Neuropsychological study of familial Alzheimer's disease caused by mutation E280A in the presenilin 1 gene

Juan Carlos Arango Lasprilla, PhD
Jaime Iglesias, PhD
Francisco Lopera, MD

Abstract

In Antioquia, Colombia, investigators have recently discovered the largest family with the E280A mutation in the presenilin 1 gene that causes one type of familial Alzheimer's disease (FAD). The current study compares two groups within this family: those diagnosed with Alzheimer's disease (AD) in its early stage (nine subjects) and relatives (carriers) who did not show any signs of dementia (nine subjects). A battery of the following neuropsychological tests was administered to subjects in both groups: the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), a Phonological Verbal Fluency test, the Visual "A" Cancellation Test, memory of three phrases, the Rey-Osterrieth Complex Figure, and the Trail Making Test Part A. Statistical analyses of the average test scores of each group showed that the AD group scored significantly ($p < 0.01$ or $p < 0.05$) lower on 29 of the 43 neuropsychological variables measured (67 percent). Therefore, this specific battery was useful in discriminating subjects with AD from their healthy relatives who are carriers of the disease. The AD group as a whole presented slight dementia with predominant deficits in memory, language, praxis, and attention. This profile is similar to those reported in subjects with sporadic AD in its early stage and confirms the findings found in other neuropsychological studies of subjects with FAD linked to mutations in chromosome 14.

Key words: familial Alzheimer's disease, presenilin 1 gene, mutation E280A, chromosome 14

Juan Carlos Arango Lasprilla, PhD, Neurosciences Group, University of Antioquia (Medellín-Colombia), Rochester Hills, Michigan.

Jaime Iglesias, PhD, Biological and Health Psychology Department, Autonomous University of Madrid, Campus de Cantoblanco, Madrid.

Francisco Lopera, MD, Neurosciences Group, University of Antioquia, Medellín, Colombia.

Introduction

Although the first reported cases of subjects with familial Alzheimer's disease (FAD) date from the 1930s,[1] it is only since the 1980s that we find a growing interest in the study of the clinical[2-5] and etiological[6,7] characteristics of this familial type of dementia.

The initial evidence gave support to the hypothesis of a possible etiological and phenotypic differentiation of this type of dementia according to age at onset—early vs. late. Patients with early-onset (< 65 years) dementia of the Alzheimer's type (DAT) presented a disorder compatible with a dominant autosomic pattern of heredity, a phenotype with a predominance of language deficits,[8-12] attentional deficits,[13,14] myoclonias and epilepsies,[15] and a much more rapid progression of the disease.[11,12,14,16] On the other hand, patients with late-onset (> 65 years) or sporadic DAT, whose etiology is still unknown, presented greater deterioration of recall memory and higher degrees of mental confusion.[17] Nevertheless, these findings have not been fully confirmed in other studies.[18-23]

From the 1990s, with the development of molecular genetics, research confirmed the involvement of the following three genes in the etiology of these early-onset forms of FAD: the amyloid precursor protein (APP) gene, located in chromosome 21;[24,25] the presenilin 1 (PS1) gene, located in chromosome 14;[26] and the presenilin 2 (PS2) gene, located in chromosome 1.[27] Despite

the advances in knowledge of the genotypic characteristics of FAD, up to now there have been very few clinical studies, and even fewer neuropsychological ones, focused on identifying the phenotypes corresponding to each of these genetic forms of FAD.

In the past ten years, scarcely any work has included data on the neuropsychological characteristics of these families with FAD. The few studies that were carried out show great methodological heterogeneity (Table 1); for example: differences in the cognitive processes evaluated, overly small samples, lack of homogeneity in the cognitive evaluation instruments used, interference from noncontrolled variables (such as subjects' educational level), nonidentification of the genotype, differences in the severity of the dementia, and inconsistency in estimating age at onset of the disease.[28] Thus, the results of these studies are also heterogeneous, with alterations of memory,[29-37] language,[29,31-35,38] attention-concentration,[35] and abstract reasoning and problem-solving,[34] as well as apraxia,[31,33-35] acalculia,[36] and visual agnosia.[32,37]

To date, 18 to 50 percent of all cases of FAD are due to mutations associated with chromosome 14,[39] and more than 70 different mutations have been reported in families of diverse ethnic origin.[40] In Antioquia, Colombia, 22 families have been identified as having a form of genetic early-onset AD caused by the mutation E280A in the presenilin 1 gene in chromosome 14. This group represents the world's largest founding effect of genetic AD; and its genetic,[41] clinical, epidemiological,[31] preclinical,[42,43] developmental,[44] and neuropathological characteristics[45,46] have been described elsewhere. Having access to this population has permitted us to obtain a more homogeneous sample of subjects in an initial state of dementia and another group of healthy family members who are carriers of the mutation.

This study had a double objective: first, to make a neuropsychological comparison using a specific cognitive evaluation battery with the aim of determining which neuropsychological tests best discriminate between ill subjects and healthy carriers (with similar sociodemographic and educational level variables); and second, to determine whether the neuropsychological deficits of the group with the disorder were similar to those described in other studies of subjects with sporadic AD and with FAD associated with chromosome 14.

Method

Subjects

The study was carried out with a sample of subjects who, after genetic testing, were confirmed to be positive for the mutation in the presenilin 1 gene (E280A, substitution of glutamic acid for alanine) in chromosome 14. These subjects belong to the families reported by Lopera.[31] All subjects were administered an evaluation protocol that consisted of a neurological examination and a psychological screening for dementia based on DSM-IV criteria, the score on the Global Deterioration Scale (GDS),[47] and an interview with a family member. The participants were divided into the following two groups:

1. Nine FAD carriers of mutation E280A with a diagnosis of DAT in its early stage and a score of 4 on the GDS.

2. Nine asymptomatic carriers who: (a) did not fulfill the DSM-IV diagnostic criteria for dementia; (b) did not have specific cognitive problems that affected work, social activities, or family life; (c) scored 1 on the GDS; and (d) did not have a history of neurological or psychiatric disorders.

