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Cognitive Decline in Patients with Familial Alzheimer's Disease Associated with E280a Presenilin-1 Mutation: A Longitudinal Study*

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ABSTRACT

Few longitudinal studies have been carried out to investigate the cognitive decline in early onset of familial Alzheimer's disease (FAD). In this study 12 patients with FAD (*M* age = 49.61 years, *SD* = 4.99), 10 patients with sporadic Alzheimer's disease (SAD) (*M* age = 71.40, *SD* =10.00), and 15 matched normal controls (*M* age = 45.01, *SD* = 7.24) were selected. A comprehensive neuropsychological battery was administered three times over a period of 18 months. Individuals designated as FAD met the criteria for dementia and were positive for the E280A presenilin 1 mutation. Participants with SAD met the criteria for dementia and were negative for the E280A presenilin 1 mutation. Normal control participants were the FAD patients' relatives, who were negative for the mutation. Two groups of neuropsychological instruments were administered: (1) The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery, and (2) additional neuropsychological tests of abstraction and constructional abilities. Patients with FAD were significantly impaired on all measures at the first examination except for reading of words. While the performance of the normal controls remained unchanged over the 18 months for most neuropsychological tests, the patients with FAD displayed a decline in verbal memory, language, constructional and abstraction tests. The greatest decline was observed on the Mini-Mental State Exam scores. Patients with SAD demonstrated a similar pattern of cognitive decline, but the decline was faster in FAD than in SAD participants.

Patients with Alzheimer's disease (AD) undergo a progressive cognitive decline (Cummings & Benson, 1992). This decline can have an early or a late onset (before or after the age of 65) (Li et al., 1995). The AD with an early onset frequently, but not always, exhibits a familial pattern.

Several groups of patients with familial AD (FAD) have been documented (Alzheimer's Disease Collaborative Group, 1995; Cook, Bard, & Austin, 1979; Goate et al., 1991; Haltia et al., 1994; Levy-Lahad et al., 1995; Lopera et al., 1997; Nee et al., 1983; Sadovnick, Tuokko, Horton, Baird, & Beattie, 1988; Sherrington et al., 1995; St. George-Hyslop et al., 1987). Individuals with a family history of autosomal dominant AD and one parent affected carry a 50% chance of developing the disease, and the age of onset within the family has been reported as relatively constant (Fox, Warrington, Seiffer, Agnew, & Rossor, 1998).

Memory deficits are usually found as the earliest dementia symptoms (Cummings & Benson,

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1992). A more rapid decline and early symptoms of aphasia and apraxia have been more commonly described in FAD than in sporadic AD (SAD) without a family pattern (Chang-Chui, Lee-Teng, Henderson, & Moy, 1985; Feldman, Chandler, Lewy, & Glaser, 1963; Frommelt, Schnabel, Kuhne, & Nee, 1991; Karlinsky et al., 1992; Lampe et al., 1994; Martin et al., 1991). Kennedy et al. (1995) reported a neuropsychological profile characterized by an initial memory deficit with early dyscalculia and an impairment in speech production with very mild anomia. Lehtovirta et al. (1996), however, failed to confirm the earlier reports of severe aphasia, agnosia and apraxia in FAD.

There are studies that have described the clinical features of FAD (Alzheimer's Disease Collaborative Group, 1995; Cook, Bard & Austin, 1979; Haltia et al., 1994; Nee et al., 1983; St. George-Hyslop et al., 1987; Sadovnick et al., 1988), but few of them have analyzed the longitudinal cognitive changes. In general, it has been observed that memory deficits precede more widespread deterioration in individuals at risk for FAD (Ardila et al., in press; Fox, Warrington, Seiffer, Agnew, & Rossor, 1998). Some longitudinal studies of cognitive decline in SAD have been reported. Tierney et al., (1996) conducted a longitudinal study of memory-impaired non-demented patients at risk for developing probable AD. In a two year follow-up, they found that the delay forms of two verbal tests were the best predictors of AD. Botwinick, Storandt, & Berg (1988) studied a group of 18 patients with mild AD and 30 normal matched controls using four testing sessions over a four year period. The patients with AD exhibited the greatest decline in tests of logical verbal memory, symbol coding and rapid sequencing compared to other neuropsychological tests. Butters, Lopez, and Becker (1996) carried out three cognitive evaluations of patients with AD over a 2-year period and suggested the possibility of identifying subgroups of cognitive decline in AD. Accordingly, they define four groups based on the type of cognitive decline. Three of the groups presented different degrees of executive function deficits in association with the memory loss. The fourth group, however, showed decline in semantic and episodic memory, albeit at a slower rate. Rebok, Brandt, and Folstein (1990) administered a neuropsychological battery at 6-month intervals over a 2-year period to 51 patients with AD and 22 matched controls. The greatest decline in patients with AD was on tests requiring lexical/semantic processing and comprehension of semantic relationships. Performance on visuospatial tests declined less rapidly. The authors emphasize the language impairment as central to AD.

