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**Early onset Alzheimer’s disease is associated with a distinct neuropsychological profile**

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Abstract

Objective: Alzheimer’s disease (AD) in younger patients is associated with a higher prevalence of atypical symptoms. We examined neuropsychological performance according to age-at-onset.

Methods: We assessed cognition in 172 patients with AD (81 early and 91 late onset) in five cognitive domains (memory, language, visuo-spatial functioning, executive functioning, attention). Dementia severity was assessed using MMSE and global cognitive decline using CAMCOG. Analyses of variance were performed with age-at-onset as between-subjects factor, and sex and education as covariates. Analysis was repeated after stratification for dementia severity (based on median MMSE).

Results: In early onset AD, age (mean±SD) was 60±4 years, 44 (54%) were female. In late onset AD, age was 72±5 years, 47 (52%) were female. Dementia severity and global cognitive decline did not differ between groups (early onset: MMSE:20±5, CAMCOG:69±15, late onset: MMSE:21±5, CAMCOG:70±15; p>0.05). Early onset patients performed worse than late onset patients on visuo-spatial functioning (p<0.01), executive functioning (p<0.001) and attention (p<0.01). Late onset patients performed worse on memory, although not significantly (p=0.11). Stratification for dementia severity showed that in mildly demented early onset patients, memory function was remarkably preserved compared to late onset patients (p<0.01). In moderate AD, differences in memory function disappeared, but early onset patients performed worse on visuo-spatial functioning (p<0.01), executive functioning (p<0.001) and attention (p<0.01) than late onset patients. Adjustment for APOE left results unchanged.

Conclusion: Early onset AD presents with a different cognitive profile and the disease course seems differently. Relative sparing of memory function in early stages stresses the need to adequately test other cognitive domains.
**Introduction**

The most common type of dementia is Alzheimer’s disease (AD), which has a clear age related prevalence. Memory deterioration typically anticipates impairment of other cognitive domains, such as language, executive functioning and visuo-spatial functioning [1].

However, AD can also occur in younger patients. AD with early onset is often defined by the arbitrary age of 65 years. Clinically, younger patients present more frequently with complaints other than forgetfulness like problems with visuo-spatial functioning or apraxia, sometimes referred to as atypical presentation [2-5]. There have been a limited number of studies on neuropsychological differences between early and late onset AD. Some studies reported more severe impairment in attention, language, visuo-spatial functioning or apraxia in patients with early onset AD, while patients with late onset AD had more severe memory impairment [6-11]. Other studies however, found no differences in cognition according to age at onset [12,13].

Limitations of the former studies include the small sample sizes and the limited scope of neuropsychological tests. Cognitive domains covered are often limited to memory and executive function, while especially visuo-spatial function is relevant in the context of early onset AD [4,8]. Furthermore, the inconsistency in results may partly be explained by differences in disease stage, which in earlier studies has not been taken into account. Differences according to age-at-onset in the mild disease stages are particularly important with respect to an early diagnosis of AD.

In the current study we used a standardized battery of neuropsychological tests, covering five cognitive domains, in a large cohort of patients with early and late onset AD. To investigate if differences in cognitive profile differed by disease stage, we stratified the analysis by dementia severity. Based on the atypical presentation which has formerly been described [2-5] and on the quite common observation of a different distribution of atrophy with prominent involvement of the posterior cortices, [14-16] we hypothesized patients with early onset AD to be more impaired on visuo-spatial functioning and less impaired on memory, compared to patients with late onset AD.
Methods

Subjects

Consecutive patients (n=215) with probable AD were retrieved from the outpatient memory clinic of the Alzheimer Center of the VU University Medical Center (VUmc) between February 2009 and November 2010. For the diagnostic procedure, they all underwent a standardized one-day assessment including medical history and family history for dementia, informant-based history, physical and neurological exam, neuropsychological assessment including the Geriatric Depression Scale (GDS), laboratory tests, electroencephalogram (EEG) and magnetic resonance imaging (MRI) of the brain. In a multidisciplinary consensus meeting, diagnoses of probable AD were made according to the diagnostic criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) [1].