Mean age at the time of evaluation was 49.67 years (SD = 4.85) in the case of the affected carriers, and 37.67 years (SD = 5.61) in the case of the healthy carriers. Educational level was low in both groups and was reflected by a similar number of years of schooling in each group: AD X = 3 (SD = 1.22) and HC X = 3.67 (SD = 1.22) (Mann-Whitney "U" = 28, p = .25). All subjects were right-handed.

Instruments

Two groups of neuropsychological tests were applied individually to each participant in the study. First, we administered the CERAD[48] evaluation battery, which includes the following tests:

1. *Verbal Fluency:* Subjects are asked to name as many animals as they can in the space of one minute. Total score is the number of animals named correctly.

2. *Naming:* Subjects are asked to identify 15 drawings of increasing complexity (high, medium, and low frequency), with a maximum of 10 seconds for each drawing. One point is awarded for each correct response, with a total possible score of 15 points.

3. *Mini-Mental State Exam (MMSE):* Although this test is part of the CERAD battery, it was not used in the present study as it includes a sub-test, spelling the word "world" backward letter by letter, which is inappropriate for speakers of

Table 1. Cognitive deficits reported in families with chromosome 14-linked familial Alzheimer's disease

Study (year)	Family's nationality	Number of subjects	Age at onset	Mutation	Memory	Attention	Language	Apraxia	Executive functions	Perception	Arithmetic
Haltia (1994)	Finnish	6	36	Unknown	Yes	?	Some	Some	?	Some	?
Lampe (1994)	German-American	16	41.6	Unknown	Yes	?	Yes	Some	Some	Some	Some
Kennedy (1995)	British	3	43	M139	Yes	Some	Yes	?	Yes	Yes	Yes
Fox (1997)	British	3	37.7	M139V	Yes	?	No	Yes	?	Yes	Yes
		3	44.3	M139V	Yes	?	Yes	Yes	?	Yes	Yes
Lopera (1997)	Colombian	15	46.8	E280A	Yes	No	Yes	Yes	?	?	?
Cook (1998)	Finnish	5	45 – 57	EXON 9	Yes	?	Yes	Yes	?	?	?
Devi (2000)	Unknown	3	< 30	434	?	?	Yes	?	?	?	?
Janssen (2000)	British	4	37.4	PSEN 1 Intron 4	Yes	?	?	?	Yes	Some	Some
Queralt (2001 A)	Spanish	1	48	M139T	Yes	Yes	Yes	?	?	?	?
Queralt (2001 B)	Spanish	3	< 50	V89L	Yes	Yes	Yes	Yes	Yes	Some	Some

Yes = Cognitive function was evaluated and deficit was found in all subjects.
Some = Cognitive function was evaluated and deficit was found in some subjects.
No = Cognitive function was evaluated and no deficit was found in any subject.
? = Cognitive function was not evaluated.

Spanish who are not accustomed to spelling words out. In its place we applied Folstein's[49] Mini-Mental test.

4. *Memory of Words:* This test assesses a subject's ability to recall information recently learned. Subjects are presented with a card on which they must read 10 words at a rate of one to two seconds per word. Immediately after subjects have read the words, the assessor asks them to recall as many words as possible. This procedure is repeated in three consecutive trials. The maximum number of correct words is 30 for the three trials.

5. *Constructional Praxis:* Subjects are presented, one by one, with four figures of increasing complexity and asked to copy them. Maximum time allowed for copying each figure (circle, rhombus, rectangle, and cube) is two minutes.

6. *Recall of Words:* This test assesses delayed memory by asking subjects to recall a list of ten words they have previously read. Maximum time allowed for this recall is 90 seconds, and one point is awarded for each word recalled correctly, with a maximum of 10 points if all words are recalled.

7. *Recognition of Words:* Subjects are presented

with a list of 20 words, from which they must identify the 10 words they read in the word recall test. Of the 20 words, 10 are correct and 10 are incorrect. Subjects must respond with "Yes" to the words they believe were on the list of words they previously read and "No" to the words that were not on that list. One point is awarded for each word correctly recognized.

8. *Recall of Line Drawings:* Subjects are asked to recall the drawings they made previously and draw them again on a blank sheet of paper. This test serves to assess visual memory.

Second, in addition to the CERAD evaluation, the following neuropsychological tests were administered:

1. *Phonological Verbal Fluency:* Subjects are asked to say as many words as possible beginning with the letter F, except proper names or derivatives (diminutives, etc.), in the space of one minute. Score is the number of correct words said by a subject in the allotted time.

2. *Visual "A" Cancellation Test:*[50] Subjects are asked to mark, as quickly as possible, all the letter A's in a series of random letters (usually 60 or more) on a piece of paper. Subjects are evaluated based on the number of A's found, the number of A's omitted, and the total time needed to complete the test.

3. *The Rey-Osterrieth Complex Figure.*[51] Subjects are presented with a design card showing a figure that contains 18 elements. They are asked to draw the figure on a blank sheet of white paper two different times. The first time, subjects are allowed to have the figure in front of them and must copy it. When they finish, the examiner takes away both drawings and asks them to reproduce the drawing from memory. Each drawing sequence a subject produces is scored a maximum of two points for each element if it is correctly drawn (one point) and in the correct location (one point), for a maximum of 36 points.

4. *Memory of Three Phrases:* This consists of three short phrases that subjects must recall word for word. Total score in the test corresponds to the number of phrases subjects correctly recall.

5. *Trail Making Test (Part A).*[52] Subjects must connect randomly located circles with the numbers one to 25 as fast as possible. Subjects are evaluated based on the number of correct connections, the number of erroneous corrections, and the total time needed to complete the test.