Recently, a large familial nucleus of FAD with an E280A presenilin-1 mutation was found in Colombia (South America). An initial clinical, epidemiological, genetic and pathological description of this group has been presented elsewhere (Alzheimer's Disease Collaborative Group, 1995; Lopera et al., 1994, 1997). It was observed that the most frequent dementia presentation was memory impairments and progressive loss of language ability. Memory complaints represented the earliest symptom of this FAD group. In addition to the memory difficulties, during the earliest dementia stages other minor cognitive impairments were also noted, including, anomia, concentration difficulties and defects in the understanding of complex verbal material (Ardila et al., in press).

The present report describes a three-step follow-up of patients with FAD and a matched control sample over a period of 18 months. Changes in their neuropsychological test scores over three consecutive testing sessions are analyzed. The major aim of the study was to describe the pattern of decline in different cognitive domains in cases of FAD associated with an E280A presenilin-1 mutation. In a subsequent analysis, the cognitive profile and the cognitive decline pattern in patients with FAD and SAD were compared.

METHOD

Participants

Twenty-two patients with FAD and 26 normal controls, matched by age and education, enrolled in the FAD Research Program at the Department of Neurology, Antioquia University (Medellin, Co-

lombia, South America) agreed to participate in this study during their first visit. From this sample, only 12 participants with FAD (age range: 39 to 55 years; educational range: 0 to 11 years) and 15 controls (age range: 40 to 59 years; education range: 0 to 12 years) completed three consecutive neuropsychological evaluations, and their data are analyzed and presented here. All participants with FAD met the criteria for dementia using the DSM-IV (American Psychiatric Association, 1994). The diagnosis of dementia was made by an examining neurologist using information from an initial interview with a family member, a standard neurological history, the Mini Mental State Exam (MMSE) and the results from the Functional Assessment Staging Test (FAST). All participants had scores below 23/30 and above 14/30 for the MMSE (5 had a MMSE > 19 and < 23; and 7 had a MMSE > 14 and < 19). A score of twenty three points has been shown to be an appropriate MMSE cut off score for dementia, among subjects with low level of education (Ardila, Rosselli, & Puente, 1994). The average MMSE (Folstein, Folstein, & McHugh, 1975) score in this group was 18.33 with a standard deviation of 3.84. None of the patients had scores higher than 7 on the Hachinscki Ischemic Scale or evidence of psychiatric disorders. Laboratory tests and either a CT or MRI were used to rule out other causes of cognitive impairment. The average length of time since the first complaints of cognitive decline was 3.92 years. All patients were positive for the presence of a mutation in the presenilin-1 gene (E280A, substitution of glutamic acid for alanine) (Alzheimer's Disease Collaborative Group, 1995; Lendon et al., 1997).

In order to compare the profile and the cognitive decline of patients with FAD and SAD, 10 patients with SAD were further selected. Patients with SAD were matched with participants with FAD according to educational level ($F = 3.01$; $p < 0.10$) and MMSE score ($F = 3.61$; $p < 0.072$). Patients with SAD, however, were significantly older than patients with FAD ($F = 61.45$; $p < 0.001$). Dementia selection criteria were similar to those used for patients with FAD.

The control sample included family members of the patients with FAD. All of the controls had a normal neurological exam and were free of psychiatric or neurological antecedents. They were functionally normal, with no complaints of memory impairment. Their average MMSE score was 28.81. All of the subjects in this control group were found to be negative for the presence of an E280A mutation in the PS1 gene. A summary of the demographic and clinical description of the three groups is presented in Table 1. The FAD and control groups did not differ significantly in age ($F = 3.49$; $p = 0.074$) or education ($F = 2.51$; $p = 0.124$). There were more females than males in both groups.

