloid PET or not in clinical settings.