Research Article

Brain Amyloid Deposition Is Associated With Lower Instrumental Activities of Daily Living Abilities in Older Adults. Results From the MAPT Study

Matthieu Lilamand,1,2,3 Matteo Cesari,1,3,5 Natalia del Campo,1,6 Christelle Cantet,1,3,5 Maria Soto,1,3,6 Pierre-Jean Ousset,1,3,5 Pierre Payoux,7 Sandrine Andrieu,3,5,8 Bruno Vellas,1,3,5 and the MAPT Study Group

Abstract

Background. Brain amyloid deposition is one of the key pathological hallmarks underlying the cognitive changes associated with Alzheimer’s disease. Growing interest has been given to the earliest clinical manifestations of amyloid plaques. However, the relationship between amyloid status and activities of everyday function remains largely unknown. In the present study, we examined the relationship between instrumental activities of daily living performance (using the ADL-PI score) and amyloid status in older adults.

Methods. Cross-sectional analyses of data from the Multidomain Alzheimer Preventive Trial (MAPT) were performed. Volunteers underwent a brain 18F-AV45 positron emission tomography examination. Bivariate analysis and regression models were conducted to study the relationships between brain amyloid deposition and the total ADL-PI score.

Results. We included 271 participants (women = 60%; age = 76 ± 4 years). Amyloid positron emission tomography was positive (standard uptake value ≥1.17) for 103 participants (38%). The ADL-PI score was lower in amyloid positive participants than in their amyloid negative counterparts (38.8 vs 40.3, p = .007). This association was also confirmed in regression models adjusted for age, gender, and familial history of Alzheimer’s disease (odds ratio = 0.94; 95% confidence interval 0.89–0.99; p = .02). This finding was consistent in cognitively normal individuals and in those with mild cognitive impairment, using the clinical dementia rating scale.

Conclusions. This study highlighted an association between early functional limitations and brain amyloid deposition in elderly subjects. These symptoms could be the clinical manifestations of amyloid plaques even in the absence of overt dementia. Further prospective studies are warranted for examining the evolution of ADL-PI score over the course of Alzheimer’s disease.

Key Words: Alzheimer’s disease—Amyloid plaques—PET imaging—ADL-PI

Alzheimer’s disease (AD) is the most common form of dementia worldwide and represents a public health priority in our aging societies. Brain deposition of amyloid-β protein is one of the major features in the pathophysiology of AD (1). The recent development of positron emission tomography (PET) imaging has enabled the observation of amyloid plaques in the brain of living persons, several years even before the onset of cognitive decline (2,3). This biomarker plays a central role in the recent consensus article on diagnostic criteria for AD (4). Cognitively normal subjects with amyloid deposits as measured with PET experience...
faster cognitive decline compared to their amyloid negative counterparts and are at higher risk of progressing to AD dementia (5,6).

However, there are still uncertainties regarding the clinical relevance of the amyloid status in older individuals. In this context, memory complaints might represent early symptoms of future dementia (7); nonetheless many amyloid positive subjects with memory complaints might never develop overt dementia. Moreover, a decline in the ability to perform activities of daily living (ADL) is required in the main definitions of AD dementia (8,9). Yet, most of the ADL scales assess very basic tasks, which are likely to be affected lately in the natural course of AD. Several instrumental ADL (IADL), that is, more complex tasks typically start to decline at the stage of mild cognitive impairment (MCI) (10,11). These changes might be subtle, hence very challenging to assess accurately. In this context, investigators of the Alzheimer’s Disease Cooperative Study developed the so-called ADL-PI (prevention instrument), which is an IADL questionnaire for primary prevention studies in dementia (12). This instrument specifically targets the earliest changes in performance of complex ADL with the goal of simplifying the assessment of this domain for primary prevention trials of AD.

Functional assessment is, indeed, of critical importance in the management of elders in predementia phase. A proper management and support for early functional limitations might represent a key for delaying the onset of dementia. However, to date, major uncertainties surround the relationship between amyloid status of older adults and functional performance. In AD patients, lower IADL scores were associated with increased amyloid burden in postmortem studies (13). Using Pittsburg Compound B PET imaging, daily functional impairment was related with greater amyloid burden in amnestic MCI subjects (but not in normal control subjects), independently of age, cognitive, and memory performances (14). Nevertheless, these relationships have never been studied in a population of elders with spontaneous memory complaints and a positive amyloid biomarker, who are at higher risk of developing AD.