The level of function of each participant was assessed using the FAST (Reisberg, 1988; Sclan & Reisberg, 1992) This measure assesses level of function within a range from 1 (no objective or subjective cognitive complains) to 16 (severe cognitive and behavioral problems). All controls had scores below 2 and patient's scores were equal to or above 2 but below 6.

Table 1. Characteristics and MMSE scores of the sample.

	Normal controls ($n = 15$)		FAD patients ($n = 12$)		SAD patients ($n = 10$)	
	M	(*SD*)	*M*	(*SD*)	*M*	(*SD*)
Age 1st visit	45.01	(7.24)	49.61	(4.99)	71.40	(10.00)
Age onset	—		44.91	(4.92)	66.50	(9.59)
Length of time since onset	—		3.92	(2.97)	4.90	(2.55)
Education (yrs)	4.73	(3.74)	2.66	(2.93)	5.00	(3.20)
Interval between visit 1 & 2	8.33	(2.12)	8.94	(2.73)	9.30	(2.54)
Interval between visit 2 & 3	10.63	(2.67)	10.21	(3.14)	9.92	(2.37)
MMSE	28.81	(0.98)	18.33	(3.84)	20.30	(2.40)
FAST	1.00	(0.00)	3.33	(1.11)	4.40	(2.06)

Note. MMSE = Mini-Mental Status Exam; FAD = Familial Alzheimer's Disease; SAD = Sporadic Alzheimer's Disease; FAST = Functional Assessment Staging Test. There were 12 females and 3 males in the control group, 7 females and 5 males in the FAD group, and 8 females and 2 males in the SAD group.

Instruments

All participants were individually administered the neuropsychological test battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Morris et al., 1989) as well as additional neuropsychological instruments to further assess constructional abilities and abstraction. This group of tests was translated into Spanish and adapted to the cultural and linguistic idiosyncrasies of the target population. The neuropsychological tests used have been described elsewhere (Lopera et al., 1997). Only data from those tests that were given on each of the three consecutive assessments were analyzed in this paper. The following are the cognitive areas and the neuropsychological tests analyzed in the present report:

(1) *General cognitive function*: (a) MMSE (Folstein, Folstein & McHugh, 1975). Maximum score is 30; (b) Raven Test (Raven, 1982). Only Part A was included. Maximum score = 12

(2) *Oral Language:* (a)Verbal fluency (CERAD); (b) Naming (CERAD), maximum total test score is 15

(3) *Written Language*: Mechanics of reading (CERAD), maximum score 10

(4) *Memory:* Verbal memory: Word Memory (CERAD), the maximum score for first trial and delayed recall is 10; the maximum score for three trials is 30. Non verbal memory: (a) Immediate Design (circle, diamond, rectangles, and cube) Recall (CERAD), maximum score = 11; (b) The immediate recall of the Rey-Osterrieth Complex Figure (ROCF) (Osterrieth, 1944; Lezak, 1995). Maximum score = 36.

(5) *Visuo-constructional* : (a) the Rey-Osterrieth Complex Figure (Osterrieth, 1944; Lezak, 1995), maximum score = 36. (b) Constructional praxis total (CERAD): Copying of simple designs (circle, diamond, rectangles, and cube). Maximum score = 11.

The Rey-Osterrieth Complex Figure and the verbal fluency tests have been previously normalized in a Colombian population using different age and educational groups (Ardila & Rosselli, 1989, 1994; Ardila, Rosselli, & Puente, 1994; Rosselli, & Ardila, 1991; Rosselli, Ardila, & Rosas, 1989).

Procedure

Each participant signed the informed consent form and received a clinical assessment during the first visit to the Dementia Research Program at the Department of Neurology of the Antioquia University (Medellin, Colombia). The clinical assessment consisted of a clinical interview, and a neurological examination. The MMSE and the FAST were administered. In addition, a close family member was interviewed for the AD groups. A standard interview protocol was used requesting information about cognitive deficits (memory, attention, language, visuo-spatial, abstraction, perceptual problems) and behavioral problems. Each participant was then scheduled for neuropsychological assessment. As mentioned in the Method section, laboratory tests and either CT's or MRI's were used to rule out neurological conditions different from AD. The progression of decline was tested in 3 consecutive visits over a period of 18 months. Due to the fact that most participants had to travel long distances to attend the assessment sessions, the follow-up was not completed precisely every nine months as designed. The interval between visit 1 and 2 was an average 8.85 months and the mean interval in between visit 2 and 3 was 10.25 months (See Table 1). There was no significant difference in the visit intervals between the groups.

