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Early onset APOE Ɛ4-negative Alzheimer's disease patients show faster cognitive decline on non-memory domains

Submitted

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Abstract

Objective: Age-at-onset and APOE Ɛ4 genotype have been shown to influence clinical manifestation of Alzheimer's disease (AD). We investigated rate of decline in specific cognitive domains according to age at onset and APOE Ɛ4 genotype.

Methods: 199 patients with probable AD underwent at least two annual neuropsychological assessments. Patients were classified according to age-at-onset (≤65 years vs >65 years) and APOE Ɛ4 genotype (positive vs negative). The neuropsychological battery compromised tests for memory, language, attention, executive and visuo-spatial functioning. For each domain compound z-scores were calculated, based on baseline performance of patients. Average duration of follow-up was 1.5±1 years. We used linear mixed models (LMM) to estimate effects of age, APOE and age*APOE on cognitive decline over time.

Results: At baseline, patients were 65±8 years, 98(49%) were female and MMSE was 22±4. LMM showed that early onset patients declined faster on executive functioning (β±SE:-0.09±0.06) than late onset patients, but age was not related to decline in other cognitive domains. APOE Ɛ4-negative patients declined faster on language than APOE Ɛ4-positive patients (β±SE:-0.1±0.06). When we took age and APOE genotype into account simultaneously, we found that compared to late onset-Ɛ4 positive patients, early onset-Ɛ4 negative patients declined faster on language (β±SE:-0.36±0.1), attention (β±SE:-0.42±0.1), executive (β±SE:-0.41±0.1) and visuo-spatial functioning (β±SE:-0.43±0.1). Late onset-Ɛ4 negative and early onset-Ɛ4 positive patients showed intermediate rates of decline. We found no differences in decline on memory.

Conclusion: We found that patients who develop AD despite absence of the two most important risk factors, show steepest cognitive decline on non-memory cognitive domains.

Introduction

Alzheimer's disease (AD) is increasingly being considered a disease in which the clinical presentation between patients may differ [1,2]. One way to look at heterogeneity of AD is by analysing rate of decline. By definition, patients with AD show cognitive decline over time, but the rate of deterioration is highly variable between individuals.

Age and the apolipoprotein (APOE) Ɛ4 gene are risk factors for AD. Moreover, both factors have been shown to modify clinical presentation and rate of cognitive decline in AD [2]. Lower age at onset and absence of the APOE Ɛ4 allele have been associated with different rates of cognitive decline [2,3]. In general, a lower age at onset seems to be associated with faster progression [2,4]. The influence of APOE Ɛ4, however, is less clear. Some studies found that presence of the Ɛ4 allele was associated with faster cognitive decline, while others found a slower cognitive decline, or concluded that there was no influence of APOE Ɛ4 on rate of cognitive decline at all [5-10].

Studies investigating both age at onset and APOE Ɛ4 in AD are rare. A recent longitudinal study assessing both age and APOE Ɛ4 had a limited follow up duration of one year and focused mainly on memory performance [11]. They found that younger patients who were APOE Ɛ4-positive showed steeper decline. By contrast, in an earlier study by our group we showed more rapid global cognitive decline in early onset than in late onset AD and this was most prominent in APOE Ɛ4-negative patients [3]. It remains unclear, however, how age at onset and APOE Ɛ4 status influence decline of specific cognitive domains other than memory.

In this longitudinal study in AD patients, we therefore aimed to investigate the rate of decline in memory, language, attention, executive and visuo-spatial functioning, according to age at onset and APOE Ɛ4 status.

Methods

Subjects

We included 199 patients with a diagnosis of probable AD and a minimum of two neuropsychological evaluations (at least one year apart) from the Amsterdam Dementia Cohort between January 2008 and December 2011 [12]. All patients underwent a standardized one-day assessment including medical history, informant-based history, physical and neurological exam including Clinical Dementia Rating (CDR), neuropsychological assessment, laboratory tests, magnetic resonance imaging (MRI) of the brain and electroencephalogram (EEG).

