The Cognitive Impact of Soluble Fibrillogenic Aβ Oligomers In Prodromal Dementia

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University of Melbourne
Disclosures

Nothing to disclose
Sperling et al., Alzheimer’s & Dementia, 2011.
Sperling et al., Alzheimer’s & Dementia, 2011.
Jansen et al., JAMA, 2015.
Tracking The Progression of Alzheimer Changes In Vivo

Mechanism

- Upstream events (e.g., Aβ dimers, oligomers)
- Aβ aggregation; deposition as cerebral diffuse plaques

Biomarker

- Aβ Imaging;
- ↓ CSF Aβ₄₂ levels
- ↓ brain metabolism (FDG);
- Brain volume loss (MRI)
- Dementia severity marked by increasing volume loss, ↑ CSF tau&ptau levels

Note: Other processes (e.g., inflammation; oxidative stress; vascular insufficiency) likely contribute
Tracking Aβ Oligomers Upstream

• Amyloid PET?
Tracking Aβ Oligomers Upstream

Fig. 1. Beta amyloid (Aβ) plaque formations. Different pools of intra- and extracellular Aβ.
Tracking Aβ Oligomers Upstream

- Amyloid PET?
- CSF$_{Aβ}$?
Tracking Aβ Oligomers Upstream

- Amyloid PET?
- CSF$_{\text{Aβ}}$?
  - Increased CSF Aβ$_{42}$:Aβ$_{40}$ ratio is associated with FTD, not AD?!
We can detect soluble Aβ oligomers in vivo.

But are they fibrillogenic?
Tracking Fibrillogenic Aβ

- We can assume the presence of fibrillogenic Aβ oligomers if there is increased tracer uptake on serial amyloid PET.
$^{18}$F-florbetaben Aβ imaging in mild cognitive impairment

Kevin Ong$^1$, Victor L Villemagne$^{1,2,3}$, Alex Bahar-Fuchs$^{1,4}$, Fiona Lamb$^{1,3}$, Gaël Chételat$^1$, Parnesh Raniga$^5$, Rachel S Mulligan$^1$, Olivier Salvado$^5$, Barbara Putz$^6$, Katrin Roth$^6$, Colin L Masters$^3$, Cornelia B Reininger$^6$ and Christopher C Rowe$^{1,2,*}$

Ong et al. Alzheimer’s Research & Therapy 2013, 5:4
http://alzres.com/content/5/1/4
RESEARCH PAPER

Aβ imaging with 18F-florbetaben in prodromal Alzheimer’s disease: a prospective outcome study

Kevin T Ong,¹ Victor L Villemagne,¹,² Alex Bahar-Fuchs,¹,³ Fiona Lamb,¹ Narelle Langdon,¹ Ana M Catafau,⁴ Andrew W Stephens,⁴ John Seibyl,⁵ Ludger M Dinkelborg,⁴ Cornelia B Reininger,⁶ Barbara Putz,⁶ Beate Rohde,⁶ Colin L Masters,² Christopher C Rowe¹

Methods

- 45 participants (age 73±6.6) referred from Memory Disorders specialists –
  - At least one cognitive test score < -1.5 SD (Petersen’s criteria).
  - Clinical diagnosis of MCI, MMSE 24-30.
- Neuropsychological tests – Logical Memory, CVLT, Rey Figure, etc.
- MRI: 3D T1-MPRAGE, T2, FLARE.
- PET: 90-110 min after 300 MBq of FBB.
- Image analysis:
  - **FBB PET** - **SUVR** using the cerebellar cortex as reference region.
  - **MRI** – Hippocampal Volume determined by *NeuroQuant®*; WMH determined by manual segmentation with *MRICro* software.
- Statistical analysis:
  - Linear regression.
  - Adjusted for age, gender, and years of education.
Methods

• MRI and FBB PET repeated at 12 and 24 months from baseline.
  – FBB PET (n=74) 98% sensitivity, 89% specificity for confirming significant plaque load in autopsy studies.