In each follow-up evaluation, the neuropsychological test battery was re-administered. Testing was performed by professional psychologists and by supervised graduate neuropsychology students. In all cases, the CERAD neuropsychological test battery was administered in one session and the administration of the other neuropsychological tests in a different session.

All participants were administered a blood test for the presence of a mutation in the Presenilin-1 (E280A, substitution of glutamic acid for alanine) (Alzheimer's Disease Collaborative Group, 1995) during their first visit. All the FAD patients were positive, while SAD and controls were negative for this mutation. The neuropsychological examiner was blind to the blood results but had access to the test results of the previous visit. Two people other than the examiner scored each of the neuropsychological tests.

Statistical Procedure

Differences between groups were analyzed for significance using a Group (normals, FAD, SAD) by Visit (1, 2, 3) two-way repeated measures ANOVA for each neuropsychological test. A $p > 0.05$ was considered non-significant. When the interaction effect was significant, a post-hoc one-way ANOVA was used to compare the groups with regard to change from Visit 1 to Visit 3. A Visit 3 minus Visit 1 difference score was obtained for each neuropsychological test.

RESULTS

Means, standard deviations, *F* and *p* values for the three groups on the CERAD and on all neuropsychological tests at each of the three visits are presented in Table 2. A significant group effect was found for all measures, except for reading of words. Across visits, patients with FAD were significantly more impaired than patients with SAD on the MMSE and Raven tests. A Visit effect was found significant for the MMSE, Raven test, FAST, Verbal Fluency, Naming, Memory of Words, and Constructional Praxis (CERAD). Nonetheless, a significant interaction was observed in the MMSE, Raven test, Word Memory (Immediate Memory, Total Correct after 3 trials, and Delayed Recall). While the controls demonstrated some score improvement, the FAD and SAD groups showed a score decline.

Table 3 presents the one-way ANOVA of the mean difference score between Visit 1 and Visit 3 for those neuropsychological tests in which the interaction Group x Visit was significant. A significant decline in both FAD and SAD test scores was observed in the Raven Test, Immediate Word Memory, and Total Words after 3 Trials. In the MMSE and Delayed Word Recall, a significant negative change from Visit 1 to Visit 3 was only observed in the FAD group.

DISCUSSION

The present longitudinal study analyzed neuropsychological decline in patients with FAD. It was found that the MMSE was the most sensitive indicator of the progression of dementia in mild to moderate FAD, over an 18-month follow-up. Significant decline was observed in several cognitive domains. Abstraction abilities as measured by the Raven Test, and verbal memory tested with Memory of Words (both immediate recall and delayed) showed a significant decline between visits 1 and 3. In these tests**,** scores of patients with FAD significantly decreased between visits 1 and 3, while the scores of the controls remained the same or showed some improvement. The decline at follow-up was also significant for simple constructional tests. The written language (Reading Words) test did not show a significant decline over visits.

Our results are consistent with previous findings that verbal memory is more vulnerable to decline in the first five years of FAD. Previous longitudinal studies have shown the predictive value of verbal memory tasks in at-risk Alzheimer subjects (Fox et al., 1998). Tierney et al. (1996) followed up 123 memory-impaired nondemented patients. After two years, 29 of these patients developed dementia. They found that those patients who presented significantly lower scores in the delay recall of the Rey Auditory Verbal Learning Test and Mental Control were those who developed dementia. Fox et al. (1998) conducted a six year longitudinal study of asymptomatic individuals at risk of early onset AD. All participants had a family history of autosomal dominant familial AD. The group of participants who went on to develop AD had significantly reduced scores on verbal recognition memory tests before becoming symptomatic. Once they met the criteria for probable dementia, verbal and visual memory was impaired as well as arithmetic abilities. No significant differences in naming tests were seen between the affected and the non-affected group in Fox et al.'s sample. Although many studies have supported the importance of memory decline as the initial symptom of FAD (Fox, Warrington, Seiffer, Agnew, & Rossor, 1998; Tierney et al., 1996; Lopera et al., 1997; Ardila et al., in press; Karlinsky et al., 1992), it is also clear from our results that the decline occurs in other cognitive domains as well.