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. Diagnoses were made in a multidisciplinary consensus meeting using international diagnostic consensus criteria. The diagnosis of probable AD patients was made using the criteria of McKhann [13,14]. Level of education was classified according to the system of Verhage ranging from 1 to 7 (low to highly educated) [15]. The local Ethics Review Board approved the study and all patients gave written informed consent for their clinical data to be used for research purposes.

Neuropsychological assessment

Cognitive functions were assessed with a standardized test battery. We used the MMSE as a measure for global cognitive decline [16]. 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) [17-19]. To examine language, we used VAT naming, category fluency (animals), the Dutch version of Controlled Oral Word Association Test (COWAT) (letter fluency), comparative questions and naming of the Arizona Battery for Communication Disorders (ABCD) [17,20-22]. For attention we used Trail Making Test (TMT) A and the forward condition of Digit Span (extended version) [23,24].

We used TMT B, the backwards condition of Digit Span (extended version) and the Frontal Assessment Battery (FAB) to examine executive functioning [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]. Additionally, the Geriatric Depression Scale (GDS) was assessed [27]. TMT A and B scores were log-transformed because they were not normally distributed. TMT A and B scores were log-transformed due to non-normal distribution, and inverted by computing the score by -1, because higher scores imply a worse performance.

Follow up

At follow-up, all subjects underwent physical and neurological exam, and a repeated neuropsychological evaluation. For the total sample, the median number of neuropsychological assessments was 2 (range 2-4) and the mean duration of follow-up was 1.5±1 years.

APOE

DNA was isolated from 10 ml blood samples in ethylenediaminetetraacetic acid (EDTA). APOE Ɛ4 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 Ɛ4 data

were available for 181 patients (early onset: N=100; late onset: N=81) and were analysed according to the presence or absence of an APOE Ɛ4 allele.

Statistical analysis

PASW Statistics 20.0 for Mac was used. For baseline demographics and raw neuropsychological data, χ^2-tests, independent samples T-test and Univariate Analysis of Variance (ANOVA) were performed when appropriate. ANOVA's were conducted with age at onset (≤65 vs > 65) or APOE Ɛ4 status (negative versus positive) as between-subjects factor and neuropsychological test as dependent variable. Sex, education and age (when appropriate) were entered as covariates.

To obtain unbiased estimation of cognitive domain scores, we imputed missing neuropsychological test scores by multiple imputation of individual test scores in PASW. The method we used was predictive mean matching, because of the non-Gaussian distribution of some of the tests. Predictors for imputation were age (at time of neuropsychological assessment), gender, education, diagnosis, CDR-score, GDS-score and all available neuropsychological tests. Fifteen imputed data sets were created. Neuropsychological baseline tests were standardized into z-scores and based on these z-scores, we calculated z-scores for each follow up for each patient, relative to baseline z-scores. Next, we computed compound z-scores for memory, language, attention, executive functioning and visuo-spatial functioning for each imputed dataset. We report pooled statistics over 15 imputed data sets.

Linear mixed models with an unstructured covariance pattern were used to assess associations between diagnosis and baseline cognition and cognitive performance over time. First, we performed a model including terms for age, time and the interaction between age and time. Second, we performed a model with terms for APOE Ɛ4 status, time and the interaction between APOE Ɛ4 status and time. In both models random effects were subject-ID and time and outcome measures were compound z-scores of the five cognitive domains. Beta±SE for diagnosis represents the association between age or APOE Ɛ4 status and baseline cognitive performance, whereas the interaction between age or APOE Ɛ4 status and time represents the association between group membership and cognitive performance over time.

Next, we combined age and APOE Ɛ4 status to create a new four-level variable 'age*APOE'. The levels were 1) late onset-Ɛ4 positive patients, 2) late onset-Ɛ4 negative patients, 3) early onset-Ɛ4 positive patients and 4) early onset-Ɛ4 negative patients. In an additional analysis, we evaluated the combined effect of age and APOE by including the newly constructed four-level variable Age*APOE as categorical term in the model (late onset-Ɛ4 positive patients as reference). We recoded the variable in order to estimate beta's and SE's for all levels of this variable. All analyses were corrected for gender and education, and age (when age at onset was not a factor in the analysis). Data of linear mixed models are presented as uncorrected beta±SE with p-values of the corrected models. For main effects the significance level was $p<0.05$ and for interactions $p\leq0.10$.