• Clinical assessment annually for 2 years then again at 4 years.
Amyloid Imaging

$^{18}$F-Florbetaben

Neocortical SUVR$_{90-110}$

**HC**

1.29±0.2

(n=15)

**MCI**

1.46±0.4

(n=45)

**AD**

2.03±0.3

(n=15)
Relationships

Aβ

HV

EM

WMH

NM
Relationships

HV
EM
Aβ
WMH
NM

$r=0.51, p<0.01$
Relationships

Aβ

HV

EM

WMH

NM

r = -0.51, p < 0.01

r = +0.60, p < 0.05
Relationships

Aβ

HV

r=+0.33, p<0.05,
corr Aβ (SUVR)

EM

r=-0.49, p<0.05,
corr HV

WMH

NM
Linear regression analyses

**At baseline (n=45)**

**SUVR & EM:** $r=-0.51$, $p<0.01$

*corr for HV:* $r=-0.49$, $p<0.05$

**HV & EM:** $r=0.60$, $p<0.05$

*corr for SUVR:* $r=0.33$, $p<0.05$

**SUVR & HV:** ns

Both Aβ and hippocampal atrophy may have a **direct** and **independent** relationship with memory impairment in MCI.
Relationships

HV

EM

Aβ

r = -0.51, p < 0.01

WMH

NM

Spearman’s ρ = -0.48, p < 0.001

r = +0.60, p < 0.05
Tracing the impact of amyloid beta in mild cognitive impairment

15 January 2013

Prof Christopher Rowe, from Austin Health, Australia and the University of Melbourne, who led the study explained why it is important, "MCI is thought to affect between one in five and one in ten of all adults over the age of 65, and, although some of these will go on to develop dementia within a few years, the majority can lead a relatively normal life. Detection of Aβ plaques in MCI indicates early Alzheimer's disease, while a negative scan eliminates this possibility. Consequently a negative scan is very reassuring while a positive scan can lead to earlier and more appropriate medical and social management."

More information: 18F-florbetaben Abeta imaging in mild cognitive impairment Kevin Ong, Victor L Villemagne, Alex Bahar-Fuchs, Fiona Lamb, Gaël Chételat, Parnesh Raniga, Rachel S
…After Two Years
### Linear regression analyses

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Baseline (excluding 9 drop outs)

- Aβ burden: $r = -0.44, p < 0.01$
- Hippocampal atrophy: $r = 0.26, \text{ns}$

$n = 36$
Linear regression analyses

**SUVR & EM:**
- At baseline (n=45): $r=-0.51, p<0.01$
- At baseline (n=36, excl 9): $r=-0.44, p<0.01$
- At 2 years (n=36): $r=-0.37, p<0.05$

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**HV & EM:**
- At baseline (n=36, excl 9): $r=0.60, p<0.05$
- At 2 years (n=36): $r=0.52, p<0.01$

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**SUVR & HV:**
- At baseline (n=36, excl 9): $r=0.26, ns$
- At 2 years: $r=0.32, p=0.06$

9 did not complete the full battery at 2 years
Linear regression analyses

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After 2 years

Hippocampal atrophy overtakes Aβ in driving memory impairment, and increasingly mediates this relationship, as disease progresses.