Our results also suggest that patients with SAD and FAD who have similar initial cognitive profiles show similar patterns of cognitive decline, but decline is faster in patients with FAD than in individuals with SAD. During the first visit, no significant differences between groups were observed in the MMSE. Scores, however, decreased more severely between visits for the FAD group than for the SAD patient group. The lack of statistical differences between the two patient groups in other neuropyschological tests, however, has to be interpreted very cautiously due to the small sample size.

Table 2. Group (Normals, Patients With FAD, Patients With SAD) by Visit (1, 2, 3) Two-Way Repeated Measures ANOVAs for Each Test Variable.

Tests	Normals (Group 1)		Patients with FAD (Group 2)		Patients with SAD (Group 3)		Group effect		Visit effect		Interaction	
	M	(*SD*)	*M*	(*SD*)	*M*	(*SD*)	*F*	*p*	*F*	*p*	*F*	*p*
GENERAL COGNITION												
Mini-Mental State Exam												
Visit 1	28.81	(0.98)	18.33	(3.84)	20.30	(2.40)	54.05	0.001	16.88	0.001	8.25	0.001
Visit 2	29.27	(1.19)	14.77	(6.01)	19.00	(3.19)	(G1 vs G2,G3; G2 vs G3)					
Visit 3	29.18	(1.32)	10.44	(6.87)	17.60	(5.30)						
Raven Test, Part A												
Visit 1	8.10	(2.28)	3.85	(2.85)	6.40	(2.31)	19.74	0.001	3.27	0.047	2.82	0.034
Visit 2	8.60	(1.83)	1.17	(3.14)	5.33	(2.00)	(G1 vs G2,G3; G2 vs G3)					
Visit 3	8.90	(1.28)	1.87	(2.79)	4.30	(2.40)						
FUNCTIONAL SCALE												
FAST												
Visit 1	1.00	(0.00)	3.33	(1.11)	4.40	(2.06)	23.61	0.001	3.71	0.033	2.12	0.096
Visit 2	1.03	(0.35)	3.40	(0.96)	5.10	(2.02)	(G1 vs G2, G3; G2 vs G3)					
Visit 3	1.10	(0.31)	4.00	(0.81)	6.10	(2.03)						
LANGUAGE												
Verbal Fluency (CERAD)												
Visit 1	17.60	(3.04)	10.91	(1.97)	8.90	(2.50)	40.01	0.001	7.65	0.001	1.71	0.161
Visit 2	17.26	(5.62)	9.33	(1.30)	6.60	(2.33)	(G1 vs G2,G3)					
Visit 3	16.66	(3.98)	6.12	(2.35)	5.70	(3.65)						
Naming (CERAD)												
Visit 1	13.00	(1.88)	9.33	(2.49)	9.90	(2.92)	16.42	0.001	5.91	0.005	1.59	0.190
Visit 2	13.06	(2.05)	8.58	(1.78)	8.60	(2.54)	(G1 vs G2,G3)					
Visit 3	12.91	(2.42)	7.12	(2.94)	7.90	(2.64)						
WRITTEN LANGUAGE												
Reading Words (CERAD)												
Visit 1	10.00	(0.00)	8.33	(3.89)	9.90	(0.46)	2.60	0.092	1.26	0.291	1.34	0.277
Visit 2	10.00	(0.00)	8.33	(3.89)	9.90	(0.26)						
Visit 3	10.00	(0.00)	7.66	(4.35)	9.90	(0.31)						

Table continues.

Table 2. continued.

