Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods. Assessment and Diagnostic Criteria

Standard Clinical and Neuropsychological Assessment

Patients underwent pre-scan standard clinical neuropsychological assessment in the coordinating center or in their own memory clinic by specifically trained raters. The clinical evaluation included: a) filling of structured forms for the collection of socio-demographic data, cognitive and medical anamnesis; b) the assessment of depression and anxiety (Brief Symptom Inventory, BSI), sleep disturbance (Profile of Elderly Quality of Life, PEQOL), and behavioral disturbances (Neuropsychiatric Inventory, NPI); c) information about daily function (Barthel Index and Functional Assessment Questionnaire, FAQ); d) rating of extrapyramidal symptoms; e) information about resource utilization (Resource Utilization in Dementia, RUD); and f) the quantification of the severity of dementia symptoms (Clinical Dementia Rating, CDR). Information required from the clinical protocol was collected with caregivers, except for the BSI (only patients).

The neuropsychological battery covered the following cognitive areas. Global cognition: Mini-Mental State Examination (MMSE), and Alzheimer’s Disease Assessment Scale – Cognitive (ADAS-COG). Long-term memory: Story Recall Test, Rey Auditory-Verbal Learning Test – immediate and delayed recall (Rey AVLT), and Recall of Rey-Osterrieth Complex Figure. Attention: Trail Making Test – Part A (TMT-A). Language: Token Test, Action and Object naming (subtest from the Battery for Analysis of Aphasic Deficits, BADA), and Letter and Category Fluency. Constructional and visuo-spatial abilities: Copy of Rey-Osterrieth Complex Figure. Upper limb apraxia: Movement imitation Test. Executive functions: Trail Making Test – Part B (TMT-B), and Wisconsin Card Sorting Test (WCST). Non-verbal reasoning: Raven’s Coloured Progressive Matrices (Raven’s CPM). The neuropsychological protocol was administered by psychologists qualified by an inter-rater reliability training. The protocol changed based on the MMSE score: with score ≥ 24, the whole battery was performed; with score < 24 (or with pathologic score at TMT-B) the WCST was excluded; and with a score < 17 only the ADAS-COG, Story Recall, Token, and Raven’s CPM tests were performed.

Diagnosis and diagnostic confidence - Diagnostic criteria

Alzheimer’s disease1; mild cognitive impairment2; nonfluent, semantic and logopenic primary progressive aphasia3; behavioural variant of frontotemporal dementia4; corticobasal degeneration5; progressive supranuclear palsy6,7; dementia with Lewy bodies8,9; multiple system atrophy10; Parkinson’s disease dementia11,12; multi-infarct dementia13; subcortical ischemic vascular dementia14.
**eTable 1.** Post-Scan Diagnosis in Patients With Inconsistent Amyloid-PET Results (58 pre-scan diagnosis of AD and negative scan and 18 pre-scan diagnosis of frontotemporal lobar degeneration (FTLD) and positive scan).