Prior to the testing, all participants were told about the purpose of the evaluation and asked for their consent to participate, in accordance with the protocol of informed consent approved by the ethics committee of the Medical Faculty at the University of Antioquia (Medellín-Colombia). Subsequently, all subjects were first administered the CERAD[48] battery of neuropsychological tests, followed by the other neuropsychological tests. Administration of the entire neuropsychological evaluation was carried out, in a session of 60 minutes, by a psychologist specializing in neuropsychological assessment, under the constant supervision of a member of the university teaching staff.

Statistical procedure

The results of both groups of subjects in the different neuropsychological tests were analyzed by means of the non-parametric Mann-Whitney "U" test for independent samples, taking into consideration two significance levels: $p < .01$ and $p < .05$.

Results

The set of results obtained in the different neuropsychological tests are shown in Tables 2 and 3. As Table 2 shows, there are statistically significant differences between the two groups both in the Mini-Mental State and in the majority of the neuropsychological tests of the CERAD battery. The FAD group scored lower than the healthy carriers group in most of the neuropsychological tests, with the following exceptions: Memory of Words (intrusions in trials 1, 2, 3 and total intrusions), Constructional Praxis (circle), and Recall of Words (total intrusions). Mean score in the MMSE, as a measure of general cognitive state, was 19 in the case of the patients and 28 in the healthy carriers group. Among Colombian subjects with low educational levels, 23 points on the MMSE has been shown to be an appropriate cutoff score for dementia;[50] therefore, relative to normal subjects with minimal education, the patient group in this study, with an average score of 19 on the MMSE, can be considered to be mildly affected with dementia.

Regarding the CERAD neuropsychological tests, in the Verbal Fluency test, we found statistically significant differences in total score and in the time intervals 0 to 15, 31 to 45, and 46 to 60 seconds. In the Naming test, we found significant differences in total naming score, as well as in the scores corresponding to naming low and medium frequency words. In the Memory of Words test,

Table 2. Comparison of performance in CERAD neuropsychological tests by subjects with Alzheimer's vs. healthy carriers									
Tests	**Alzheimer's patients**			**Healthy carriers**			**Mann-Whitney U test for independent samples**		
	N	**X**	**SD**	**N**	**X**	**SD**	**U**	**p**	**Sig**
MMSE	9	19	2.55	9	28	1.8	.00	.000	**
Verbal Fluency									
0 – 15 sec	9	3.89	1.17	9	5.89	1.54	12	.010	*
16 – 30 sec	9	3.22	1.56	9	4.22	1.2	20	.064	NS
31 – 45 sec	9	2	.71	9	3.44	1.01	11	.007	**
46 – 60 sec	9	1.44	.88	9	2.89	1.17	13	.012	*
Total fluency	9	10.56	2.55	9	16.33	4.27	8	.004	**
Naming									
High frequency	9	4.78	.44	9	4.89	.33	36	.539	NS
Medium frequency	9	3	1.12	9	4.33	.87	14.5	.017	*
Low frequency	9	2.56	1.33	9	3.78	.67	19.5	.049	*
Total naming	9	10.33	2.4	9	13	1.22	14	.018	*
Memory of Words									
Reading	9	8.89	3.33	9	10	.00	36	.317	NS
Trial 1	9	1.89	.78	9	4.33	.5	.000	.000	**
Intrusions	9	.44	.73	9	.22	.44	35	.535	NS
Trial 2	9	3	1.12	9	5.33	.71	3.5	.001	**
Intrusions	9	.67	.71	9	.22	.44	26	.136	NS
Trial 3	9	3.22	1.3	9	7.22	.97	.000	.000	**
Intrusions	9	.33	.71	9	.11	.33	35.5	.496	NS
Total correct	9	8.11	2.93	9	16.89	1.45	.000	.000	**
Total intrusions	9	1.22	1.20	9	.67	.87	29.5	.303	NS
Constructional Praxis									
Circle	9	2	.00	9	1.78	.44	31.5	.145	NS
Rhombus	9	2	1.12	9	2.89	.33	21	.040	*
Rectangle	9	1.44	.88	9	2	.00	27	.066	NS
Cube	9	1.22	1.39	9	3.44	1.01	10	.005	**
Total praxis	9	6.67	2.83	9	10.11	1.05	11.5	.009	**
Recall of Words									
Total correct	9	1.22	1.20	9	6.78	.83	.000	.000	**
Total intrusions	9	.89	1.76	9	.89	1.27	35.5	.598	NS
Recognition of Words									
Correct "yes"	9	6.78	3.42	9	10	.00	18	.012	*
Correct "no"	9	8.11	2.57	9	10	.00	22.5	.029	*
Recall of Drawings									
Circle	9	.89	1.05	9	1.67	.71	24.5	.100	NS
Rhombus	9	.22	.67	9	1.89	1.45	15.5	.011	*
Rectangle	9	.00	.00	9	1.44	.88	9	.001	**
Cube	9	.44	1.01	9	1.67	1.87	24.5	.107	NS
Total	9	1.56	1.88	9	6.67	2.87	6	.001	**
* $p < .05$; ** $p < .01$; NS = not significant.									

we found highly significant differences in the total of correct words and in trials 1, 2 and 3. In the Constructional Praxis test, the differences found in total score were highly significant; the differences between the scores on the rhombus and the cube tests were also significant. As for the Recall of Words tests, differences in the total correct words were highly significant. Differences in the Recognition of Words tests were also significant (for both correct "yes" responses and correct "no" responses). Finally, the differences in the tests of Recall of Drawings were significant in total recall, and in the parts corresponding to the rectangle and the rhombus.

Table 3 shows the results for the rest of the neuropsychological tests applied. FAD patients scored markedly lower than healthy carriers (including more omissions and time invested in the Visual "A" Cancellation test, and more errors and time taken in the Trail Making Test "A"). Almost all the comparisons (except those corresponding to the correct responses and to the errors in the Trail Making Test "A") produced highly significant results. In the Phonological Verbal Fluency test, the differences were significant. In the Visual Cancellation test, all the parameters compared were significant. In the Rey Complex Figure test, the differences between the two groups were highly significant for both copying and recall. Difference of means for the total of the Memory of Three Phrases was also significant. Finally, the scores corresponding to the Trail Making Test "A" showed highly significant differences in the time taken to complete the test.

