The Prevalence of Amyloid Positivity by Age, APOE Genotype and Cognitive Status - Implications for the Diagnosis of Alzheimer’s Disease

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Outline

• Background
• Prevalence of amyloid in normals and MCI
  – Influence of APOE
• Prevalence of amyloid in demented
  – Influence of APOE
• Diagnosis and prognosis
• Ongoing work
• Conclusions
Most dementias are proteinopathies

<table>
<thead>
<tr>
<th>Dementia</th>
<th>Aβ</th>
<th>tau</th>
<th>p-tau</th>
<th>α-synuclein</th>
<th>TDP-43</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>DLB</td>
<td>X</td>
<td>X</td>
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<tr>
<td>FTD</td>
<td>X</td>
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<td>PSP</td>
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<tr>
<td>CBD</td>
<td>X</td>
<td>X</td>
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<tr>
<td>CTE</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Alzheimer: 3 fundamental processes

- Plaques
- Tangles
- Synapse loss
Amyloid in vivo
Entering a new era: the case of AD

- Prodromal AD: diagnosing AD before dementia
- Preclinical AD: AD without symptoms
- Clinical trials include earlier populations; target protein needs to be identified
- Patients want to be informed
- Dementia field follows the oncology pathway: Personalized / precision medicine
- Emphasizes the need for biomarkers for diagnosis, tracking disease and measure effect
- Healthcare providers and payors need to be informed and prepared.
### [\(^{18}\text{F}\)] labeled Amyloid PET tracers

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Image 1</th>
<th>Image 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florbetapir (Amyvid)</td>
<td><img src="image1" alt="Florbetapir Image 1" /></td>
<td><img src="image2" alt="Florbetapir Image 2" /></td>
</tr>
<tr>
<td>Florbetaben (Neuraceq)</td>
<td><img src="image3" alt="Florbetaben Image 1" /></td>
<td><img src="image4" alt="Florbetaben Image 2" /></td>
</tr>
<tr>
<td>Flutemetamol (Vizamyl)</td>
<td><img src="image5" alt="Flutemetamol Image 1" /></td>
<td><img src="image6" alt="Flutemetamol Image 2" /></td>
</tr>
</tbody>
</table>
Amyloid binding is associated with decline

Florbetapir F 18 amyloid PET and 36-month cognitive decline: A prospective multicenter study

PM Doraiswamy, RA Sperling, K Johnson, EM Reiman, TZ Wong, MN Sabbagh, CH Sadowsky, AS Fleisher, A Carpenter, AD Joshi, M Lu, M Grundman, MA Mintun, DM Skovronsky, MJ Pontecorvo. For the AV45-A11 Study Group
**Figure.** Paired Representative Florbetapir-PET Scans and β-Amyloid Antibody 4G8 Immunohistochemistry Photo Micrographs

- **A** Participant age at death, 82 y
  - Mean cortical SUV = 0.87, PET score = 0
  - β-Amyloid burden = 0.15%
  - Low likelihood of Alzheimer disease
  - 500 μm

- **B** Participant age at death, 78 y
  - Mean cortical SUV = 1.17, PET score = 2
  - β-Amyloid burden = 1.63%
  - High likelihood of Alzheimer disease
  - 500 μm

- **C** Participant age at death, 70 y
  - Mean cortical SUV = 1.68, PET score = 4
  - β-Amyloid burden = 7.92%
  - High likelihood of Alzheimer disease
  - 500 μm
Prevalence of amyloid positivity

- Subject-level meta-analysis
  - Non-demented subjects (Jansen et al JAMA 2015)
    - Normal cognition, subjective cognitive impairment, mild cognitive impairment
    - Amyloid assessed in CSF or by PET imaging
    - Data from 55 studies
  - Demented subjects (Ossenkoppele et al JAMA 2015)
    - AD and other dementias
    - Amyloid assessed by PET imaging
    - Data from 29 studies
7578 Records identified through database search

→ Controls/MCI

6979 Excluded based on review of title and abstract
3701 Other topic, method, or design
1760 Duplicates
618 Included patients with dementia or other diseases
601 Review, opinion, case study, book, or abstract only
299 Animal study

599 Full-text articles assessed for eligibility

→ Dementia

3250 Records identified through database searching

3023 Records excluded based on review of title and abstract
1376 Other topic, method, or design
768 Duplicates
396 Inclusion of controls and/or MCI patients only
351 Review, opinion, case study, book, or abstract only
132 Animal studies

227 Full-text articles assessed for eligibility

→ Controls/MCI

555 Studies excluded after full review
533 Duplicates
7 Included patients with neurological or psychiatric diseases
6 Biomarker cutoff determined using population under study
3 No biomarker cutoff available
3 Full text not available
1 Amyloid not measured in patients without dementia
1 No clear diagnosis
1 Pilot study