Results

In table 1, demographics and baseline performance on neuropsychological tests are shown for early versus late onset patients and APOE Ɛ4-negative versus APOE Ɛ4-positive patients. There were no differences between early and late onset patients regarding sex, education, disease duration, GDS or CDR. At baseline, early onset patients performed worse on MMSE than late onset patients (21±4 versus 22±4; $p<0.05$). Early onset patients performed also worse than late onset patients on comparative questions, letter fluency, Digit Span forward, TMT A, Digit Span backwards, fragmented letters, dot counting and number location (all $p<0.05$).

Regarding APOE Ɛ4 status, there were no differences in demographics. On neuropsychological tests, APOE Ɛ4-positive patients performed worse on VAT and RAVLT delayed (both $p<0.05$) than APOE Ɛ4-negative patients. APOE Ɛ4-negative patients performed worse on naming (ABCD) ($p<0.05$) than APOE Ɛ4-positive patients. On compound cognitive domain scores, APOE Ɛ4-negative patients performed worse on language compared to APOE Ɛ4-positive patients (-0.1 versus 0.21; $p<0.05$). On the other domains we found no differences between APOE Ɛ4-positive and negative patients: memory (Ɛ4+ -0.05 versus Ɛ4- 0.14; $p=0.14$), attention (Ɛ4+ -0.01 versus Ɛ4- -0.04; $p=0.85$), executive functioning (Ɛ4+ 0.29 versus Ɛ4- 0.08; $p=0.22$) or visuo-spatial functioning (Ɛ4+ 0.09 versus Ɛ4- 0.17; $p=0.59$).

To compare the trajectories of cognitive decline according to age and APOE Ɛ4 we conducted linear mixed models (table 2). At baseline, early onset patients performed worse on attention than late onset patients ($p<0.01$) and over time, they declined faster on executive functioning than late onset patients ($p\leq0.10$). APOE Ɛ4-positive patients did not differ from APOE Ɛ4-negative patients at baseline, but APOE Ɛ4-negative patients declined faster on language than APOE Ɛ4-positive patients ($p\leq0.10$).

Table 1. Baseline demographics and raw neuropsychological data according to age at onset and APOE Ɛ4 status.

	Onset		APOE status	
	Late	**Early**	**Ɛ4+**	**Ɛ4-**
N+	87	112	120	61
Age	72±4	59±5*	65±8	65±10
Sex, female	42 (48%)	56 (50%)	55 (46%)	33 (54%)
Education^	5±1	5±1	5±1	5±1
Disease duration, y	2.9±2	3.3±1.7	3.1±1.8	3.2±2
# of NPO	2 (2-4)	2 (2-4)	2 (2-4)	2 (2-4)
GDS	2.2±2	2.6±2	2.6±2	2.2±2
CDR	1±0.4	1±0.5	1±0.4	1±0.5
MMSE	22±4	21±4*	21±4	22±4
Memory				
VAT	7±4	6±4	5.7±4	7.1±4*
RAVLT° total immediate recall	23±8	24±8	24±8	22±7
RAVLT° delayed	1.9±2	2.3±3	1.8±3	2.6±3*
Language				
VAT naming	11±2	11±1	11±2	11±1
ABCD Naming	16±3	17±4	16.8±3	15.2±4*
Comparative questions	5.7±0.6	5.1±1.2*	5.4±1	5.4±1
Animal fluency	13±6	13±5	12.8±5	12.4±5
Letter fluency	28.2±12	24.3±12*	26.1±12	24.8±10
Attention				
Digit span forward	11.7±3	10.5±3*	10.9±3	11±3
TMT a §	72±41	105±82*	90±70	91±64
Executive functioning				
Digit span backwards	7.4±2	5.9±2*	6.6±3	6.3±2
TMT b §	202±113	208±114	212±126	206±94
FAB	12.9±4	12.1±4	12.4±4	12.4±3
Visuo-spatial functioning				
Frag. Letters	17.4±4	14.5±6*	15.7±5	16.1±5
Dot Counting	9.3±1	8.5±2*	8.8±2	9.1±2
Number location	8.6±2	8±2*	8.3±2	8.2±2