Discussion

The first objective of this study was to determine whether there were statistically significant differences in a battery of specific neuropsychological assessments between: 1) a group of subjects with FAD in its initial stages caused by the mutation E280A in the presenilin 1 gene of chromosome 14, and 2) a group of healthy carriers of that mutation from the same family. The results of the study show the FAD subjects to be characterized by scoring lower in 41 of the 43 neuropsychological variables measured (95.3 percent) and that, in 29 of the 43, the differences were statistically significant (67 percent). This confirms the hypothesis that measures of neuropsychological performance obtained by means of a battery for evaluating the different cognitive processes (memory, attention, language, and praxis) can be useful for the diagnosis of people with FAD in its initial stages in comparison to a group of normal subjects without cognitive deterioration who are carriers of the mutation.

This study analyzed the neuropsychological profile of the group of FAD patients and compared it to the profile of subjects with sporadic AD in its early stage. In the tests of spoken language, FAD subjects in the current study produced a significantly lower number of words, both in the semantic category of animals and in the phonetic category (words beginning with the letter "F"), which coincides with the findings that subjects with sporadic AD in its initial stage present deficits of verbal and phonetic fluency in comparison to the control group.[53-56] Likewise, we found that FAD subjects' scores in the naming test of the CERAD were significantly lower than those of the healthy subjects group, which is in accordance with the indications of other researchers, who found naming deficits to be common in initial and moderate stages of sporadic AD.[57-61] The low scores obtained by the FAD group in the CERAD verbal fluency and naming tests could be interpreted as reflecting an alteration related to semantic knowledge, which may already be affected in the initial stages of the sporadic form of the disease,[57,62-65] even though such a conclusion requires the support of a much more detailed study of semantic memory in future investigations.

In the word-reading test, no statistically significant differences were found between the groups analyzed in this study, which is not surprising, since it has already been reported that subjects with sporadic AD in its initial stages adequately maintain their ability to read words aloud,[66] even in cases where there is considerable alteration of written comprehension ability.[67-71]

Memory deficits tend to be one of the most important clinical symptoms among the diagnostic criteria of the illness in question.[72] In the present study, FAD subjects presented statistically significant differences (scoring lower) with respect to the healthy subjects in the different tests assessing verbal memory in the short term (CERAD Memory of Words test and the Memory of Three Phrases) and recall (CERAD Recall of Words), as well as in those evaluating delayed visual memory (CERAD Recall of Drawings and the Recall of the Rey Complex Figure) and recognition memory (CERAD Recognition of Words). These results agree with those of other authors in that subjects with sporadic AD in its initial stages, by comparison with the control group, present deficits in the tests evaluating short-term[59,73,74] and delayed recall.[22,75,76] These results may indicate that subjects with FAD in its initial stages present an alteration in the learning and retention of new information, which may be the result of a dysfunction of mesial temporal structures such as the hippocampus,[77] the amygdala,[78,79] or the entorhinal cortex,[80,81] which are often altered in the initial stages of the sporadic form of the disease.

Subsequent to the appearance of memory disorders, attention tends to be the first cognitive domain to undergo alterations in subjects with the sporadic form of AD.[82] In the initial stages, the most elementary aspects of attention—such as arousal and alertness level, attention span,

Table 3. Comparison of performance in other neuropsychological tests by subjects with Alzheimer's vs. healthy carriers									
Tests	**Alzheimer's patients**			**Healthy carriers**			**Mann-Whitney U test for independent samples**		
	N	**X**	**SD**	**N**	**X**	**SD**	**U**	**P**	**Sig**
Phonological Verbal Fluency (letter F)	7	5.14	3.02	8	9.38	3.34	9.5	.029	*
Visual "A" Cancellation									
Correct	6	9.67	3.93	9	15.44	1.01	1	.002	**
Omissions	6	6.33	3.93	9	.56	1.01	1	.002	**
Time	6	125.17	64.09	9	.58	25.93	8.5	.029	*
Rey Complex Figure									
Copy	7	5.71	5.17	8	26.69	6.98	1.5	.002	**
Recall	7	.14	.24	8	12.56	6.72	.000	.001	**
Memory of Three Phrases	7	.00	.00	9	1.11	1.05	10.5	.010	*
Trail Making Test "A"									
Correct	5	22.8	2.17	9	23.33	.71	21	.827	NS
Errors	8	2	2.51	9	.56	.73	28.5	.430	NS
Time	8	220.5	68.51	9	127.6	43.63	9	.009	**
* $p < .05$; ** $p < .01$; NS = non-significant.									

and sustained attention—tend to be preserved in these subjects.[79,83-86] However, recent studies have reported that subjects with sporadic AD may present deficits of selective attention[82,83,86,87] and divided attention[82,86,87] in the initial stages of the demential syndrome. For the assessment of attentional processes in this study, the Visual "A" Cancellation test and the Trail Making Test (part A), both of which are widely used in investigation for assessing selective attention,[88-91] were used. However, attentional processes involve a wide range of cognitive functions, and most measures, including the ones used in this study, are multifaceted.