91 Unique studies identified
80 Published studies
11 Unpublished studies

→ Dementia

227 Full-text articles assessed for eligibility

→ Controls/MCI

7 Articles excluded after full review
4 Inclusion of prodromal Alzheimer disease only
3 Pilot or preliminary articles

227 Full-text articles assessed for eligibility

40 Unique cohorts identified (220 articles)

→ Dementia

3 Cohorts excluded (articles published after the inclusion stop [5 articles])

37 Cohorts for which individual patient data sought (215 articles)

→ Controls/MCI

8 Cohorts excluded (study contact person refused or did not respond [30 articles])

29 Cohorts included in the analysis (185 articles)

1897 Patients
1359 Alzheimer disease
288 Frontotemporal dementia
138 Vascular dementia
51 Dementia with Lewy bodies
61 Corticobasal syndrome

55 Studies included in individual participant meta-analysis (n = 8694 participants)
Prevalence amyloid positivity in non-demented subjects
Prevalence amyloid positivity in non-demented subjects

- Normal cognition (n=2914): 37%
- SCI (n=697): 16%
- MCI (n=3971)
Prevalence amyloid positivity in non-demented subjects: effect of APOE
Prevalence amyloid positivity in non-demented subjects: effect of APOE
Prevalence amyloid positivity in non-demented subjects: effect of APOE

A) APOE-ε4 negative

- Normal cognition (n=1614)
- SCI (n=322)
- MCI (n=1650)

B) APOE-ε4 positive

- Normal cognition (n=673)
- SCI (n=211)
- MCI (n=1468)

60% 45%
Prevalence amyloid positivity in non-demented subjects: effect of APOE

(A) APOE-ε4 negative

- Normal cognition (n = 1614)
- SCI (n = 322)
- MCI (n = 1650)

(B) APOE-ε4 positive

- Normal cognition (n = 673)
- SCI (n = 211)
- MCI (n = 1468)

- Age, y
- Amyloid positivity, %

- 60%
- 45%
- 90%
- 85%
Prevalence amyloid positivity in nondemented subjects: effect of APOE
### Implications for screening for amyloid positivity

#### eTable 6. Number needed to screen according to age, cognitive status and APOE genotype

<table>
<thead>
<tr>
<th>Group</th>
<th>50 yr (95% CI)</th>
<th>60 yr (95% CI)</th>
<th>70 yr (95% CI)</th>
<th>80 yr (95% CI)</th>
<th>90 yr (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants with normal cognition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total group</td>
<td>10.0 (7.7-12.5)</td>
<td>6.3 (5.3-7.7)</td>
<td>4.3 (3.7-5.3)</td>
<td>3.0 (2.6-3.6)</td>
<td>2.3 (2.0-2.7)</td>
</tr>
<tr>
<td>APOE-ε4-</td>
<td>16.7 (11.1-25.0)</td>
<td>10.0 (7.7-14.3)</td>
<td>5.9 (4.8-7.1)</td>
<td>3.6 (3.0-4.3)</td>
<td>2.4 (2.0-3.0)</td>
</tr>
<tr>
<td>APOE-ε4+</td>
<td>6.7 (4.8-10.0)</td>
<td>3.4 (2.7-4.5)</td>
<td>2.1 (1.9-2.4)</td>
<td>1.5 (1.4-1.6)</td>
<td>1.2 (1.1-1.3)</td>
</tr>
<tr>
<td>APOE-ε4ε4</td>
<td>2.8 (2.0-4.0)</td>
<td>1.7 (1.4-2.4)</td>
<td>1.3 (1.1-1.7)</td>
<td>1.1 (1.0-1.4)</td>
<td>1.0 (1.0-1.3)</td>
</tr>
<tr>
<td><strong>Patients with MCI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total group</td>
<td>3.7 (3.3-4.3)</td>
<td>2.7 (2.4-3.0)</td>
<td>2.0 (1.9-2.2)</td>
<td>1.7 (1.5-1.8)</td>
<td>1.4 (1.3-1.5)</td>
</tr>
<tr>
<td>APOE-ε4-</td>
<td>5.3 (4.2-7.1)</td>
<td>3.8 (3.2-4.5)</td>
<td>2.9 (2.6-3.2)</td>
<td>2.2 (2.0-2.5)</td>
<td>1.8 (1.6-2.1)</td>
</tr>
<tr>
<td>APOE-ε4+</td>
<td>2.5 (2.1-3.0)</td>
<td>1.8 (1.6-2.0)</td>
<td>1.4 (1.4-1.5)</td>
<td>1.2 (1.2-1.3)</td>
<td>1.1 (1.1-1.2)</td>
</tr>
<tr>
<td>APOE-ε4ε4</td>
<td>1.6 (1.3-2.1)</td>
<td>1.3 (1.2-1.4)</td>
<td>1.1 (1.1-1.2)</td>
<td>1.1 (1.0-1.2)</td>
<td>1.0 (1.0-1.1)</td>
</tr>
</tbody>
</table>
### Implications for screening for amyloid positivity-2

