

Family history of dementia does not influence the progression of Alzheimer's disease at two years: Results from the REAL.FR Study

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Abstract

The purpose of this study was to determine whether a family history of dementia in a first-degree relative influenced the progression of Alzheimer's disease (AD) after two years of follow-up. Patients were recruited in the REAL.FR (Réseau sur la Maladie d'Alzheimer Français) study and underwent behavioral, global, nutritional, and medical evaluation with assessment of cognitive function and independence every six months. At inclusion, 113 patients reported a family history of dementia, and 358 patients had no family history of dementia. There was no statistical difference for any factors between the two groups at baseline. After two years of follow-up, a similar percentage of patients were still followed in each group, and although most parameters showed significant deterioration, there was no difference between the two groups, indicating that a family history of dementia does not appear to influence the progression of AD.

Key words: Alzheimer's disease, family history of dementia, progression

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Introduction

Alzheimer's disease (AD) is a chronic progressive disorder whose onset and course are influenced by many different risk factors. It is now well known that increasing age, low level of education,¹ presence of apolipoprotein (ApoE) $\epsilon 4$ allele,^{2,3} and a family history of dementia⁴ are major predictive factors for onset of the disease. It has been demonstrated that patients with at least one first-degree relative with dementia are at significantly higher risk of AD.⁴ Huang et al.⁵ demonstrated that the association of a family history of dementia and ApoE $\epsilon 4$ allele was a factor of increased risk for the disease. Although the influence of a family history of dementia on the onset of AD is well established, its impact on the course of the disease is not clear. To date, no study has focused specifically on the influence of a family history of dementia on the cognitive, functional, and behavioral evolution of AD. Some studies seeking patient characteristics predictive of accelerated cognitive decline yielded only contradictory results: Stern et al.⁶ found that a family history of dementia did not affect the rate of disease progression in 111 AD patients, whereas Rasmusson et al.⁷ in a similar study of 132 subjects, reported that a history of dementia in a first-degree relative was one of the factors predicting a more rapid cognitive decline. It would be of great interest for clinicians to know whether a family history of dementia does in fact influence the progression of the disease.

We investigated the influence of a family history of dementia on the progression of patients with AD after two years of follow-up. We studied a large group of AD patients who have received pluridisciplinary management and regular six-month evaluations since 2000.

Materials and methods

Study design

REAL.FR (Réseau sur la Maladie d'Alzheimer Français) is a prospective multicenter study with a four-year follow-up. The methodology has been described in detail elsewhere.⁸ Subjects are evaluated every six months in one of the 16 participating centers.

Participants

Among a cohort of AD patients who were enrolled between 2000 and 2002 in the REAL.FR study, 471 subjects were selected who at inclusion had precise knowledge of presence or absence of dementia in a first-degree relative.

Patient selection

Patients included in the REAL.FR study fulfilled the NINCDS-ADRDA⁹ and DSM-IV criteria.¹⁰ They had to present with a mild to moderate form of the disease (Mini-Mental State Examination [MMSE] score between 12 and 26),¹¹ be ambulatory, be living in their own homes, and be cared for by a clearly identified caregiver. At inclusion, the patients underwent a full medical examination (computed tomography scan, thyroid tests), and we recorded the presence or absence of a family history of dementia. We excluded from the study patients with severe AD, those who were institutionalized, and those with a concomitant disorder that could affect the short-term prognosis.

Outcome measures

Every six months, patients underwent standardized pluridisciplinary evaluation that included the following:

- cognitive evaluation with administration of the MMSE¹¹ and the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog) subscale¹²;
- evaluation of the capacity to carry out the activities of daily living, using the Activities of Daily Living (ADL) scale¹³ and the Instrumental Activities of Daily Living (IADL) scale¹⁴ for the more complex activities;
- evaluation of behavioral disturbance with the Neuropsychiatric Inventory (NPI)¹⁵; and
- overall evaluation using the Clinical Dementia Rating (CDR).¹⁶

At each visit, all current treatments, in particular, specific treatments for AD, were carefully recorded. Nutritional status was also assessed with the Mini-Nutritional Assessment (MNA).¹⁷

During follow-up, all events occurring between two visits, in particular admissions to hospital or to institutions; use of new support or home assistance services; or changes among the patient's family and friends were carefully recorded together with deaths, entry to an institution where follow-up was not possible, and other reasons for premature discontinuation such as withdrawal of consent, medical problems of patient or caregiver, or loss to follow-up.