A sensitive IADL measure might be of great help to detect early manifestations of dementia. Therefore, in the present study, we aimed to examine the association between the functional status (assessed with the ADL-PI score) and the brain amyloid status, using AV-45 PET imaging, in a population of elders recruited in the Multidomain Alzheimer Preventive Trial (MAPT).

Methods

Population

All the participants were enrolled in a neuroimaging ancillary study of MAPT, which was previously described elsewhere (15,16). In the MAPT study, participants were 70 years or older, community-dwelling, with good functional status, and reporting spontaneous memory complaints to their general practitioner. Demented subjects (and/or subjects with Mini-Mental Status Examination (MMSE) (17) score <24) were excluded. All the participants provided written informed consents. The MAPT used a four-group design, including three treatment groups (omega-3 alone, multidomain intervention alone, omega-3 plus multidomain intervention) and a placebo group, and the primary outcome measure was change in cognitive function over a 3-year follow-up. The protocol was approved by the Institutional Review Board of Toulouse, France, and conducted in accordance with the declaration of Helsinki. Overall, 1,680 participants were included in the MAPT trial. The protocol is registered on a public-access clinical trial database (www.clinicaltrials.gov; Number: NCT01513252).

The AV45-PET ancillary study started in July 2010 after obtaining appropriate funding. The MAPT participants enrolled in one of the five PET centers (Toulouse, Bordeaux, Montpellier, Limoges, and Nice) were offered to undergo an AV45-PET scan. The participants who accepted signed additional consent were included in this ancillary study. This ancillary MAPT study protocol was approved by the French Ethical committee located in Toulouse in December 2007. From the 1,680 participants in the MAPT study, 271 subjects who had already been assigned to one of the four groups of the trial, were enrolled in this ancillary study at baseline (n = 10), 6 months (n = 51), 12 months (n = 94), 24 months (n = 111), and 36 months (n = 5). Since during the follow-up participants experienced different rates of cognitive decline, we used the Clinical Dementia Rating (CDR) scale (18) for distinguishing cognitively normal (ie, CDR = 0) subjects from cognitively impaired (ie, CDR ≥ 0.5) participants.

Covariates

Demographic characteristics and educational background, health and medical history, medication intake, and cardiovascular risk factors were obtained through a standardized questionnaire. Sociodemographic characteristics included age, sex, education, and education background (total years of education completed) here classified into four categories. Clinical conditions of interest were family history of dementia, history of cancer, hypertension, diabetes mellitus, osteoarthritis, and history of depression. Body mass index was calculated as the weight divided by the square of the adult height. Blood pressure was measured with a semi-automated monitor after a 10-minute rest in supine position. A formal neuropsychological assessment, including the MMSE test, was also conducted. Physical performances were assessed using the Short Physical Performance Battery (19). Depression was evaluated with the 15-item Geriatric Depression scale (20). All these assessments were performed by physicians who specialized in cognitive disorders, trained neuropsychologists, and nurses.

PET Scan

Subjects were examined using whole-body hybrid PET-computed tomography scanners, including a PET-CT 690 (GE Healthcare), a Discovery RX VCT (General Electric), and three TruePoint HiRez (Siemens Medical Solutions). All tomographs operated in three-dimensional detection mode. All PET sinograms were reconstructed with a three-dimensional iterative algorithm, with corrections for randomness, scatter, photon attenuation, and decay, which produced images with an isotropic voxel of 2 x 2 x 2 mm3 and a spatial resolution of approximately 5 mm full width at a half maximum at the field-of-view centre. All cerebral emission scans began 50 minutes after a mean injection of 4 MBq/kg weight of 18F-AV45 (Borbetapir). For each subject, 10- or 15-minute frames were acquired to ensure movement-free image acquisition. PET images were assessed quantitatively using the standard uptake value ratio (SUVr) in the specific regions of interest (hippocampus, pons, centrum semiovale, postcingular, precuneus, frontal medial orbital and occipital, frontal parietal, temporal, anterior cingulate, left and right posterior putamen, left and right anterior putamen, left and right caudate), which were defined in relation to the
Figures 1 by guest

