Increased plasma amyloid-β oligomer level associated with cognition deficit in Alzheimer’s Disease

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Alzheimer’s disease (AD) is the most common cause of dementia.

The amyloid cascade hypothesis proposes that AD is caused by an imbalance between amyloid-β (Aβ) production and clearance.

Aβ monomers, soluble oligomers, insoluble fibrils, and plaques increased.

Soluble Aβ oligomers might be more neurotoxic in the early AD.

Background

Brookmeyer, R. et al. 2007
Hardy, J. et al. 2002
Background

• Aβ oligomers may cause a highly selective neuron death.

• The brain Aβ oligomer accumulation probably triggers the astrocyte activation, contributing to inflammation in the brain.

• The level of soluble Aβ oligomer correlated with the extent of synaptic loss.

• Walter Gulisano et al. found that Aβ oligomer impaired long-term potentiation

Glabe, C.et al. 2008
Selkoe, D. J. 2008
Gulisano, W. et al. 2018
• Using flow cytometry and fluorescence resonance energy transfer, Santos et al. detected Aβ oligomers in CSF, which might reflect the AD-related pathology in the brain.

• Using the Multimer Detection System (MDS) assay kit, Wang and Kim found the hepanein plasma levels of Aβ oligomers was associated with the level of CSF Aβ42 and PiB-PET SUVR in AD.

• Increased CSF Aβ oligomer level was correlated with cognitive decline in AD.

Santos, A. N. et al. 2007
Jongbloed, W. et al. 2015
Wang, M. J. et al. 2017
Objectives

- To investigate the difference of the plasma Aβ oligomer concentration between AD and cognitively normal control (NC)

- To explore the relationship between plasma Aβ oligomer level and cognitive function
Methods

• A cross-sectional comparison study

• AD group: 30

• Normal control group: 28
Cognitive Assessment

Cognition

- Attention
- Digit span
- Reasoning
- Picture completion
- Episodic Memory
- Common objects memory test
- Mini-Mental State Examination
  Alzheimer's Disease Assessment Scale-cognitive subscale
- Visuospatial
  Read and set time
  Drawing block design
- Language
  Animal naming test
- Executive Function
  Stroop test
- Reasoning
The Multimer Detection System (MDS)

- Capture $\alpha\beta$ Reaction
- Detecting $\alpha\beta$ Reaction
- Washing
- Epitope-overlapping antibodies
- Monomer
- Multimer

PeopleBio Inc., Korea
Wang, M. J. et al. 2017
## Demographic characteristics for the study population

<table>
<thead>
<tr>
<th></th>
<th>AD group (n=30)</th>
<th>Control group (n=28)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>76.5 (6.3)</td>
<td>72.2 (7.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sex (M/F, n)</td>
<td>15/15</td>
<td>7/21</td>
<td>0.05</td>
</tr>
<tr>
<td>Education (years), mean (SD)</td>
<td>13.6 (2.7)</td>
<td>14.3 (1.9)</td>
<td>0.27</td>
</tr>
<tr>
<td>APOE ε4 carries/ non-carries (n)</td>
<td>16/14</td>
<td>5/23</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Results

Cognitive performance scores in overall cognitive function

<table>
<thead>
<tr>
<th></th>
<th>MMSE</th>
<th>ADAS-Cog</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NC</td>
<td>***</td>
<td>***</td>
</tr>
</tbody>
</table>

**Total score**

**AD** and **NC** compared in MMSE and ADAS-Cog.
Results

Cognitive performance scores in episodic memory

<table>
<thead>
<tr>
<th></th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immediate recall</strong></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>4.0</td>
</tr>
<tr>
<td>NC</td>
<td>8.0</td>
</tr>
<tr>
<td><strong>Delay recall 5min</strong></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>2.0</td>
</tr>
<tr>
<td>NC</td>
<td>8.0</td>
</tr>
<tr>
<td><strong>Delay recall 30min</strong></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>2.0</td>
</tr>
<tr>
<td>NC</td>
<td>8.0</td>
</tr>
</tbody>
</table>

* *** indicates statistical significance.
Results

Comparison of plasma Aβ oligomer levels
Results

Plasma Aβ oligomer levels and demographics

Age

Gender

APOE
Results

Correlation of plasma oligomer level and overall cognitive function

- MMSE score
  - AD: $r = -0.18$, $p > 0.05$
  - NC: $r = 0.50$, $p < 0.01$
  - 95% CI: -0.52 ~ 0.20
  - 95% CI: 0.17 ~ 0.73

- ADAS-Cog score
  - AD: $r = -0.40$, $p < 0.05$
  - NC: $r = 0.11$, $p > 0.05$
  - 95% CI: -0.67 ~ -0.05
  - 95% CI: -0.27 ~ 0.46

Aβ oligomer
Results

Correlation of plasma oligomer level and episodic memory

- **Immediate Recall:**
  - AD: $r = -0.14$, $p > 0.05$
  - NC: $r = -0.42$, $p < 0.05$
  - 95% CI: -0.54 to 0.17

- **Delayed Recall 5min:**
  - AD: $r = -0.25$, $p > 0.05$
  - NC: $r = -0.44$, $p < 0.05$
  - 95% CI: -0.59 to 0.10

- **Delayed Recall 30min:**
  - AD: $r = -0.25$, $p > 0.05$
  - NC: $r = -0.44$, $p < 0.05$
  - 95% CI: -0.65 to 0.01
• Plasma Aβ oligomer levels are significantly different between AD group and normal control group.
• Plasma Aβ oligomer concentration correlated with cognitive function especially in episodic memory in AD.
Limitations

- Sample size
  - Relatively small
  - Need larger sample to validate

- Confirmation of diagnosis of AD
  - Lack of the CSF or imaging biomarkers to validate the diagnosis
  - Future study to validate with the CSF or molecular imaging markers
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Methods

- **Plasma Aβ oligomers Detection:**
  - Heparin-anti-coagulated and EDTA-anti-coagulated plasma;
  - Centrifuged at 850 × g for 30 minutes at room temperature;
  - The Multimer Detection System (MDS)-AD assay kit (PeopleBio Inc., Korea);
Methods

• **Inclusion Criteria for AD:**

  • Meeting the criteria for dementia cited in the International Classification of Diseases, 10th Revision (ICD-10) and the criteria for probable AD of the National Institute of Neurological and Communicative Disorders and the Stroke/Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA);

  • Aged between 60 and 90 years;

  • Education years ≥ 6 years;

  • Having modified Hachinski ischemic score ≤ 4.
Methods

• Inclusion Criteria for NC:

• Showing normal cognitive performance;

• Aged between 60 and 90 years;

• Education years≥ 6 years;

• Subjects who did not have complaint of memory decline.
Methods

- **Exclusion Criteria:**
  - Having major medical problems, such as tumor, cerebral-vascular events;
  - Having psychiatric problems, such as depression;
  - Having a history of related mental disorders;