Statistical analysis

We first compared baseline parameters between AD patients with a family history of dementia in a first-degree relative ($n = 113$) and those with no family history of dementia ($n = 358$). This was done by classic methods chi-squared test for qualitative variables, analysis of variance for quantitative variables. For each of the modalities of the qualitative variables, the number and frequency are given; continuous variables are expressed as means and standard deviations.

After two-year follow-up, we compared attrition in each group using the chi-squared test. Bivariate analysis was then carried out to examine changes at two years in cognitive and noncognitive parameters according to the family history of dementia using Wilcoxon's nonparametric test. The Kruskal-Wallis test was used to compare changes in these parameters between the two groups.

Results

Baseline characteristics

One hundred thirteen (24 percent) patients reported a family history of dementia in at least one first-degree relative. Demographic and clinical characteristics of the subjects in each group are presented in Table 1. No significant difference emerged between the two groups.

Overview of follow-up

The two years of follow-up were completed by a similar proportion of patients in each group: 217 (60.61 percent) patients with no family history of dementia and 76 (67.26 percent) with a history ($p = 0.2042$) (Figure 1). The incidence of premature discontinuation did not differ significantly between the two groups: there were similar percentages of deaths (5.31 percent of the patients with a family history of dementia vs. 8.10 percent for the others,

Table 1. Comparison of patient characteristics at inclusion according to family history of dementia

Baseline parameters	Patients with no family history of dementia (n = 358)	Patients with family history of dementia (n = 113)	p*
Patient age (years)	78.05 ± 6.54	76.76 ± 7.45	0.2190
Patient gender (percent)			0.9092
Female	261 (72.9)	83 (73.45)	
Male	97 (27.1)	30 (26.55)	
Age at time of diagnosis (years)	77.03 ± 6.63	75.38 ± 7.43	0.1004
Age at onset of first symptoms (years)	74.93 ± 6.69	73.09 ± 7.93	0.0598
Level of education, n (percent)**			0.2469
Technical school or higher education	72 (20.34)	24 (21.43)	
Secondary school	69 (19.49)	31 (27.78)	
Completed primary school	141 (39.83)	36 (32.14)	
Primary school or no education	72 (20.34)	21 (18.75)	
Specific AD treatment, n (percent)	282 (78.77)	87 (76.99)	0.6888
Living arrangement, n (percent)			0.5272
Home with spouse	211 (58.94)	69 (61.06)	
Home alone	95 (26.54)	32 (28.32)	
Home with family member	40 (11.17)	11 (9.73)	
Other	12 (3.35)	1 (0.88)	
MMSE score (/30)	20.26 ± 4.03	19.86 ± 4.41	0.6760
ADAS-Cog score (/70)	17.11 ± 7.64	18.85 ± 8.71	0.1021
CDR-SB score (/18)	6.20 ± 3.18	6.69 ± 3.12	0.2663
ADL score (/6)	5.47 ± 0.83	5.47 ± 0.78	0.4773
IADL score (/8)	4.46 ± 2.21	4.14 ± 1.96	0.2738
NPI (freq x grav) (/144)	15.79 ± 15.79	13.77 ± 13.23	0.6849
Weight (kg)	62.29 ± 13.09	63.07 ± 11.88	0.8280
MNA score (/30)	22.86 ± 15.99	21.32 ± 14.32	0.9167

* Scheffe for patient age, age at time of diagnosis, age at onset of first symptoms, MMSE score, ADAS-Cog score, CDR-SB score, NPI score, weight, and MNA score; Kruskal-Wallis for ADL and IADL scores; chi-squared test for patient gender, level of education, specific AD treatment, and living arrangement.