ADL-PI score
The ADL-PI scale consists of 15 IADL tasks and covers a large range of activities usually performed by older subjects. This instrument was designed and validated to identify early changes in complex ADL among elders (12). These activities include handling money, shopping, travel beyond the neighborhood, remembering plans and appointments, communicating with other people, preparing food and/or beverages, doing household chores, following television programs or movies, planning complex activities, and carrying out such activities. Descriptions of each activity are carefully worded, so as to provide a broad range of options for carrying out the ADL. For each item, participants had to self-report how well they performed the related activity: as usual/no difficulty = 3 points; with a little difficulty = 2 points; with a lot of difficulty = 1 point or they did not do this activity = 0 point. Therefore, the total score of the ADL-PI score is out of 45 points.

Statistical Analyses
Clinical data from the closest clinical visit to the AV-45 PET examination were considered in the present analysis. The mean time-lapse between clinical visit and amyloid assessment was less than 3 months. Information regarding family history of dementia was available for 178 participants only.

Firstly, descriptive analyses of the overall sample were performed to depict the sociodemographic, physical, and medical characteristics of participants recorded during the closest clinical visit to the PET examination. Results are provided as means (standard deviations) for quantitative variables and numbers (percentage) for qualitative variables.

Secondly, multinomial regression models were used to study the relationship between amyloid deposition and the total ADL-PI score, as well as confounding factors, that is, age, gender, and familial history of AD. The same analysis was repeated considering the ADL-PI variable in tertiles. Results are presented as odds ratios with 95% confidence interval. The interaction of the CDR variable on ADL-PI variable in tertiles. Results are presented as odds ratios with 95% confidence interval. The interaction of the CDR variable on the relationship between amyloid deposition and the total ADL-PI performance and the amyloid load assessed with the SUVr (Figures 1 and 2).

In the logistic regression analysis, including age, gender, and familial history of AD, the total ADL-PI score remained significantly associated with amyloid plaques (odds ratio = 0.94; 95% confidence interval 0.89–0.99; \( p = .02 \)). So did the ADL-PI score in tertiles (see Table 2; \( p \) for trend = .04). The lower tertile (ie, ADL-PI ≤38/45) was significantly associated with the presence of brain amyloid deposition (odds ratio = 2.34; 95% confidence interval 1.22–4.52). Age, gender, and familial history of AD were not associated with plaques in these analyses. The CDR score, indicating MCI or cognitively normal status did not affect the association between amyloid deposition and the ADL-PI score (\( p \) value for interaction = .86).

We also examined whether individual items of the ADL-PI tool were related to positive PET imaging (data not shown). Only two of them were found to be associated with positive amyloid status. The item “ability to remember current events that he/she heard or read about” was significantly more impaired in amyloid positive subjects (39.2% vs 25.3%, \( p = .02 \)). Another item: “ability to plan or organize complex activities for him/herself or for groups of people, for example travel, running errands, participating in group activities or carrying out hobbies or pastimes” was also more impaired in amyloid positive individuals (43.1% vs 27.7%, \( p = .01 \)).