Age at diagnosis of 65 years or younger was considered as early onset AD. The duration of the cognitive complaints as reported by the patient and, or caregiver was recorded to estimate the disease duration at time of diagnosis. Inclusion criteria for the current study were: a diagnosis of probable AD, and available MMSE, CAMCOG and at least one neuropsychological test in each of the cognitive domains. Of the 215 patients, 43 patients did not fulfil the inclusion criteria. This resulted in a study sample of 172 patients (81 patients with early onset AD and 91 patients with late onset AD). 17 Patients were treated with pharmacological Alzheimer therapy at time of diagnosis; Memantine (N=1), Rivastigmine (N =6) and Galantamine (N =10). The diagnosis of probable AD was confirmed by the presence of a Presenilin 1 (PSEN1) mutation in one 76 year-old patient.

Level of education was classified according to the system of Verhage ranging from 1 to 7 (low to highly educated) [17]. The study was conducted in accordance with regional research regulations and conformed to the Declaration of Helsinki. The local Medical Ethics Committee approved the study and all patients gave written informed consent for their clinical and biological data to be used for research purposes.

Neuropsychological assessment

We used a standardized test battery to assess cognitive functions. To assess dementia severity we used the Mini-Mental State Examination (MMSE) and the Cambridge Cognitive Examination (CAMCOG) for global cognitive decline [18,19]. For memory, we used the Visual Association Test (VAT) and total immediate recall and delayed recall of the Dutch version of the Rey auditory verbal learning task (RAVLT) [20-22]. To examine language, we used VAT naming, category fluency (animals) and the Dutch version of Controlled Oral Word Association Test (COWAT) (letter fluency) [20,23-25]. We used three subtests of the Visual Object and Space Perception Battery (VOSP) to assess visuo-spatial functioning, namely (i) incomplete letters, (ii) dot counting and (iii) number location [26]. For the attention domain we used Trail Making Test (TMT) A and the forward condition of Digit Span (extended version) [27, 28]. We used TMT B and the backwards condition of Digit Span (extended version) to examine executive functioning [27,28].

APOE and CSF

DNA was isolated from 10 ml blood samples in ethylenediaminetetraacetic acid (EDTA). Apolipoprotein (APOE) genotype was determined at the Neurological Laboratory of the Department of Clinical Chemistry of the VUmc with the LightCycler APOE mutation detection method (Roche Diagnostics GmbH, Mannheim, Germany). APOE data were available for 161 patients (early onset: N=74; late onset: N=87) and were analysed according to the presence or absence of an APOE Ɛ4 allele. CSF was obtained by a lumbar puncture. Amyloid β(1-42) (Aβ42),
total tau and tau phosphorylated at threonine-181 (Ptau\textsubscript{-181}) were measured by sandwich ELISA (Innogenetics, Gent, Belgium) \cite{29}. CSF analyses were performed at the VUmc Department of Clinical Chemistry. Cut-off levels in our lab for A\textbeta{}42 are <550, total tau >375 and ptau >52 \cite{29}. CSF was available for 140 patients (early onset: N=71; late onset: N=69).

**Statistical analysis**

PASW Statistics 18.0 for Mac was used. TMT A and B scores were log-transformed because they were not normally distributed. All neuropsychological data were standardized into z-scores, to allow comparison of different neuropsychological tests within patients. TMT A and B scores were inverted by computing \(-1 \times z\)-score, because higher scores imply a worse performance. In patients where the TMT B (N= 72) was aborted, for example because of lack of time, we estimated TMT B by multiplying the time needed to complete TMT A with the mean B/A index. The mean B/A index for all patients who completed both TMT A and B (N=90) was 3.48. In order to create the five cognitive domains the mean z-scores of the available tests in every domain were calculated. Independent samples T-test were conducted for demographics of patients. \(\chi^2\)-tests were used when appropriate. Univariate analyses of variance (ANOVA) were performed with age at onset as between-subjects factor. Sex and education were entered as covariates. We repeated the analysis after stratification for dementia severity, based on median MMSE, creating two groups: mildly demented (MMSE>21) and moderately demented (MMSE≤21). We repeated the analyses, additionally adjusting for APOE \(\varepsilon4\) status. For all analyses, the significance level was set at \(p<0.05\).
Results

Demographics are listed in table 1. In early onset AD age (mean±SD) was 60±4 years and 44 patients (54%) were female. In patients with late onset AD age was 72±5 years and 47 patients (52%) were female. There were no differences between groups in sex, education, disease duration, GDS, family history of dementia, number of patients treated with pharmacological therapy, number of APOE Ɛ4-positive patients or levels of CSF biomarkers (table 1).

Table 1. Demographics of patients with early and late onset Alzheimer’s disease.