$n=36$
Changes in FBB SUVR over 2 years

SUVR increased by 2.2% (0.037) per year in those with high Aβ at baseline, p<0.01
Early progressive memory loss

• Possibly driven by soluble fibrillogenic Aβ oligomers just upstream to deposited Aβ plaques.
Aβ imaging with 18F-florbetaben in prodromal Alzheimer’s disease: a prospective outcome study

Kevin T Ong,1 Victor L Villemagne,1,2 Alex Bahar-Fuchs,1,3 Fiona Lamb,1 Narelle Langdon,1 Ana M Catafau,4 Andrew W Stephens,4 John Seibyl,5 Ludger M Dinkelborg,4 Cornelia B Reininger,6 Barbara Putz,6 Beate Rohde,6 Colin L Masters,2 Christopher C Rowe1

Table 2  Mild cognitive impairment: bivariate correlates of progression to Alzheimer’s dementia over the first 2 years of follow-up

<table>
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<tr>
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<th>Progressed to AD</th>
<th>PPV (%) (95% CI)</th>
<th>NPV (%) (95% CI)</th>
<th>Accuracy (95% CI)</th>
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<td></td>
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</tr>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBB+ (by SUVR)**</td>
<td>18</td>
<td>6</td>
<td>75.0%</td>
<td>90.5%</td>
</tr>
<tr>
<td>FBB− (by SUVR)</td>
<td>2</td>
<td>19</td>
<td>(60% to 82%)</td>
<td>(74% to 98%)</td>
</tr>
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POST HOC ANALYSES:
To compare the risk factors (co-variates) below for MCI progression to AD

1. Age.
2. Years of education
3. Gender.
4. High cerebral amyloid load (FBB+).
5. Hippocampal atrophy.
6. Poor EM.
7. Poor nonmemory-related cognitive function (NM).
8. Clinical dementia rating sum of boxes (CDR SOB).
10. Number of cardiovascular risk factors.
Methods

• **Cox regression.**

• Compare (& simultaneously correct) effects of several risk factors on unwanted events occurring.
Independent predictors of MCI progression to AD within 2 years

- FBB+
  - HR 12.7 [1.9, 82.3], p<0.01
- NM
  - HR 6.5 [1.7, 24.9], p<0.01
- CDR SOB
  - HR 2.6 [1.3, 5.1], p<0.01
Independent predictors of MCI progression to AD within 2 years

<table>
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<th>FBB-, n=21</th>
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<td>• ns</td>
<td>• NM</td>
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<td>- HR 6.6 [1.7, 26.4], p&lt;0.01</td>
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<td>- HR 2.2 [1.1, 4.4], p&lt;0.05</td>
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– Amyloid dysregulation ordered first in early AD diagnoses.
POST HOC ANALYSES:

To compare the risk factors (co-variates) below for MCI progression to AD:

1. Age.
2. Years of education
3. Gender.
4. High cerebral amyloid load (FBB+).
5. Hippocampal atrophy.
6. Poor EM.
7. Poor nonmemory-related cognitive function (NM).
8. Clinical dementia rating sum of boxes (CDR SOB).
10. Number of cardiovascular risk factors.
11. Increase in FBB tracer uptake (≡ presence of fibrillogenic Aβ oligomers)
Increased tracer uptake

- Did not predict Alzheimer’s disease.
  - Two & four years follow-up: HR ns!
- Predicted all cause dementia.
  - Two years follow-up: HR 4.8, p=0.027.
  - Four years follow-up: HR 6.9. p=0.010.
Summary

1. Early memory decline and hippocampal atrophy may be caused by soluble fibrillogenic Aβ oligomers upstream to Aβ plaques.
   - Memory loss typically starts first in AD.
1. Early memory decline and hippocampal atrophy may be caused by soluble fibrillogenic Aβ oligomers upstream to Aβ plaques.
   • Memory loss typically starts first in AD.

2. Fibrillogenic Aβ oligomers upstream to Aβ plaques are non-specific for AD dementia!
   • Aβ plaque accumulation may be the cause of AD (Amyloid Cascade Hypothesis).
   • Is Aβ plaque accumulation in AD a means to buffer the effects of Aβ-amyloidosis in non-AD?
Limitations

- Single centre.
- Limited data.
- Serial scanning increases noise.
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• Gael Chetelat

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• Andrew Stephens
• Ludger Dinkelborg
• Cornelia Reininger
• Barbara Putz
• Beate Rohde

Participants and their families

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