Discussion
In this neuroimaging ancillary study of the MAPT trial, including 271 participants who underwent AV45-PET imaging, the presence of amyloid plaques was associated with lower ADL-PI score, independently of age, gender, and family history of dementia. This relationship was consistent in CDR = 0 (cognitively normal) and CDR = 0.5 (MCI) individuals. The mean difference between amyloid positive and negative individuals was of 1.5 point out of 45. The clinical significance of this variation would be performing one or two tasks with little difficulty (12). The ADL-PI score has been specifically elaborated to target the earliest changes in performance of complex ADL in elderly patients. This scale was also designed to be applicable to participants enrolled in primary prevention trials, such as the MAPT study. Therefore, these results are consistent with the emerging evidence of a relationship between amyloid burden and early functional limitations in cognitively impaired elders (13,14). However, we have highlighted this association in a larger elderly population. Specifically, the association between brain amyloid deposition and limitations in complex instrumental activities might already be observed in older individuals diagnosed as cognitively normal after a comprehensive neuropsychological assessment.
IADL disabilities have already been suggested to act like a substrate accelerating cognitive decline in older adults (23). Nevertheless, evidence for a relationship between amyloid burden and IADL limitations is still sparse and mostly limited to objectively cognitively impaired subjects. Marshall and colleagues have shown an association between Pittsburg Compound B and IADL impairment in MCI patients but not in normal control subjects (13). It is noteworthy that investigators used the Functional Activities Questionnaire (24) to assess the IADL, which is very similar to the ADL-PI instrument. Yet, their study only included 55 subjects (19 normal individuals with no available information about possible memory complaints). However, cognitive impairment, regardless of the amyloid status, is an established determinant of functional decline (25). In the present study, using the 1.17 cutoff to define amyloid positivity, there was no significant association between the MMSE score and brain amyloid deposition. Yet, a trend between poorer episodic memory performance (assessed with the Free and Cued Selective Reminding Test free recall) and amyloid plaques \( p = .04 \) was observed, consistent with a previous publication (26). It is also noteworthy that 47.2% of our sample had a mean CDR score of 0.5 which is the usual cutoff of MCI (27).

On the other hand, amyloid positive participants showed significantly lower ADL-PI scores. This association held after adjusting for age, gender, and familial history of AD. These three potential confounding factors were not associated with amyloid plaques in these models. Furthermore, the subjects with ADL-PI score ≤28 showed increased odds for brain amyloid plaques.

**Table 1. Characteristics of the Participants With Memory Complaints According to Their Amyloid Status**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SUVr &lt; 1.17 N = 168</th>
<th>SUVr ≥ 1.17 N = 103</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>76.1 (4.3)</td>
<td>76.0 (4.5)</td>
<td>.77</td>
</tr>
<tr>
<td>Male gender, N (%)</td>
<td>66 (39.2)</td>
<td>42 (39.6)</td>
<td>.81</td>
</tr>
<tr>
<td>Education, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>88 (52.3)</td>
<td>59 (57.3)</td>
<td>.82</td>
</tr>
<tr>
<td>10–12 years</td>
<td>25 (14.9)</td>
<td>14 (13.6)</td>
<td></td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>51 (30.4)</td>
<td>29 (28.2)</td>
<td></td>
</tr>
<tr>
<td>Family history of dementia, N (%)</td>
<td>39 (23.2)</td>
<td>22 (21.4)</td>
<td>.77</td>
</tr>
<tr>
<td>Hypertension, N (%)</td>
<td>80 (47.6)</td>
<td>43 (41.7)</td>
<td>.38</td>
</tr>
<tr>
<td>Cancer history, N (%)</td>
<td>15 (8.9)</td>
<td>13 (12.6)</td>
<td>.41</td>
</tr>
<tr>
<td>Cardiovascular disease, N (%)</td>
<td>42 (25.0)</td>
<td>26 (25.2)</td>
<td>.98</td>
</tr>
<tr>
<td>Diabetes, N (%)</td>
<td>11 (6.5)</td>
<td>9 (8.7)</td>
<td>.63</td>
</tr>
<tr>
<td>Osteoarthritis, N (%)</td>
<td>52 (31.0)</td>
<td>33 (32.0)</td>
<td>.89</td>
</tr>
<tr>
<td>Depression history, N (%)</td>
<td>26 (15.5)</td>
<td>16 (15.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Usual gait speed &lt;0.8 m/s, N (%)</td>
<td>15 (8.9)</td>
<td>9 (8.7)</td>
<td>.96</td>
</tr>
<tr>
<td>SPPB score /12</td>
<td>10.6 (1.5)</td>
<td>10.6 (1.7)</td>
<td>.86</td>
</tr>
<tr>
<td>MMSE score /30</td>
<td>28.4 (1.4)</td>
<td>28.0 (2.1)</td>
<td>.11</td>
</tr>
<tr>
<td>GDS score /15</td>
<td>2.6 (2.5)</td>
<td>3.3 (3.0)</td>
<td>.14</td>
</tr>
<tr>
<td>CDR score, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>=0</td>
<td>88 (52.7)</td>
<td>54 (20.0)</td>
<td>.86</td>
</tr>
<tr>
<td>=0.5</td>
<td>80 (29.7)</td>
<td>47 (17.5)</td>
<td></td>
</tr>
<tr>
<td>ADL-PI score/45</td>
<td>40.3 (5.0)</td>
<td>38.8 (5.2)</td>
<td>.007</td>
</tr>
</tbody>
</table>

Notes: SUVr = standardized uptake value; SPPB = Short Physical Performance Battery; MMSE = Mini-Mental Status Examination; GDS = Geriatric Depression scale; ADL-PI = Activities of Daily Living-Prevention Instrument; CDR = Clinical Dementia Rating.