<table>
<thead>
<tr>
<th>Pre-scan diagnosis</th>
<th>AD</th>
<th>FTLD</th>
<th>Post-scan diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid-PET</td>
<td>negative</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 (21%)</td>
<td>13 (72%)</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>3 (5%)</td>
<td>0</td>
<td>Suspected non amyloid pathology</td>
</tr>
<tr>
<td></td>
<td>11 (19%)</td>
<td>5 (28%)</td>
<td>FTLD</td>
</tr>
<tr>
<td></td>
<td>1 (2%)</td>
<td>0</td>
<td>Dementia with Lewy bodies</td>
</tr>
<tr>
<td></td>
<td>16 (28%)</td>
<td>0</td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td></td>
<td>3 (5%)</td>
<td>0</td>
<td>Subjective memory impairment</td>
</tr>
<tr>
<td></td>
<td>10 (17%)</td>
<td>0</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>2 (3%)</td>
<td>0</td>
<td>Other&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup>Amnesic MCI not due to AD and endocrine disorder.
**eTable 2. Summary Table of the Main Results of Currently Available Studies on the Clinical Incremental Value of Amyloid-PET (including the present study, gray line).**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Inclusion criteria</th>
<th>Prevalence of Aβ+ in the whole sample %</th>
<th>Prevalence of Aβ– in AD patients % (N)</th>
<th>Prevalence of Aβ+ in non-AD patients % (N)</th>
<th>Diagnostic change</th>
<th>Cognition-specific medications</th>
<th>Non-cognition-specific medications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current study</strong></td>
<td>228</td>
<td>Pt. under evaluation for cognitive impairment due to uncertain diagnosis (suspect of AD)</td>
<td>60%</td>
<td>35% (165)</td>
<td>48% (63)</td>
<td>27% 79% (58) 53% (30)</td>
<td>32% 7% (91) 45% (137)</td>
<td>12% 5% (91) 6% (137)</td>
</tr>
<tr>
<td>Grundman et al., 2013&lt;sup&gt;15&lt;/sup&gt;</td>
<td>229&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Pt. under evaluation for cognitive impairment due to uncertain diagnosis (suspect of AD)</td>
<td>49%</td>
<td>38% (86)</td>
<td>57% (21 non-AD patients), 39% (122 'Indeterminate' patients)</td>
<td>55% 97% (33) 100% (12)$</td>
<td>31% 27% (116) 25% (113)</td>
<td>7% 7% (116) 3% (113)</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Type of Study</td>
<td>Diagnosis at Onset</td>
<td>Diagnosis at Prodromal AD</td>
<td>Diagnosis at Prodromal MCI</td>
<td>Diagnosis at Prodromal FTD</td>
<td>Diagnosis at Prodromal CD</td>
<td>Diagnosis at Prodromal DLB</td>
</tr>
<tr>
<td>----------------------------</td>
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<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td>Zwan et al., 2014&lt;sup&gt;16&lt;/sup&gt;</td>
<td>80</td>
<td>Case series study</td>
<td>Pt. with early onset dementia due to uncertain diagnosis</td>
<td>65% 24% (63)</td>
<td>24% (17)</td>
<td>20% 85% (13)</td>
<td>75% (4)</td>
<td>-</td>
</tr>
<tr>
<td>Jiménez-Bonilla et al., 2015&lt;sup&gt;17&lt;/sup&gt;</td>
<td>64</td>
<td>Case series study</td>
<td>17% (12, prodromal AD) 39% (33, including SMC, NA-MCI, FTD, CD and DLB) 100% (7, including A-MCI and prodromal AD) 23% (13)</td>
<td>58%</td>
<td>17% (12)</td>
<td>24% (24, including SMC, NA-MCI, FTD, CD and DLB)</td>
<td>31%</td>
<td>-</td>
</tr>
<tr>
<td>Frederiksen et al., 2012&lt;sup&gt;18&lt;/sup&gt;</td>
<td>57</td>
<td>Case series study</td>
<td>47% 12% (16) 29% (24, including SCC, depression and other diseases) 50% (4, including AD, A-MCI and prodromal AD) 43% (7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mitsis et al., 2014&lt;sup&gt;19&lt;/sup&gt;</td>
<td>30</td>
<td>Case series study</td>
<td>- - - 33% (+30% clarification)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Zannas et al., 2014&lt;sup&gt;20&lt;/sup&gt;</td>
<td>11</td>
<td>Same of Grundman et al., 2013</td>
<td>55% 25% (4) 43% (7, including non-AD and 'Indeterminate') 64%¥ 100% (1) 100% (3)</td>
<td>64%¥</td>
<td>100% (1)</td>
<td>100% (3)</td>
<td>36%</td>
<td>20% (5)</td>
</tr>
<tr>
<td>Rabinovici et al., 2014&lt;sup&gt;21&lt;/sup&gt;</td>
<td>-</td>
<td>Previous diagnosis of AD and resulted Aβ– at amyloid-PET</td>
<td>- - - - - 65% (34)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

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(N) represents the number of subject of the defined category. Reading example: in Grundman et al. (2013), 33 patients with a previous diagnosis of AD had negative amyloid-PET scan, and 97% of them had their previous diagnosis changed.

SCC: subjective cognitive complaint.

* 122 patients out of 229 received an ‘Indeterminate’ diagnosis (i.e.: the clinician described syndromes but not etiological diagnoses).

** 13 out of 57 received an ‘Indeterminate’ diagnosis.

§ Patients with ‘Indeterminate’ diagnosis were not considered.

¥ Data presentation differ from the original study: to facilitate the direct comparison of findings, we recomputed according to the method used in the present work. I.e.: Changes in the clinical stages within the same etiopathological diagnoses were not considered as "diagnostic changes".
References