**eTable 6. Number needed to screen according to age, cognitive status and APOE genotype**

<table>
<thead>
<tr>
<th>Group</th>
<th>50 yr</th>
<th>60 yr</th>
<th>70 yr</th>
<th>80 yr</th>
<th>90 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants with normal cognition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOE-ε4-</td>
<td>23.6 (15.8-35.5)</td>
<td>14.2 (10.9-20.3)</td>
<td>8.3 (6.8-10.1)</td>
<td>5.1 (4.3-6.2)</td>
<td>3.5 (2.8-4.3)</td>
</tr>
<tr>
<td>APOE-ε4+</td>
<td>22.6 (16.9-33.9)</td>
<td>11.7 (9.2-15.4)</td>
<td>7.1 (6.3-8.1)</td>
<td>5.0 (4.6-5.5)</td>
<td>4.1 (3.9-4.4)</td>
</tr>
<tr>
<td>APOE-ε4ε4</td>
<td>89.6 (64.5-129.0)</td>
<td>55.6 (45.4-76.8)</td>
<td>40.3 (35.8-54.7)</td>
<td>35.4 (32.9-43.6)</td>
<td>34.3 (32.6-41.4)</td>
</tr>
<tr>
<td><strong>Patients with MCI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOE-ε4-</td>
<td>9.9 (7.9-13.5)</td>
<td>7.3 (6.1-8.6)</td>
<td>5.4 (4.8-6.1)</td>
<td>4.2 (3.7-4.7)</td>
<td>3.4 (3.0-3.9)</td>
</tr>
<tr>
<td>APOE-ε4+</td>
<td>5.3 (4.5-6.4)</td>
<td>3.8 (3.5-4.2)</td>
<td>3.0 (2.9-3.2)</td>
<td>2.6 (2.5-2.7)</td>
<td>2.4 (2.3-2.5)</td>
</tr>
<tr>
<td>APOE-ε4ε4</td>
<td>14.7 (12.3-19.7)</td>
<td>11.9 (11.1-13.1)</td>
<td>10.8 (10.0-11.6)</td>
<td>9.9 (9.6-11.0)</td>
<td>9.7 (9.5-10.6)</td>
</tr>
</tbody>
</table>

* If APOE genotype is unknown, participants need to be screened for this first. The number needed to screen now indicate the number of participants for whom APOE genotyping needs to be performed in order to find one participant with that APOE-ε4 carrier status who is amyloid positive. It is calculated as the inverse of the point estimates for the prevalence of amyloid pathology multiplied by the APOE-ε4 background prevalence in our sample.
Comparison prevalence amyloid positivity and AD-type dementia

A Prevalence of Alzheimer disease and amyloid positivity

- Prevalence of amyloid positivity in normal cognition
- Prevalence of AD-type dementia

Prevalence, %

Age, y

0 20 40 60 80 100
Comparison prevalence amyloid positivity and AD-type dementia

Prevalence of Alzheimer disease and amyloid positivity

Prevalence of amyloid positivity in normal cognition

Prevalence of AD-type dementia

25 years
Comparison prevalence amyloid positivity and AD-type dementia
Comparison prevalence amyloid positivity and AD-type dementia

B Lifetime risk of Alzheimer disease and amyloid positivity by APOE genotype

Jansen et al. JAMA 2015
Comparison prevalence amyloid positivity and AD-type dementia

B  Lifetime risk of Alzheimer disease and amyloid positivity by APOE genotype

Amyloid positivity in normal cognition

Lifetime risk for AD-type dementia

Amyloid positivity vs Lifetime Risk, %

0  20  40  60  80  100

Age, y
Comparison prevalence amyloid positivity and AD-type dementia

B. Lifetime risk of Alzheimer disease and amyloid positivity by APOE genotype.
Relation with memory score

1a. normal cognition
1b. mild cognitive impairment

1a Frequency of memory impairment (z-score <= -1.28) in participants with normal cognition, n=2544
1b Frequency of memory impairment in participants with MCI, n=2960

Jansen et al in preparation
Relation with MMSE score

2a. normal cognition

Abnormal amyloid
Normal amyloid

2b. mild cognitive impairment

Frequency of low MMSE (MMSE <= 27) in participants with normal cognition, n=2885
Frequency of low MMSE in participants with MCI, n=4126

Jansen et al in preparation
Summary prevalence amyloid positivity in non-demented subjects