Values are presented as mean±standard deviation, number (percent) or median (range). Cognitive profiles are divided into neuropsychological tests. APOE Ɛ4 data were available for 181 patients. + = N differs for every neuropsychological test since raw data are presented, ^ = education according to the Verhage system, § = higher scores means worse performance, GDS = Geriatric Depression Scale, CDR = Clinical Dementia Rating, MMSE = Mini-Mental State Examination, VAT = Visual Association Test, RAVLT = Rey auditory verbal learning task, ABCD = Arizona Battery for Communication Disorders, TMT = Trail Making Test, FAB = Frontal Assessment Battery.

* = significant difference $p<0.05$ early versus late onset or APOE Ɛ4- versus APOE Ɛ4+.

Table 2. Estimated effects of age and APOE Ɛ4 on baseline- and annual change in compound scores for different cognitive domains.

	Memory	Language	Attention	Executive functioning	Visuo-spatial functioning
Baseline cognitive score					
Age	-0.14±0.09	0.06±0.09	0.26±0.09*	0.14±0.10	0.14±0.01
APOE	-0.17±0.12	0.14±0.11	0.06±0.12	0.03±0.13	0.04±0.13
Annual cognitive change					
Age	0.01±0.04	0.5±0.06	0.09±0.06	0.09±0.06**	0.12±0.08
APOE	0.06±0.05	0.10±0.06**	0.06±0.07	0.04±0.06	0.04±0.08

Data are presented as Beta(standard error). Beta's represent uncorrected estimated baseline performance or estimated change over time. P-values for differences between groups are given for the models corrected for gender and education, and if appropriate, corrected for age. Age and APOE Ɛ4 were evaluated in separate analyses. Age (N=199; early onset (N=112) and late onset (N=87)) and APOE Ɛ4 (N=181; positive (N=120) and negative (N=61)).

* p<0.01, ** p<0.10.

Table 3. Estimated effect of age at onset and APOE Ɛ4 on baseline- and annual change in compound scores for different cognitive domains.