In this study, the subjects with FAD presented statistically significant differences in the Visual "A" Cancellation test and the Trail Making Test (part A) in the time variable, in comparison with the healthy subjects, who obtained better scores. This indicates that subjects with FAD in its initial stages appear to present deficits in tasks that have been used to evaluate selective attention, by comparison with a control group. However, it is important to note that the patients scored significantly lower on the Trail Making Test "A" only on the time variable and not the total number of correct or erroneous responses. Therefore, the results should be interpreted with caution due to the fact that these tests for attentional processes are admittedly nonspecific; and low scores, especially on time variables, could be due to other factors not related to attention, such as processing speed, visual scanning, and quick motor response.[89]

Numerous studies have indicated the alteration of visoconstructional processes as one of the characteristics generally found in subjects with sporadic AD.[92-98] To measure visoconstructional praxis, the CERAD copying tests (circle, rhombus, rectangle, and cube) and the Rey Figure test, one of those most commonly used for assessing visuoconstructional and visuospatial abilities,[50] were used. The results show that FAD subjects presented statistically significant differences in comparison to the healthy subjects in all the tests used for evaluating these functions, a finding

that coincides with those of other researchers who stress the frequency of visoconstructional alterations in subjects with the sporadic form of the disease.

In summary, in this study, the neuropsychological profile of the subjects with FAD in its initial stages is characterized by a predominance of mnemic, linguistic, praxic, and attentional deficits, making it similar to the typical profile described in studies of subjects with sporadic AD in its initial stages. This clinical finding is not surprising, considering that Lippa and his colleagues[99] did not find any major pathological differences in the regional distribution of some common neuropathological features they compared in FAD presenilin 1 and sporadic AD patients. Therefore, the clinical manifestations would also be expected to be similar between groups, as found in the present study. It is to be hoped that the detailed study of these familial forms of AD, which currently represent only a small percentage of the total number of patients with AD, can be applied, and will contribute in the future to a better understanding of the sporadic form of the disease.

To assess profile similarities or differences, the neuropsychological profile in this study's clinical population was compared to the profiles of FAD subjects having other specific mutations in the presenilin 1 gene of chromosome 14 according to studies by other researchers. The group of subjects with FAD had an average age at onset of the disorder of 50.9 years, with a standard deviation of 6.92 years, which is in accordance (Table 1) with the age at onset of the disease (under 65 years) in the different families with FAD associated with chromosome 14 described in the literature.

Although there are few studies that analyze the neuropsychological characteristics of subjects with this familial form of the illness, the neuropsychological deficits found in this study are largely in line with those found by other researchers. Nine out of ten studies have found memory deficits in FAD patients. Praxic and language alterations are also common in these subjects, having been found in four and seven studies, respectively, while attentional deficits have been reported in just two studies. However, other deficits—such as acalculia and deficits of problem-solving, abstract reasoning, and conceptualization—were not found in the present work; given the low educational level of the sample, tests for the assessment of such deficits were not used. It should be pointed out that, if the FAD subjects presented constructive apraxia and deficits in memory, language, and attention, it is highly probable they would have similar difficulties in carrying out neuropsychological tests that require a higher cognitive level such as those related to arithmetic and executive functions—conceptualization, abstract reasoning, and problem solving, among others—since such abilities depend on the integrity of these basic processes.

In conclusion, the battery of neuropsychological tests used in this study was useful for differentiating the group of FAD carriers from a group of healthy carriers of the same mutation. The neuropsychological profile of subjects with FAD caused by the mutation E280A in the presenilin 1 gene of chromosome 14 includes deficits of memory, language, praxis, and attention, making it similar to that reported in subjects with sporadic AD in its initial stages. Furthermore, these symptoms coincide in large part with those reported in studies on families with FAD associated with chromosome 14. All of this leads us to consider that the clinical phenotype of sporadic AD and FAD associated with chromosome 14 in the initial stages may be similar. Thus, future studies with homogeneous populations, both genetically and phenotypically, carried out with the aim of identifying each one of the specific deficits and examining their onset, evolution, and prognosis, may lead to a better understanding of the forms of sporadic AD that are currently one of the main causes of death throughout the world.

Acknowledgments

This investigation was made possible through a scholarship given to the principal author by the Spanish Agency for International Cooperation and through funding awarded to the third author as part of the University of Antioquia's 2001-2003 Sustainability Program (Medellín, Colombia). The authors also wish to thank David Weston for his translation of the original Spanish language text.

References

1. Lowenberg K, Waggoner RW: Familial organic psychosis (Alzheimer's type). *Arch Neurol Psychiatry.* 1934; 31: 737-754.
2. Bird TD, Lampe TH, Nemens EJ, et al.: Familial Alzheimer's disease in American descendants of the Volga Germans: Probable genetic founder effect. *Ann Neurol.* 1988; 23(1): 25-31.
3. Bird TD, Sumi SM, Nemens EJ, et al.: Phenotypic heterogeneity in familial Alzheimer's disease: A study of 24 kindreds. *Ann Neurol*. 1989; 25(1): 12-25.
4. Nee LE, Polinsky RJ, Eldridge R, et al.: A family with histogically confirmed Alzheimer's disease. *Arch Neurol*. 1983; 40(4): 203-208.
5. Sadovnick AD, Tuokko H, Horton A, et al.: Familial Alzheimer's disease. *Can J Neurol Sci.* 1988; 15(2): 142-146.
6. George-Hyslop ST, Haines JL, Farrer LA, et al.: Genetic linkage studies suggest that Alzheimer's disease is not a single homogeneous disorder. *Nature.* 1990; 347: 194-197.
7. Schellenberg GD, Bird TD, Wijsman EM, et al.: Absence of linkage of chromosome 21q21 markers to familial Alzheimer's disease. *Science*. 1988; 241: 1507-1509.
8. Brian A, Ryans BS: Clinical symptoms associated with age at onset in Alzheimer disease. *Am J Psychiatry*. 1994; 151: 1646-1649.
9. Chui HC, Teng EL, Henderson VW, et al.: Clinical subtypes of dementia of the Alzheimer type. *Neurology.* 1985; 35(11): 1544-1550.
10. Filley CM, Kelly J, Heaton RK: Neuropsychologic features of early- and late-onset Alzheimer's disease. *Arch Neurol.* 1986; 43(6): 574-576.
11. Koss E, Edland S, Fillenbaum G, et al.: Clinical and neuropsychological differences between patients with earlier and later onset of Alzheimer's disease: A CERAD analysis, Part XII. *Neurology.* 1996; 46(1): 136-141.