<table>
<thead>
<tr>
<th></th>
<th>Early Onset AD</th>
<th>Late Onset AD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of women, N (%)</td>
<td>81 (54%)</td>
<td>91 (52%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Age in years</td>
<td>81 60 ± 4</td>
<td>91 72 ± 5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Level of education</td>
<td>81 5 ± 1</td>
<td>91 5 ± 1</td>
<td>0.20</td>
</tr>
<tr>
<td>Disease duration</td>
<td>81 3.3 ± 2.4</td>
<td>90 3.5 ± 2.7</td>
<td>0.72</td>
</tr>
<tr>
<td>Geriatric Depression Scale</td>
<td>66 3 ± 3</td>
<td>67 3 ± 3</td>
<td>0.97</td>
</tr>
<tr>
<td>Number of patients with family history of dementia, N (%)</td>
<td>81 37 (44%)</td>
<td>91 45 (50%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Number of patients treated with pharmacological therapy, N (%)</td>
<td>81 10 (12%)</td>
<td>91 7 (8%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Number of APOE Ɛ4 carriers, N (%)</td>
<td>74 46 (62%)</td>
<td>87 57 (65%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Aβ42</td>
<td>71 455 ± 121</td>
<td>69 497 ± 170</td>
<td>0.10</td>
</tr>
<tr>
<td>Tau</td>
<td>71 618 ± 377</td>
<td>69 717 ± 549</td>
<td>0.21</td>
</tr>
<tr>
<td>Ptau</td>
<td>71 89 ± 39</td>
<td>69 99 ± 55</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Values presented as mean ± standard deviation. Independent samples T-test were conducted with age at onset as between-subject factor. χ²-tests were used when appropriate. Cut-off levels in our lab for Aβ42 are <550, total tau >375 and ptau >52 [29].

Adjusted for education and sex, dementia severity and global cognitive decline, as measured by MMSE and CAMCOG, were not different between early and late onset AD, see table 2. No differences on the VAT were found. Patients with early onset AD performed better than patients with late onset AD on total immediate recall and delayed recall of the Dutch RAVLT. Patients with early onset AD performed worse on incomplete letters, dot counting, number location, TMT A, Digit Span forward, TMT B and Digit Span backward than patients with late onset AD. Regarding the language tests, both groups performed at the same level.
Table 2. Neuropsychological test performance of patients with early and late onset Alzheimer’s disease.

<table>
<thead>
<tr>
<th>Test</th>
<th>Early Onset AD</th>
<th>Late Onset AD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>N=81</td>
<td>N=91</td>
<td>0.20</td>
</tr>
<tr>
<td>CAMCOG</td>
<td>N=81</td>
<td>N=91</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- VAT</td>
<td>N=81</td>
<td>N=87</td>
<td>0.79</td>
</tr>
<tr>
<td>- RAVLT*, total immediate recall</td>
<td>N=72</td>
<td>N=81</td>
<td>0.05</td>
</tr>
<tr>
<td>- RAVLT*, delayed recall</td>
<td>N=72</td>
<td>N=79</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- VAT naming</td>
<td>N=81</td>
<td>N=88</td>
<td>0.33</td>
</tr>
<tr>
<td>- Category Fluency</td>
<td>N=71</td>
<td>N=84</td>
<td>0.60</td>
</tr>
<tr>
<td>- Letter Fluency</td>
<td>N=63</td>
<td>N=81</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>Visuo-spatial Functioning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Incomplete Letters</td>
<td>N=53</td>
<td>N=62</td>
<td>0.02</td>
</tr>
<tr>
<td>- Dot Counting</td>
<td>N=54</td>
<td>N=61</td>
<td>0.01</td>
</tr>
<tr>
<td>- Number Location</td>
<td>N=74</td>
<td>N=83</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Executive Functioning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- TMT B §</td>
<td>N=73</td>
<td>N=89</td>
<td>0.001</td>
</tr>
<tr>
<td>- Digit Span backward</td>
<td>N=79</td>
<td>N=88</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- TMT A §</td>
<td>N=73</td>
<td>N=89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Digit Span forward</td>
<td>N=80</td>
<td>N=89</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Performance on neuropsychological testing presented as mean ± standard deviation. Cognitive profiles are divided into neuropsychological tests. Univariate analyses of variance were performed with age at onset as between-subject factor. Sex and education were entered as covariates. According to the Verhage-system, * Dutch version of the Rey auditory verbal learning task (RAVLT). § Higher scores imply worse performance.