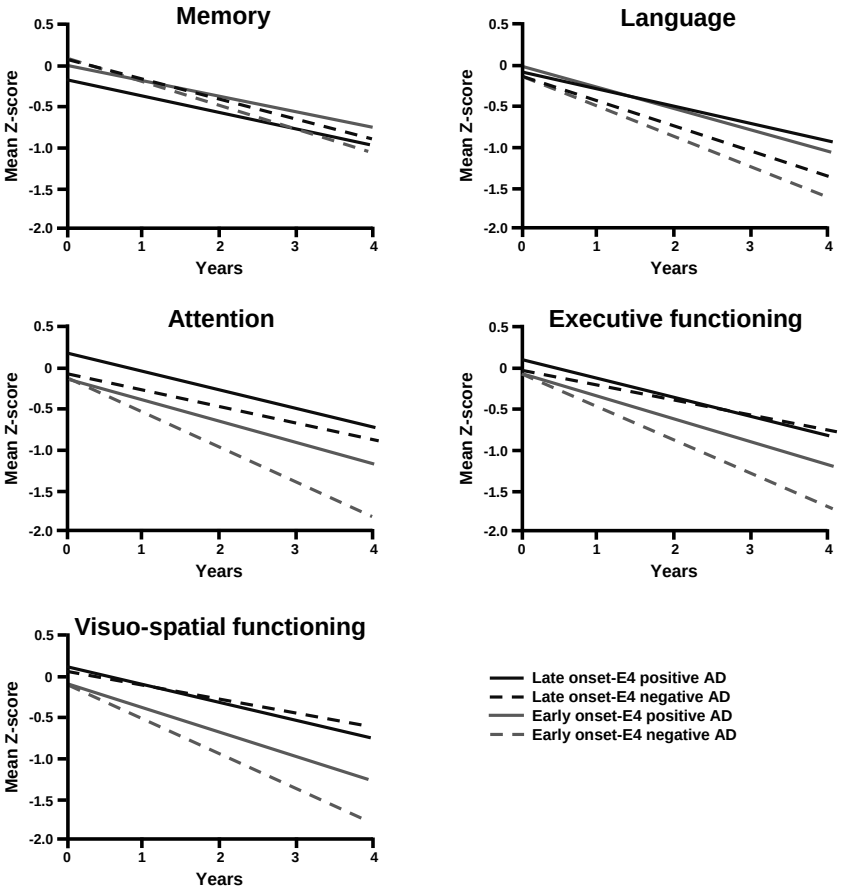
	Memory	Language	Attention	Executive functioning	Visuo-spatial functioning
Baseline cognitive score					
Late onset-Ɛ4 positive (ref)	-0.19±0.1	-0.07±0.1	0.17±0.1	0.096±0.1	0.12±0.1
Late onset-Ɛ4 negative	0.09±0.1	-0.099±0.1	-0.07±0.1	-0.02±0.1	0.06±0.1
Early onset-Ɛ4 positive	0.01±0.1	-0.0001±0.1	-0.13±0.1*	-0.11±0.1	-0.08±0.1
Early onset-Ɛ4 negative	0.09±0.1	-0.12±0.1	-0.14±0.1*	-0.05±0.1	-0.09±0.1
Annual cognitive change					
Late onset-Ɛ4 positive (ref)	-0.2±0.1	-0.21±0.1	-0.22±0.1	-0.23±0.1	-0.22±0.1
Late onset-Ɛ4 negative	-0.25±0.1	-0.3±0.1	-0.2±0.1	-0.19±0.1	-0.17±0.1
Early onset-Ɛ4 positive	-0.19±0.1	-0.25±0.1	-0.26±0.1	-0.27±0.1	-0.3±0.1
Early onset-Ɛ4 negative	-0.29±0.1	-0.36±0.1**	-0.42±0.1**	-0.41±0.1**	-0.43±0.1**

Late onset APOE ε4+ served as a reference group. Data are presented as Beta(standard error). Beta's represent uncorrected estimated baseline performance or estimated change over time. P-values for differences between groups, with late onset-E positive as reference, are given corrected for gender and education. Early APOE Ɛ4- (N=35), Early APOE Ɛ4+ (N=65), Late APOE Ɛ4- (N=26) and Late APOE Ɛ4+ (N=55).

* p<0.01, ** p≤0.10.

Next, we investigated the combined influence of age and APOE on cognitive decline (table 3 and figure 1). Compared to late onset-Ɛ4 positive, early onset-Ɛ4 negative and early onset-Ɛ4 positive performed worse on attention at baseline (both p<0.05). Over time, early onset-Ɛ4 negative patients declined faster than late onset-Ɛ4 positive on attention, executive functioning, language and visuo-spatial functioning (all p≤0.10). Late onset-Ɛ4 negative and early onset-Ɛ4 positive patients showed intermediate rates of decline. There was no effect on rate of memory decline.

Figure 1. Estimated cognitive performance over time according to age at onset and APOE Ɛ4 status.



Lines represent beta's as presented in table 3.

Discussion

The main finding of this study is that younger patients, especially when they are APOE Ɛ4-negative, show faster decline in language, attention, executive and visuo-spatial functioning than older, particularly APOE Ɛ4-positive patients.

Few studies investigated rate of global cognitive decline in AD according to age and showed conflicting results. One study, using the Blessed Dementia Scale but no neuropsychological measures, found faster decline in late onset AD [28]. Another study, using the 57 item-modified MMSE and the Blessed Dementia Scale to rate decline, found that early onset AD declined faster than late onset AD on the MMSE-items assessing attention and naming/recall [29]. In our study, using an extensive cognitive examination, we found that younger patients declined faster on executive functioning than late onset patients. Furthermore, the effect of age seemed to be modulated by APOE Ɛ4 genotype.