12. Seltzer B, Sherwin I: A comparison of clinical features in early- and late-onset primary degenerative dementia: One entity or two? *Arch Neurol.* 1983; 40(3): 143-6.
13. Loring DW, Largen JW: Neuropsychological patterns of presenile and senile dementia of the Alzheimer type. *Neuropsychologia.* 1985; 23(3): 351-357.
14. Jacobs D, Sano M, Marder K, et al.: Age at onset of Alzheimer's disease: Relation to pattern of cognitive dysfunction and rate of decline. *Neurology*. 1994; 44: 1215-1220.
15. Martin JJ, Gheuens J, Bruyland M, et al.: Early onset Alzheimer's disease in 2 large Belgian families. *Neurology*. 1991; 41(1): 62-68.
16. Capitani E, Della Salla S, Spinnler H: Controversial neuropsychological issues in Alzheimer's disease: Influence of onset-age and hemispheric asymmetry of impairment. *Cortex.* 1990; 26(1): 133-145.
17. Lehtovirta M, Soininen H, Helisalmi S, et al.: Clinical and neuropsychological characteristics in familial and sporadic Alzheimer's disease: Relation to apolipoprotein E polymorphism. *Neurology*. 1996; 46(2): 413-419.
18. Edwards JK, Larson EB, Hughes JP, et al.: Are there clinical and epidemiological differences between familial and non-familial Alzheimer's disease? *J Am Geriatr Soc.* 1991; 39(5): 477-483.
19. Luchins DJ, Cohen D, Hanrahan P, et al.: Are there clinical differences between familial and nonfamilial Alzheimer's disease? *Am J Psychiatry*. 1992; 149(8): 1023-1027.
20. Pérez Trullen JM : Análisis de la afectación de la función lingüística en la enfermedad de Alzheimer. *Arch Neurobiol (Madr)*. 1995; 58(1): 99-113.
21. Selnes OA, Carson K, Rovner B, et al.: Language dysfunction in early- and late-onset possible Alzheimer's disease. *Neurology*. 1988; 38(7): 1053-1056.
22. Swearer JM, O'Donnell BF, Drachman DA, et al.: Neuropsychological features of familial Alzheimer's disease. *Ann Neurol*. 1992; 32(5): 687-694.
23. Warrington EK, Agnew SK, Kennedy AM, et al.: Neuropsychological profiles of familial Alzheimer's disease associated with mutations in the presenelin 1 and amyloid precursor protein genes. *J Neurol.* 2001; 248: 45-50.
24. Goate AM, Chartier MC, Mullan MC, et al.: Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature*. 1991; 394: 704-706.
25. St. George-Hyslop PH, Tanzi RE, Polinsky RJ, et al.: The genetic defect causing familial Alzheimer's disease maps on chromosome 21. *Science*. 1987; 235: 885-890.
26. Sherrington R, Rogaev EI, Liang Y, et al.: Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature*. 1995; 375(6534): 754-760.
27. Levy-Lahad E, Wasco W, Poorkaj P, et al.: Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science.* 1995; 269: 973-977.
28. López S, Garre J: Capacidad discriminante del rendimiento neuropsicológico en la enfermedad de Alzheimer. *Rev Neurol*. 2000; 31(6): 534-535.
29. Crook R, Verkkoniemi A, Perez-Tur J, et al.: A variant of Alzheimer's disease with spastic paraparesis and unusual plaques due to deletion of exon 9 of presenilin 1. *Nat Med.* 1998; 4(4): 452-455.
30. Janssen JC, Hall M, Fox NC, et al.: Alzheimer's disease due to an intronic presenilin 1 (PSNE1 intron 4) mutation: A clinicopathological study. *Brain*. 2000; 123(Pt 5): 894-907.
31. Lopera F, Ardila A, Martínez A, et al.: Clinical features of early-onset Alzheimer disease in a large kindred with an E280A presenilin-1 mutation. *JAMA*. 1997; 277(10): 793-799.
32. Haltia M, Viitanen M, Sulkava R, et al.: Chromosome 14-encoded Alzheimer's disease: Genetic and clinicopathological description. *Ann Neurol*. 1994; 36(3): 362-367.
33. Kennedy AM, Newman SK, Frackowiak RS, et al.: Chromosome 14 linked familial Alzheimer's disease: A clinico-pathological study of a single pedigree. *Brain*. 1995; 118(Pt 1): 185-205.
34. Lampe TH, Bird TD, Nochlin D, et al.: Phenotype of chromosome 14-linked familial Alzheimer's disease in large kindred. *Ann Neurol*. 1994; 36(3): 368-378.
35. Queralt R, Ezquerra M, Castellví M, et al.: Detection of the presenilin 1 gene mutation (M139T) in early-onset familial Alzheimer disease in Spain. *Neurosci Lett.* 2001; 299(3): 239-241.
36. Fox NC, Kennedy AM, Harvey RJ, et al.: Clinicopathological features of familial Alzheimer's disease associated with the M139V mutation in the presenilin 1 gene: Pedigree but not mutation specific age at onset provides evidence for a further genetic factor. *Brain*. 1997; 120(Pt 3): 491-501.
37. Queralt R, Ezquerra M., Lleó A, et al.: A novel mutation (V89L) in the presenilin 1 gene in a family with early onset Alzheimer's disease and marked behavioral disturbances. *J Neurol Neurosurg Psychiatry.* 2002: 72(2): 266-269.
38. Devi G, Fotiou A, Jyrinji D, et al.: Novel presenilin 1 mutations associated with early onset of dementia in a family with both early-onset and late-onset Alzheimer disease. *Arch Neurol*. 2000; 57(10): 1454-1457.
39. Cruts M, Van Broeckhoven C: Presenilin mutations in Alzheimer's disease. *Hum Mutat.* 1998; 11(3): 183-190.
40. Tandon A, Rogaeva E, Mullan M, et al.: Molecular genetics of Alzheimer's disease: The role of beta-amyloid and the presenilins. *Curr Opin Neurol.* 2000; 13(4): 377-384.
41. Lendon CL, Martínez A, Berhens IM, et al.: E280A PS-1 mutation causes Alzheimer's disease but age of onset is not modified by ApoE alleles. *Hum Mutat.* 1997; 10(3): 186-195.
42. Ardila A, Lopera F, Roselli M, et al.: Neuropsychological profile of large kindred with familial Alzheimer's disease caused by the E280A single presenilin 1 mutation. *Arch Clin Neuropsychol*. 2000; 15(6): 515-528.
43. Johnson KA, Lopera F, Jones K, et al.: Presenilin-1-associated abnormalities in regional cerebral perfusion. *Neurology.* 2001; 56(11): 1545-1551.
44. Roselli M, Moreno S, Ardila A, et al.: Familial Alzheimer's disease associated with E280A preseniline 1 mutation: A longitudinal study. *J Clin Exp Neuropsychol.* 2000; 22(4): 483-495.
45. Duque-Castaño A, Roldán MI, Arango-Viana JC, et al.: Hallazgos neuropatológicos en la enfermedad de Alzheimer de inicio temprano (mutación E280A-PS1). *Rev Neurol*. 1999; 29(1): 1-6.
46. Lemere C, Lopera F, Kosik K, et al.: The E280A presenilin 1 Alzheimer mutation produces increased AB42 deposition and severe cerebellar pathology. *Nature Med.* 1996; 2(10): 1146-1150.
47. Reisberg B, Ferris SH, de Leon MJ, et al.: Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry.* 1982; 139(9): 1136-1139.
48. Morris JC, Heyman A, Mohs RC, et al.: The Consortium to Establish a Registry for Alzheimer's Disease (CERAD): Part I - Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology.* 1989; 39(9): 1159-1165.
49. Folstein MF, Folstein SE, McHugh PR: Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975; 12(3): 189-198.
50. Ardila A, Rosselli M, Puente A: *Neuropsychological Evaluation of the Spanish Speaker.* New York, NY: Plenum Press, 1994.
51. Osterrieth PA: Le test de copie d'une figure complexe. *Archives de Psychologie.* 1944; 30: 206-356.
52. Reitan RM, Davison LA. *Clinical Neuropsychology: Current Status and Applications*. New York, NY: John Wiley & Sons, 1974.
53. Butters N, Granholm E, Salmon D, et al.: Episodic and semantic memory: A comparison of amnesic and demented patients. *J Clin Exp Neuropsychol.* 1987; 9(5): 479-497.
54. Epker MO, Lacritz LH, Cullum CM: Comparative analysis of