** Data were missing for four patients in the group with no family history and one patient in the other group.

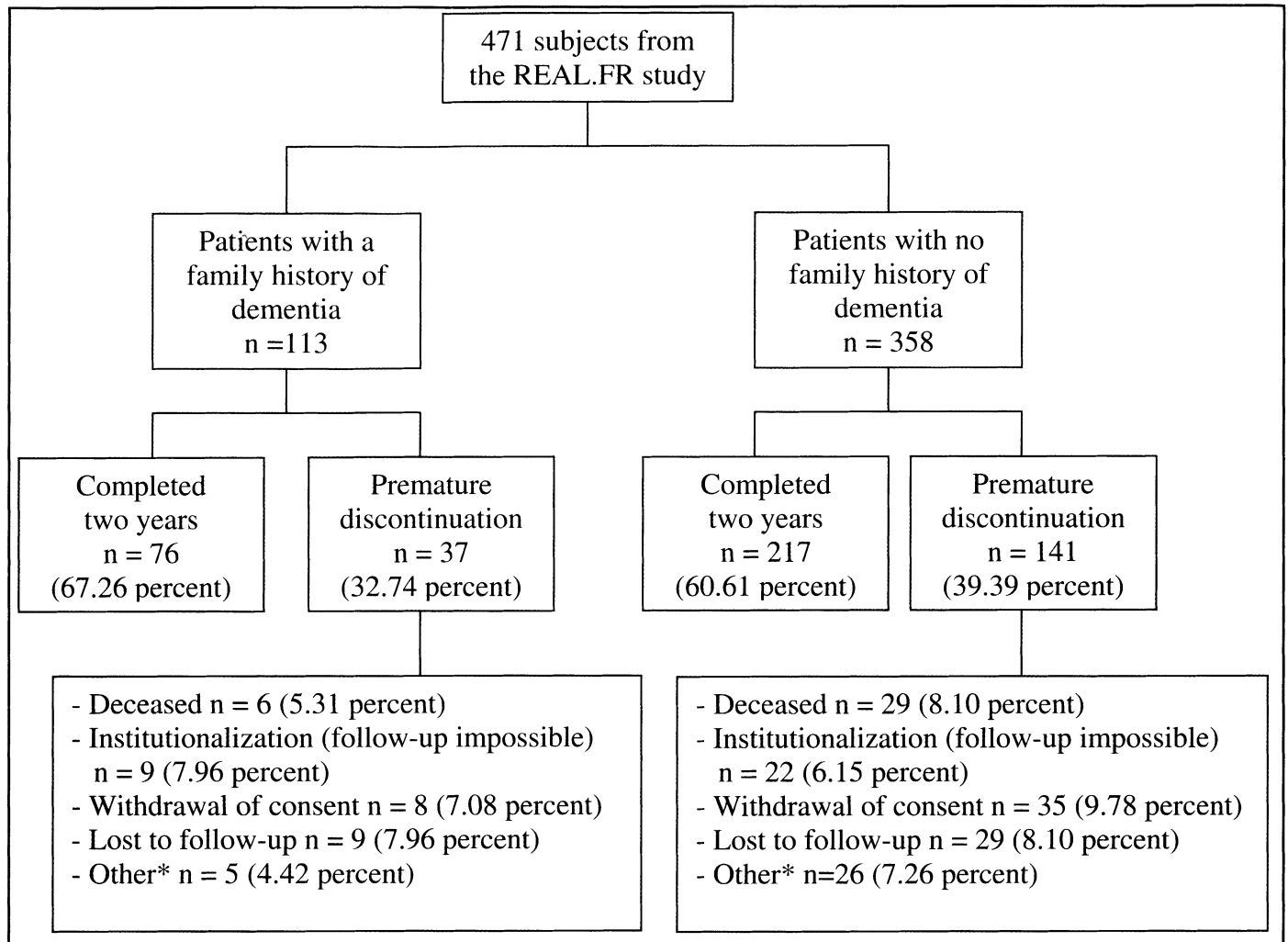


Figure 1. Overview of the two years of follow-up. *Patient's or caregiver's medical problem, relocation to another area, etc.

$p = 0.2329$), institutionalization (7.96 vs. 6.15 percent, $p = 0.4568$), withdrawal of consent (7.08 vs. 9.78 percent, $p = 0.3855$), loss to follow-up (7.96 vs. 8.10 percent, $p = 0.9630$), and discontinuation for other reasons (4.42 vs. 7.26 percent, $p = 0.2888$) in each group (Figure 1). Similarly, the percentages of subjects hospitalized during follow-up (44.71 vs. 41.98 percent, $p = 0.6613$) and of those who were specifically treated for AD for two years (95 vs. 87.72 percent, $p = 0.2158$) were equivalent in both groups.

Outcome measures

- **Cognitive status:** In both patient groups, MMSE and ADAS-Cog scores were significantly different from baseline values after two years of follow-up (Table 2), indicating marked decline in cognitive status. However, there was no statistical difference between the two groups.