APOE Ɛ4 and rate of cognitive decline have more often been studied, with conflicting results [5-10,30,31]. Some of these former studies used only the MMSE and, or sample sizes were small. In all studies, except one [30], age was considerable higher than in our, relatively young, sample. Besides that, mean MMSE was also higher in our cohort, which may indicate that our patients were in an earlier stage of the disease, in which possible differences in cognitive decline are more easily observed than later in the disease. We found APOE Ɛ4-negative patients to decline faster than APOE Ɛ4-positive patients on language.

In an earlier study, we found that early onset patients who were APOE Ɛ4-negative showed most rapid decline on the MMSE [3]. In the current study, in a large cohort of AD patients and covering all cognitive domains, we found that these patients decline faster on all cognitive domains except memory. Another recent study investigated age at onset and APOE Ɛ4 status in cognitive changes in young-old AD patients (≤75 years) and very-old patients (>80 years) [11]. They showed that, over time, the young-old APOE Ɛ4-positive patients declined faster on immediate recall and language than very-old APOE Ɛ4-positive patients. This study found no differences in rate of decline in the APOE Ɛ4-negative groups, as we did for early onset negative patients. Reasons for these apparently contradictory findings could be that their young-old patients had a mean age of 71 years, which is comparable to our late onset patients, and the modulating effect of APOE Ɛ4 may pertain especially to patients with an even earlier onset. We found that early onset APOE Ɛ4-negative patients decline faster on visuo-spatial functioning. This finding is in line with the observation that young patients more often have visuo-spatial impairment and APOE Ɛ4-negative patients are associated with a non-memory profile [32-34]. It seems that if AD develops, despite of the two main risk factors, the cognitive decline is faster with a atypical, non-memory predominance.

The faster cognitive decline in early onset patients, particularly when they are APOE Ɛ4-negative may be related to location of neural damage. It is conceivable that genetic characteristics drive distribution of pathology, and in fact, APOE Ɛ4-negative patients have been shown to have more frontal and parietal atrophy, while APOE Ɛ4-positive patients had more temporal/ hippocampal atrophy [35,36]. Moreover, in an earlier study by our group, we have shown that APOE Ɛ4-negative AD patients with an early onset were at higher risk for more global brain atrophy than older APOE Ɛ4-positive patients who had more pronounced hippocampal atrophy [37]. Furthermore, using Pittsburgh compound B and fluorodeoxyglucose PET scans our group found that APOE Ɛ4-negative patients had more frontal amyloid burden and more metabolic impairment in occipital and posterior cingulate

cortices compared to APOE Ɛ4-positive patients [38]. These structural findings give support for a biological underpinning of the faster decline in attention, language, executive functioning and visuo-spatial functioning.

We found that young APOE Ɛ4-negative AD patients declined fastest on non-amnestic domains. In Mild Cognitive Impairment (MCI), the clinical stage before dementia, heterogeneity in cognitive profiles is already observed. In total, four subtypes can be distinguished: amnestic MCI and non-amnestic MCI, and both can involve single or multiple cognitive domains [39]. The proportion of patients with amnestic MCI that progress to Alzheimer's disease is higher than the proportion of patients with non-amnestic MCI, which is associated with the presence of APOE Ɛ4 [40]. Our results indicate, however that once the stage of AD is reached, the non-amnestic patients show faster cognitive decline.

Amongst the strengths of our study are the longitudinal set-up and the comprehensive neuropsychological assessment covering five cognitive domains. With this extensive neuropsychological assessment we were able to investigate the main cognitive domains and give a detailed picture of cognitive decline in AD. A possible limitation of this study is the limited duration of follow-up. Nonetheless, obtaining detailed, neuropsychological follow-up data is very difficult and labour-intensive, and hence our sample is one of the largest to date. The patients described in our study are relatively young, which might limit generalizability. Nonetheless, we feel that the relative young age is also an advantage, as dementia at a younger age is often thought to be more pure, with less mixed pathology, and therefore the patterns of decline may be more specific.

In conclusion, our findings imply that patients who are missing the two most important risk factors for AD (a high age and presence of APOE Ɛ4) show the fastest cognitive decline, particularly in non-memory domains, suggesting that these patients form a distinct subgroup. This may have implications for design of future clinical trials. Future studies should focus on non-memory domains as well.

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