qualitative verbal fluency performance in normal elderly and demented populations. *J Clin Exp Neuropsychol.* 1999; 21(4): 425-434.
55. Hodges JR, Salmon DP, Butters N: The nature of the naming deficit in Alzheimer's and Huntington's disease. *Brain.* 1991; 114: 1547-1558.
56. Martin A, Cox C, Browers P, et al.: A note on different patterns of impaired and preserved cognitive abilities and their relation to episodic memory deficits in Alzheimer's patients. *Brain Lang*. 1985; 26: 181-185.
57. Daum I, Riesch G, Sartori G., et al.: Semantic memory impairment in Alzheimer's disease. *J Clin Exp Neuropsychol.* 1996; 18(5): 648-665.
58. Laiacona M, Barbarotto R, Capitani E: Semantic category dissociations in naming: Is there a gender effect in Alzheimer's disease? *Neuropsychologia.* 1998; 36(5): 407-419.
59. Sánchez JL, Sayago AM: Diagnóstico precoz y evolución de la enfermedad de Alzheimer. *Rev Neurol.* 2000; 30(2): 121-127.
60. Smith SR, Chenery HJ, Murdoch BE: Semantic abilities in dementia of the Alzheimer type. *Brain Lang*. 1989; 36(4): 533-542.
61. Chertkow H, Bub D: Semantic memory loss in dementia of Alzheimer's type: What do various measures measure? *Brain*. 1990; 113(Pt 2): 397-417.
62. Chan AS, Butters N, Salmon DP: The deterioration of the semantic networks in patients with Alzheimer's disease: A cross-sectional study. *Neuropsychologia.* 1997; 35(3): 241-248.
63. Hodges JR, Salmon DP, Butters N: Differential impairment of semantic and episodic memory in Alzheimer's and Huntington's diseases: A controlled prospective study. *J Neurol Neurosurg Psychiatry*. 1990; 53(12): 1089-1095.
64. Taussig IM, Fernandez-Guinea S: Los tests de fluidez verbal como predictores de la demencia de tipo Alzheimer: Una comparación entre sujetos angloparlantes e hispanohablantes. *Clínica y Salud.* 1995; 6(3): 283-296.
65. Huff FJ, Corkin S, Growdon JH: Semantic impairment and anomia in Alzheimer's disease. *Brain Lang.* 1986; 28(2): 235-249.
66. Peña J: *Enfermedad de Alzheimer - Del Diagnóstico a la Terapia: Conceptos y Hechos*. Barcelona: Fundación La Caixa, 1999.
67. Chui H: Dementia: A review emphasizing clinicopathologic correlation and brain-behavior relationships. *Arch Neurol.* 1989; 46(7): 806-814.
68. Cummings JL, Houlihan JP, Hill MA: The pattern of reading deterioration in dementia of the Alzheimer type: Observations and implications. *Brain Lang*. 1986; 29(2): 315-323.
69. Gonzalez Montalvo J, del ser Quijano T, Bermejo Pareja F: Demencia: Lenguaje e inteligencia previa. *Arch Neurobiol (Madr)*. 1990; 53(5): 162-170.
70. Huppert FA, Tym E: Clinical and neuropsychological assessment of dementia. *Br Med Bull.* 1986; 42(1): 11-18.
71. Rapcsak S, Arthur S, Bliklen D, et al.: Lexical agraphia in Alzheimer's disease. *Arch Neurol.* 1989; 46(1): 65-68.
72. Allegri RF, Harris P, Feldman M, et al.: Perfiles cognitivos diferenciales entre la demenciafrontotemporal y la demencia tipo Alzheimer. *Rev Neurol.* 1998; 27(157): 463-466.
73. Moss MB, Albert MS, Butters N, Payne M: Differential patterns of memory loss among patients with Alzheimer's disease, Huntington's disease, and alcoholic Korsakoff's syndrome. *Arch Neurol.* 1986; 43(3): 239-246.
74. Hart RP, Kwentus JA, Taylor JR, et al.: Productive naming and memory in depression and Alzheimer's type dementia. *Arch Clin Neuropsychol.* 1988; 3: 313-322.
75. Welsh KA, Butters N, Hughes JP, et al.: Detection of abnormal memory decline in mild cases of Alzheimer's disease using CERAD neuropsychological measures. *Arch Neurol*. 1991; 48: 278-281.
76. Welsh KA, Butters N, Hughes JP, et al.: Detection and staging of dementia in Alzheimer's disease. *Arch Neurol*. 1992; 49(5): 448-452.