- Higher in MCI than in cognitively normal and SCI
- Strongly dependent on age and APOE genotype
- Amyloid positivity in cognitively normal subjects precedes AD-type dementia by >25 years
Prevalence amyloid positivity in demented subjects
Prevalence amyloid positivity in demented subjects: effect of APOE

[Graph showing the prevalence of amyloid positivity across different age groups and diagnoses, with APOE ε4+ highlighted.]
Prevalence amyloid positivity in demented subjects: effect of APOE

**C** APOE ε4+

**D** APOE ε4−
Prevalence amyloid positivity in demented subjects
## Effect amyloid positivity on MMSE score in non-AD dementia

<table>
<thead>
<tr>
<th></th>
<th>Amyloid positive</th>
<th>Amyloid negative</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any dementia</td>
<td>20.6</td>
<td>23.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DLB</td>
<td>19.6</td>
<td>25.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VaD</td>
<td>19.5</td>
<td>22.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FTLD</td>
<td>22.4</td>
<td>23.9</td>
<td>0.17</td>
</tr>
<tr>
<td>CBS</td>
<td>21.6</td>
<td>23</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Ossenkoppele et al JAMA 2015
Diagnostic accuracy amyloid positivity for distinction from AD
Summary prevalence amyloid positivity in demented subjects

- Amyloid positivity converges at high age across dementias
- Not all subjects with a clinical AD diagnosis are amyloid positive
- Clinical diagnosis AD and e4+:
  - >90% amyloid positive
- Clinical diagnosis AD and e4-:
  - At age 70: 90% amyloid positive
  - At age 90: 65% amyloid positive
- Amyloid positivity common in non-AD dementia
- Odds ratio decreases for clinical dementia subtype diagnosis
- Clinical relevance?
- Misdiagnosis?
- Co-morbidity?
Diagnosis and prognosis

- Amyloid markers for diagnosis
- Injury markers for prognosis

**AD stages:**

<table>
<thead>
<tr>
<th>AD stage</th>
<th>Cognition</th>
<th>AD biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical stage</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>MCI stage</td>
<td>MCI</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Dementia stage</td>
<td>Dementia</td>
<td>Abnormal</td>
</tr>
</tbody>
</table>
Prognosis preclinical AD (n=311): progression to MCI

NIA-AA stage 0
Normal amyloid and tau

NIA-AA stage 1
Abnormal amyloid and normal tau

NIA-AA stage 2/3
Abnormal amyloid and abnormal tau
Prognosis prodromal AD (n=1607): progression to AD-type dementia

NIA-AA low likelihood
Normal amyloid and tau

NIA-AA conflicting
Normal amyloid and abnormal tau
Abnormal amyloid and normal tau

NIA-AA high likelihood
Abnormal amyloid and abnormal tau

Vos et al Brain 2015
Injury markers predict time to dementia in subjects with MCI and amyloid pathology

Figure 2: Decline in Mini-Mental State Examination (MMSE) score in subjects with mild cognitive impairment (MCI) and abnormal CSF Aβ_{1-42} according to CSF total tau (t-tau) and hippocampal volume.

A) CSF t-tau
- CSF t-tau normal
- CSF t-tau abnormal

B) Hippocampal atrophy
- No hippocampal atrophy
- Hippocampal atrophy

C) Combination of CSF t-tau and hippocampal atrophy
- Both markers normal
- One marker abnormal
- Both markers abnormal
Prognosis AD dementia stage

- Low abeta low tau
- Low abeta high tau
- Low abeta very high tau
Mrs H, 1911

- Grew up in Rotterdam
- At age 28 she moved to Groningen
- Grew up in a family of musicians and became a musician herself (piano teacher)
- Oldest of 6 children
- 3 children

- Lab: ApoE 3/3
- MMSE 27/30

- One cigarette per week for 14 years (till age of 50)
- 69-90 years:
  - 3 glasses of (white/red) wine a week
- wide social network, lots of friends
Neuropsychological examination
Mrs H. 1911; MTA 2/2; Faz 2; ApoE 3/3
Mrs H. 1911; MMSE 27; amyloid angiopathy
Mrs H, 1911. C^{11}PIB at 103
Pathology

Braak 3 tau/tangles
Thal 3/5 plaques.
CAA 1/3 (Thal).

Temporal Abeta

Frontal abeta (10x)
Heritability

White matter lesions in monozygotic twin pair

Correlation in PET amyloid binding between monozygotic twins

Konijnenberg/Ten Kate in preparation
Conclusions

- Field has changed dramatically due to biomarkers
- Amyloid positivity strongly related to age and APOE
- In normal aging and dementia(s)
- Diagnostic information decreases with age
- By itself not diagnostic for AD and not be used outside of clinical context
- May be used to select patients for interventions
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Frans Verhey

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