Tests	Normals (Group 1)		Patients with FAD (Group 2)		Patients with SAD (Group 3)		Group effect		Visit effect		Interaction	
	M	(*SD*)	*M*	(*SD*)	*M*	(*SD*)	*F*	*p*	*F*	*p*	*F*	*p*
MEMORY												
Word Memory (CERAD)												
Immediate Memory (Trial 1)												
Visit 1	4.00	(1.25)	1.91	(0.66)	2.00	(1.24)	39.99	0.001	1.51	0.227	2.53	0.050
Visit 2	3.86	(0.74)	1.50	(0.79)	1.30	(0.94)	(G1 vs G2,G3)					
Visit 3	4.41	(1.88)	0.88	(0.60)	1.40	(0.85)						
Total correct words after 3 trials												
Visit 1	17.73	(3.26)	7.83	(2.03)	8.30	(2.62)	73.58	0.001	10.40	0.001	7.55	0.001
Visit 2	16.80	(3.38)	5.83	(2.44)	7.00	(3.23)	(G1 vs G2,G3)					
Visit 3	18.75	(3.59)	3.55	(2.65)	4.80	(2.97)						
Delayed Word Recall												
Visit 1	6.26	(1.48)	1.91	(1.24)	1.00	(0.66)	218.01	0.001	2.04	0.139	2.70	0.040
Visit 2	6.38	(1.33)	1.08	(0.79)	0.50	(0.97)	(G1 vs G2,G3)					
Visit 3	7.00	(1.65)	0.33	(0.70)	0.50	(0.97)						
Word Recognition												
Visit 1	10.00	(0.00)	6.33	(3.14)	8.90	(1.66)	16.61	0.001	1.24	0.295	1.76	0.148
Visit 2	9.93	(0.15)	5.25	(3.38)	8.30	(1.76)	(G1 vs G2,G3)					
Visit 3	9.91	(0.28)	6.77	(3.96)	6.30	(3.88)						
Immediate Design Recall												
Visit 1	7.66	(2.60)	2.08	(1.72)	1.30	(1.94)	69.01	0.001	2.89	0.064	0.72	0.577
Visit 2	9.86	(6.99)	2.16	(1.58)	0.80	(1.61)	(G1 vs G2,G3)					
Visit 3	7.81	(2.67)	0.88	(1.96)	0.60	(1.34)						
ROCF-Immediate Recall												
Visit 1	8.96	(7.65)	0.81	(1.28)	0.88	(1.16)	23.63	0.001	1.25	0.295	1.87	0.132
Visit 2	9.86	(6.99)	1.04	(1.83)	1.22	(2.94)	(G1 vs G2,G3)					
Visit 3	10.41	(5.83)	0.62	(1.18)	1.00	(1.33)						

Table continues.

Table 2. continued.

Tests	Normals (Group 1)		Patients with FAD (Group 2)		Patients with SAD (Group 3)		Group effect		Visit effect		Interaction	
	M	(*SD*)	*M*	(*SD*)	*M*	(*SD*)	*F*	*p*	*F*	*p*	*F*	*p*
VISUO-CONSTRUCTIONAL												
ROCF-copy												
Visit 1	24.30	(10.42)	4.02	(3.86)	8.88	(8.17)	17.90	0.001	8.35	0.702	0.70	0.590
Visit 2	23.64	(9.10)	6.79	(7.65)	7.77	(9.23)	(G1 vs G2,G3)					
Visit 3	24.87	(6.44)	4.68	(5.94)	4.90	(8.74)						
Constructional praxis total (CERAD)												
Visit 1	10.13	(1.55)	5.83	(2.97)	7.20	(2.89)	13.95	0.001	8.40	0.001	1.37	0.256
Visit 2	10.38	(1.50)	5.16	(2.48)	6.40	(2.01)	(G1 vs G2,G3)					
Visit 3	10.09	(1.61)	4.11	(3.72)	5.60	(2.31)						

Note. FAD = Familial Alzheimer's Disease; SAD = Sporadic Alzheimer's Disease; FAST = Functional Assessment Staging Test; CERAD = Consortium to Establish a Registry for Alzheimer's Disease test battery; ROCF = Rey-Osterrieth Complex Figure.

Table 3. One way ANOVA of the mean difference score between Visit 1 and Visit 3 among the three groups.