**Figure 1.** Relationship between amyloid load and instrumental activities of daily living in elderly subjects with memory complaints.
Two individual items of the ADL-PI scale were significantly associated with brain amyloid deposition in our analysis. Interestingly, each of these assesses distinctive cognitive tasks. One of them addresses episodic memory whereas the second one considers cognitive planning that is a complex executive function. The latter item has already been pointed out to be sensitive for CDR 0.5 vs CDR 0 (12), whereas the former one has not. Accordingly, we assume that in older subjects with memory complaints, IADL functions might be affected before conventional screening tools for cognitive impairment (such as the MMSE score) in this population.

Several consequences may be drawn from these observations. Firstly, mild functional limitations in IADL should be given greater interest in the assessment of elders with memory complaints. Such changes might be the very early clinical manifestations of brain amyloid deposits. Secondly, the ADL-PI could be useful in prescreening procedures for clinical trials aiming at studying the prodromal AD phase. In this population of older individuals, positive amyloid biomarkers and early functional limitations represent primary targets for preventive interventions aiming at delaying the onset of dementia.

The main strength of this study is the number of participants (n = 271) who underwent PET examination. The studied population provides insights into the earliest manifestations of neurodegenerative decline. The present study also has limitations. The 1.5 between-group difference in ADL-PI score is significant, albeit should be put into perspective when taking into account the standard deviation (ie, 5 points) of this variable. The cross-sectional design does not allow us to interpret the causality between functional limitations and amyloid deposits. It cannot be excluded that third factors potentially and differently explaining our findings might have not been included in our analyses. However, we still tested a wide range of physical, cognitive, and clinical variables as potentially associated with the presence/absence of plaques before choosing the covariates of our models. PET scans were not performed at the same follow-up visit. Yet, we hypothesized that clinical data have not changed significantly over this time-lapse. The SUVr threshold of 1.17 or greater is commonly used to signify pathologic levels of amyloid associated with AD (22). However, recent studies have affirmed the existence of original amyloid pathology in cases with SUVr as low as 1.11 (28,29). The higher 1.17 threshold used in the present study is also likely to be related with a more clinically significant amyloid load than the 1.11 cutoff.

**Conclusion**

The present study emphasizes the emerging evidence of an association between brain amyloid plaques and IADL impairment. These subtle functional limitations could represent the earliest clinical manifestation of the amyloid plaques in elders without dementia. Further prospective studies are warranted to examine the evolution of functional and cognitive performances in these amyloid positive older individuals.

### Table 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADL-PI score (tertiles)/45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;42</td>
<td>1.00</td>
<td>Reference</td>
<td>.04</td>
</tr>
<tr>
<td>39–42</td>
<td>1.36</td>
<td>0.73–2.54</td>
<td>.33</td>
</tr>
<tr>
<td>≤38</td>
<td>2.34</td>
<td>1.22–4.52</td>
<td>.01</td>
</tr>
<tr>
<td>Age</td>
<td>0.98</td>
<td>0.92–1.04</td>
<td>.41</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>0.89</td>
<td>0.52–1.52</td>
<td>.66</td>
</tr>
<tr>
<td>Family history of Alzheimer’s disease</td>
<td></td>
<td></td>
<td>.71</td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.77</td>
<td>0.40–1.48</td>
<td>.43</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.86</td>
<td>0.49–1.53</td>
<td>.61</td>
</tr>
</tbody>
</table>

**Notes:** OR = odds ratio; 95% CI = 95% confidence interval; ADL-PI = Activities of Daily Living-Prevention Instrument.
Supplementary Material

Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

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