77. Hyman BT, Van Horsen GW, Damasio AR, et al.: Alzheimer's disease: Cell specific pathology isolates the hippocampal formation. *Science*. 1984; 225(4667): 1168-1170.
78. Herzog AG, Kemper TL: Amygdaloid changes in aging and dementia. *Arch Neurol.* 1980; 37(10): 625-629.
79. Laakso MP, Hallikainen M, Hänninen T, et al.: Diagnosis of Alzheimer's disease: MRI of hippocampus vs. delayed recall. *Neuropsychologia*. 2000; 38(5): 579-584.
80. Braak H, Braak E: Evolution of the neuropathology of Alzheimer's disease. *Acta Neurol Scand Suppl.* 1996; 165: 3-12.
81. Small SA: Age-related memory decline: Current concepts and future directions. *Arch Neurol.* 2001; 58(3): 360-364.
82. Perry RJ, Hodges JR: Attention and executive deficits in Alzheimer's disease: A critical review. *Brain.* 1999; 122(Pt 3): 383-404.
83. Perry RJ, Watson P, Hodges JR: The nature and staging of attention dysfunction in early (minimal and mild) Alzheimer's disease: Relationship to episodic and semantic memory impairment. *Neuropsychologia*. 2000; 38(3): 252-271.
84. Zec RF: Neuropsychological functioning in Alzheimer's disease. In Parks RW, Zec RF, Wilson RS (eds.), *Neuropsychology of Alzheimer's Disease and Other Dementias.* London: Oxford University Press, 1993.
85. Parasuraman R, Haxby JV: Attention and brain function in Alzheimer's disease: A review. *Neuropsychology*. 1993; 7: 242-272.
86. Foldi NS, Lobosco JJ, Schaefer LA: The effect of attentional dysfunction in Alzheimer's disease: Theoretical and practical implications. *Semin Speech Lang.* 2002; 23(2): 139-150.
87. Rizzo M, Anderson SW, Dawson J, et al.: Visual attention impairments in Alzheimer's disease. *Neurology.* 2000; 54(10): 1954-1959.
88. Solfrizzi V, Panza F, Torres F, et al.: Selective attention skills in differentiating between Alzheimer's disease and normal aging. *J Geriatr Psychiatry Neurol*. 2002; 15(2): 99-109.
89. Moore M, Mateer C: *Cognitive rehabilitation an integrative neuropsychological approach.* New York, NY: The Guilford Press, 2001.
90. Amieva H, Lafont S, Auriacombe S, et al.: Analysis of error types in Trail Making Test evidences an inhibitory deficit in dementia of the Alzheimer type. *J Clin Exp Neuropsychol*. 1998; 20(2): 280-285.
91. Greenlief CL, Margolis RB, Erker GJ: Application of the Trail Making Test in differentiating neuropsychological impairment of elderly persons. *Percept Mot Skills.* 1985; 61(3 Pt 2): 1283-1289.
92. Sunderland T, Hill JL, Mellow AM, et al.: Clock drawing in Alzheimer's disease: A novel measure of dementia severity. *J Am Geriatr Soc.* 1989; 37(8): 725-729.
93. Brantjes M, Bouma A: Qualitative analysis of the drawings of Alzheimer patients. *Clin Neuropsychol*. 1991; 5: 41-52.
94. Fisher NJ, Rourke BP, Bieliauskas L, et al.: Neuropsycholgical subgroups of patients with Alzheimer's disease. *J Clin Exp Neuropsychol.* 1996; 18(3): 349-370.
95. Gainotti G, Marra C, Villa G, et al.: Sensitivity and specificity of some neuropsychological markers of Alzheimer dementia. *Alzheimer Dis Assoc Disord.* 1998; 12(3): 152-162.
96. Henderson VW, Mack W, Williams BW: Spatial disorientation in Alzheimer's disease. *Arch Neurol.* 1989; 46(4): 391-394.
97. Kirk A, Kertesz A: On drawing impairment in Alzheimer's disease. *Arch Neurol.* 1991; 48(1): 73-77.
98. Rouleau I, Salmon DP, Butters N, et al.: Quantitative and qualitative analyses of clock drawings in Alzheimer's and Huntington's disease. *Brain Cogn.* 1992; 18(1): 70-87.
99. Lippa CF, Saunders AM, Smith TW, et al.: Familial and sporadic Alzheimer's disease: Neuropathology cannot exclude a final common pathway. *Neurology*. 1996; 46(2): 406-412.