Tests	Normals (Group 1)		FAD (Group 2)		SAD (Group 3)		*F*	*p*	Group Differences
	M	(SD)	M	(SD)	M	(SD)			
MMSE	0.37	(1.20)	–7.89	(5.79)	–2.70	(3.77)	11.15	0.001	G1 vs G2; G2 vs G3
Raven A	0.80	(1.75)	–1.98	(3.02)	–2.10	(2.10)	4.58	0.020	G1 vs G2, G3
CERAD									
Immediate Memory (Trial 1)	0.41	(1.40)	–1.03	(0.65)	–0.60	(0.67)	7.03	0.003	G1 vs G2, G3
Total words after 3 trials	1.02	(2.44)	–4.28	(2.50)	–3.50	(1.50)	14.67	0.001	G1 vs G2, G3
Delayed Word Recall	0.74	(1.35)	–1.58	(1.43)	–0.50	(1.17)	5.82	0.007	G1 vs G2; G2 vs G3 G2 vs. G3

Note. FAD = Patients with Familial Alzheimer's Disease; SAD = Patients with Sporadic Alzheimer's Disease; MMSE = Mini-Mental Status Exam; CERAD = Consortium to Establish a Registry for Alzheimer's Disease test battery.

Karlinsky et al. (1992) stated that during the early phase of FAD, language and visuospatial functions appear relatively intact, as does global performance on cognitive screening. According to the authors, the earliest clinical manifestations reflect deficits in memory, cognitive processing speed and attention to complex cognitive sets. Later, deficits in concept formation are seen. These conclusions are based on the analysis of five cases. Our results showed that, on average, at 5 years post-onset, most of the tests were affected. In fact, only Reading Words was not significantly affected.

Constructional abilities as measured by the copy of simple geometric designs (CERAD) and the copy of the ROCF were about 2 standard deviations below the mean of the control group at the first visit. A significant cognitive decline was observed only in the copying of simple designs. The possible explanation for the lack of decline over the ROCF is that the initial performance of the group was extremely low. Accordingly, a floor effect may have affected the subsequent results. The ROCF is a complex task influenced by level of education (Rosselli & Ardila, 1991). Our sample had a very low level of education, and, although we used a control group, even for this normal healthy group the mean score was low and no improvement across visits was seen. The ROCF, therefore, does not appear to be the best yardstick for assessing constructional decline in FAD subjects who have low levels of education.

Despite observing no significant decline between visits on some tests, two different situations must be distinguished: (1) The situation in which there was truly no decline, the test performance remaining relatively stable, despite the dementia process. This situation was observed for the Reading Words test. (2) The situation in which there were no observable differences between visits because of a floor effect. Performance was so impaired on the first visit that the test was not sensitive to decline. This situation was observed in memory (Delayed Word Recall, Immediate Design Recall, ROCF-Immediate Recall), and constructional (ROCF-Copy and Constructional praxis total) tests.

The present study is important because it is one of the few longitudinal studies with FAD participants, and because all members of the sample were tested for the mutation. Studies that have examined the pattern of decline of AD using elderly patients have the confounding effect of other variables such as variability in age decline and the comorbidity of vascular problems (Fox, et al., 1998). Most of the longitudinal studies have used individuals at-risk for FAD. We can be certain that the cognitive changes in our sample were due to FAD and that the controls were not symptomatic for FAD, because blood analysis was used to confirm or rule out the presence of the mutation in Presenilin-1 for all participants. Some potential limitations, however, of the present study should be noted. First of all, the sample size is small. From an initial sample of 22 FAD patients and 26 matched controls, only 12 individuals with FAD and 15 controls came for the two follow-up evaluations. Most of the patients came from rural areas where access to the city was not always possible. It may also be that those patients who came for follow up were precisely those who presented more accelerated declines and for this reason may represent a different group from those who did not follow-up. The fact that the same rate of attrition of the FAD group was observed in the control group, however, argues against this second possibility. The second limitation of our study is the low level of education of our sample, which may affect the ability to generalize from our results to those patients who have higher levels of education. It has been hypothesized that education may influence the expression of AD (Katzman, 1993) and the mortality of patients with AD (Stern, Tang, Denaro, & Mayeux, 1995). Hill et al. (1993) reported that more highly educated patients die earlier than less educated patients. Although the influence of education in the expression of FAD is unknown, it may be an influential variable as well as in AD.

In summary, this study demonstrates that a mild decline takes place in FAD patients over 18 months of follow-up. The main decline takes place in verbal memory, constructional, and abstraction abilities. Except for the rate of progres-

sion, no significant differences were observed between FAD and SAD individuals. More neuropsychological studies on the cognitive decline of FAD are required to establish the differences between different types of FAD. Replications of this study may help us to better understand the differences between FAD and SAD. Only further research will establish the generalizability of these findings.

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