Figure 1 shows the performance on five cognitive domains of both groups. Patients with early onset AD performed worse on tasks demanding visuo-spatial functioning (p<0.01), executive functioning (p<0.001) and attention (p<0.01) than patients with late onset AD. On memory tasks, patients with early onset AD performed relatively better than patients with late onset AD, but this did not reach significance (p=0.11). We found no differences between early and late onset AD in language performance (p=0.21).
Figure 1. Mean neuropsychological Z-scores by age at onset of Alzheimer’s disease.

![Graph showing mean Z-scores by age at onset of Alzheimer’s disease]

The x-axis shows the five cognitive domains: memory, language, visuo-spatial functioning, executive functioning and attention. The y-axis shows the mean z-scores for patients with early onset AD (N=81) and late onset AD (N=91). Univariate analyses of variance were performed with age at onset as between-subject factor and sex and education as covariates.

** p<0.001  * p<0.01  # p=0.11

When we additionally adjusted for APOE Ɛ4, the effect of age on memory tasks between patients with early onset AD and patients with late onset AD became significant (p=0.02), while the results for other cognitive domains remained essentially unchanged. When looking at their neuropsychological profile, patients with late onset AD performed worst on memory and better on executive functioning and attention. Patients with early onset AD showed a different profile as they performed worst on visuo-spatial functioning and best on memory.

When we repeated the analyses without the patients who were treated with pharmacological therapy (N=17) the results did not change essentially; patients with early onset AD performed worse on visuo-spatial functioning (p<0.01), executive functioning (p<0.001) and attention (p<0.001) and tended to perform worse on language (p=0.10) than patients with late onset AD. The effect of age on memory performance between patients with early onset AD and patients with late onset AD became almost significant (p=0.07).

Subsequently, we repeated the analysis after stratification for dementia severity. In mildly demented patients, age was 60±4 years in early onset (n=35) and 73±5 in late onset (n=50). We found no differences regarding sex (p=0.31), education (p=0.11), MMSE (p=0.80) or CAMCOG (p=0.36). Figure 2 illustrates that in mildly demented patients, those with early onset AD performed better on memory than those with late onset AD (p<0.01). There were no differences in performance on any of the other cognitive domains. Additional adjustment for APOE left the results unchanged. Looking at their cognitive profiles, mildly demented patients with late onset AD performed worst on memory, while other cognitive domains were relatively spared. Patients with early onset AD however, had a remarkably preserved memory, whereas other domains were more impaired.

Figure 2. Mean neuropsychological Z-scores by age at onset in mild Alzheimer’s disease (MMSE > 21).
Cognitive domains: memory, language, visuo-spatial functioning, executive functioning and attention. The y-axis shows the mean z-scores for mildly demented patients (MMSE > 21) with early onset AD (N=35) and late onset AD (N=50). Univariate analyses of variance were performed with age at onset as between-subject factor and sex and education as covariates.

* p<0.01
In moderately demented patients, age was 60±4 years in early onset (n=46) and 72±4 in late onset (n=41). There were no differences according to sex (p=0.51), education (p=0.49), MMSE (p=0.91) or CAMCOG (p=0.56). Figure 3 illustrates that in moderately demented patients, patients with early onset AD performed worse on visuo-spatial functioning (p<0.01), executive functioning (p<0.001) and attention (p<0.01) than those with late onset AD. There was no difference in performance on memory and language. Additional adjustment for APOE Ɛ4 did not change the results.

**Figure 3.** Mean neuropsychological Z-scores by age at onset in moderate Alzheimer’s disease (MMSE ≤ 21).
Discussion

The main conclusion of this study is that patients with early onset AD, despite comparable dementia severity and disease duration, performed worse on tasks demanding visuo-spatial functioning, executive functioning and attention than patients with late onset AD, while their memory function seemed relatively preserved. Especially, in mildly demented early onset patients, memory was remarkably preserved, while other cognitive domains were already clearly affected. In moderately demented early onset patients, memory performance had dropped to the level of late onset AD but visuo-spatial functioning, executive functioning and attention were even more severely impaired.

Our results show that patients with early onset AD presented with a different cognitive profile than patients with late onset AD, and that these differences were already present in the early clinical stages. To date, it is not clear why these subgroups present with different cognitive profiles. Still, it is becoming increasingly clear that AD is a highly heterogeneous disorder. Probably, it is not age-at-onset per se that determines the cognitive profile, but some other — as yet unknown — underlying genetic and/or biological factors that predispose for both an earlier age-at-onset and a different clinical manifestation. APOE is a genetic risk factor, which is also known to influence the clinical phenotype [30, 31]. In this study, we adjusted for APOE genotype, and results remained essentially unchanged. This implies that there must be other factors than APOE contributing to the neuropsychological profile as well.