- **Global status:** We also observed a significant deterioration assessed by the clinical dementia rating-sum of the boxes (CDR-SB) score that was significantly higher than its baseline value after two years in each group, but the difference between the two groups was not significant (Table 2).

- **Independence:** ADL and IADL scores decreased significantly after two years of follow-up but did not differ according to family history of dementia (Table 2).

- **Behavioral disturbances:** Change in NPI score indicated a significant worsening of behavioral problems in both groups. However, as observed for cognitive status, global status, and independence, the difference between the two groups after two years was not statistically significant (Table 2).

Table 2. Disease progression after two years of follow-up: Comparison between the two groups of subjects according to the family history of dementia

Parameters	Family history of dementia	Disease progression at two years	p Wilcoxon	p Kruskal-Wallis
MMSE	No	-4.22 ± 4.33	< 0.0001	0.2111
	Yes	-4.68 ± 4.01	< 0.0001	
ADAS-Cog	No	5.80 ± 7.19	< 0.0001	0.8814
	Yes	4.97 ± 5.82	< 0.0001	
CDR-SB	No	3.98 ± 3.32	< 0.0001	0.7760
	Yes	4.04 ± 3.38	< 0.0001	
ADL	No	-0.97 ± 1.30	< 0.0001	0.7314
	Yes	-1.04 ± 1.34	< 0.0001	
IADL	No	-1.77 ± 1.66	< 0.0001	0.8349
	Yes	-1.63 ± 1.52	< 0.0001	
NPI (freq x grav)	No	3.23 ± 16.53	0.0124	0.9156
	Yes	3.90 ± 13.60	0.0470	
Weight (kg)	No	0.09 ± 5.16	0.8541	0.9557
	Yes	0.07 ± 4.52	0.8339	
MNA	No	-0.50 ± 3.18	0.1776	0.2381
	Yes	-1.32 ± 4.07	0.0404	

p Wilcoxon, progression in each group; p Kruskal-Wallis, comparison of progression between the two groups.

- **Nutritional status and weight:** Despite the significant decrease in MNA score only for patients with a positive family history of AD, change in nutritional status was not statistically different between the two groups of subjects. Mean weight in each group did not change significantly, and the difference of progression between the two groups after two years of follow-up was not significant (Table 2).

Discussion

The aim of this study was to determine whether a family history of dementia in a first-degree relative influenced the progression of AD. First, we showed that patient characteristics in each group were similar at baseline. During follow-up, attrition in the group of

patients with a family history of dementia did not significantly differ from attrition in the group without, indicating that this factor did not influence participation in follow-up or the number of deceased, institutionalized, or hospitalized subjects. The percentage of premature discontinuation (almost 40 percent) is the principal study limitation as this reduces the number of subjects. But when compared with other studies, attrition in our cohort did not seem to be more important: in the CERAD,¹⁸ after two years of follow-up, less than 60 percent of the patients included had been evaluated.

After two years of follow-up, most parameters showed a significant change from their baseline values, indicating overall deterioration of patient status in both groups. However, we found no difference in disease progression between the two groups. Unlike Rasmusson et al.,⁷ who found in a cohort of 132 AD patients that a history of

dementia in a first-degree relative was one of the characteristics predicting a more rapid cognitive decline, we observed no influence of family history of dementia on cognitive decline in AD. The main difference between these two studies was that in REAL.FR most patients in both groups were specifically treated for AD (mainly with acetylcholinesterase inhibitors [AChEIs]). Patients taking AChEIs have recently been reported to be 2.5 times more likely to decline slowly.¹⁹ In our study, the annual rate of change on the MMSE was about 2.3 points for patients with a positive family history of dementia and 2.1 points for those without, whereas it was reported to be 3.4 points in the CERAD study,²⁰ in which no patients were receiving AChEIs. As there was no difference after two years of follow-up between our two groups, it seems that the specific treatment and management proposed in the REAL.FR study had a positive impact on the progression of the disease that was not influenced by a family history of dementia. The benefits of such management on the natural course of AD have already been demonstrated in the REAL.FR cohort after one year of follow-up²¹⁻²³ and will be studied again after two years.

Overall status deteriorated in both patient groups, but no significant difference in disease progression was observed after two years of follow-up. Cognitive decline also slowed similarly in both groups, certainly due to the effect of AChEIs and of specific management. So, after two years of follow-up, progression of AD in the REAL.FR cohort was not influenced by a family history of dementia in a first-degree relative.

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