Compared to late onset AD, early onset patients performed worst on tests demanding visuo-spatial functioning, in line with another study [8]. Regardless of disease stage, it was the most impaired cognitive domain in early onset AD. Earlier studies showed conflicting results regarding memory between early and late onset AD [6, 7, 12]. We observed that patients with early onset AD had a relatively preserved memory function in comparison to patients with late onset AD, especially in the early stage of AD. This finding stresses the need to incorporate sensitive tests on other domains than memory in diagnostic work-up.

We found no differences in language according to age at onset in contrast with a number of studies that found more severe language impairment in early onset AD [7, 9, 11]. Two of these former studies were conducted just after or around the publication of the NINCDS-ADRDA criteria. At that time there were no criteria to diagnose semantic dementia (SD) and progressive non-fluent aphasia (PNFA) [32, 33], both hallmarked by an early onset. It is conceivable that the observed language differences in these former studies are attributable to a subset of misdiagnosed patients who nowadays would have been diagnosed with SD or PNFA. Alternatively, our language tests may not have been sensitive enough to reveal subtle differences between early and late onset AD.

Contrary to our hypothesis, we found that the differences between early and late onset AD were most prominent in the cognitive domain of executive functioning. We found more impaired executive functioning and attention particularly in more advanced early onset AD. A small study found no difference in executive functioning between early and late onset AD [12], in contrast to another study which found that an earlier age at onset was associated with more impairment in executive functioning [10]. Impairment of attention in early onset AD is concordant with a number of other studies [6-8, 34] Our clinical findings are in agreement with imaging studies revealing a relatively preserved hippocampus in early onset AD, while other cortical areas such as occipital and (fronto)parietal cortex show more prominent atrophy [3, 14-16, 35]. Although it is tempting to presume that there will be a one to one relationship between pattern of atrophy and cognitive profile, this is by no means self-evident. Future study should
therefore focus on unravelling the mechanisms underlying the differences in cognitive profile by studying these relationships.

A possible limitation of this study is that we did not have post-mortem data available, so the possibility of misdiagnosis cannot be excluded. Nevertheless, we have an extensive standardized work-up and all patients fulfilled clinical criteria of probable AD. Furthermore, CSF biomarkers were available for the majority of patients and average biomarker levels were congruent with a diagnosis of AD in both groups, rendering the possibility of misdiagnosis less likely. Another limitation is the cross-sectional design of the study, which precludes us from drawing firm conclusions about the disease course in early and late AD. Moreover, no specific tests for praxis and gnosis were included in our neuropsychological assessment. Among the strengths of this study, are the large cohort of patients with AD, with a wide variety in age at onset, and the standardized neuropsychological test battery. This battery included tests assessing visuo-spatial functioning, a domain which is often not incorporated in the neuropsychological assessment of dementia. In this study these tests proved their value.

Our study has important implications. First, this neuropsychological study confirms the clinical observation that patients with early onset AD frequently have a non-memory, atypical, presentation. Particularly in the mild stages of the disease, memory is often preserved, stressing the need to adequately assess other cognitive domains in the neuropsychological assessment to avoid misdiagnosis. Especially the cognitive domain of visuo-spatial functioning is often not adequately covered in the neuropsychological test battery, while in fact it is of the highest relevance in the diagnostic work-up of patients with early onset AD. Furthermore, the analyses stratified by MMSE, as a measure of disease severity, seem to imply that the course of cognitive impairment differs according to age-onset.

We are currently following our patients longitudinally with repeated neuropsychological testing to study if indeed, symptoms develop in a different order in specific subgroups. It is tempting to assume that the cognitive symptoms follow the distribution of underlying neuropathology [36]. If this is true, then it may follow that the Braak stages as described in the early nineties may not hold for all patients, and need to be adapted for specific subgroups [37]. Modern imaging techniques, including MRI and amyloid PET can help greatly, as they make it possible to track the development of disease over time [15,30].

In conclusion, we found that patients with early onset AD have a different cognitive profile than patients with late onset AD, providing further evidence for the heterogeneity in clinical manifestation of AD. This seems to reflect variability in pathways leading to the disease and understanding these may lead to new targets for therapy. Ultimately, understanding differences in neuropsychological profiles may therefore contribute to the development of personalized treatment of AD.

**Acknowledgments**

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