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# Neuropsychological Profile of a Large Kindred with Familial Alzheimer's Disease Caused by the E280A Single Presenilin-1 Mutation

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*It was hypothesized that subjective memory complaints represent the earliest sign of dementia in carriers of the presenilin-1 (PS1) mutation. A total of 122 subjects (44 males, 78 females) were included in this study. Forty of them were positive for the mutation in the PS1 gene (mutation positive, MP) whereas 82 showed negative results (mutation negative, MN). Subjects were active, functionally normal, even though some of them complained of memory difficulties. Two groups of neuropsychological instruments were administered: (a) The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery (Morris et al., 1989), and (b) some additional neuropsychological tests (Raven Test, Wechsler Memory Scale, Rey-Osterrieth Complex Figure, Boston Naming Test, Naming of Categories, Boston Diagnos-*

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*tic Aphasia Examination, Memory of Three Phrases, Knopman Test, Digit Symbol, and Visual "A" Cancellation Test). Performance in both groups was quite similar. In a secondary analysis, the MP group was subdivided into two subgroups: without and with memory complaints. When comparing both subgroups, a better performance in the first subgroup was found throughout the different subtests. Statistically significant differences were observed in the following test scores: Mini-Mental State Examination, Naming Test (Low Frequency), Memory of Words Test, Recall of Drawings, Wechsler Memory Scale (Logical Memory, Associative Learning, and Total Score), Rey-Osterrieth Complex Figure (Immediate Recall Condition), Boston Diagnostic Aphasia Examination (Complex Ideational Material Subtest), Memory of Three Phrases Test, Serial Verbal Learning (maximum score and Delayed Recall), Knopman Test (First Trial, Second Trial, and Recall after 5 Minutes), Digit Symbol, and Visual "A" Cancellation Test (Additions). Results supported the hypothesis that memory complaints represent the earliest symptom of familial Alzheimer's disease. In addition to the memory difficulties, other minor cognitive impairments were also found, particularly, mild anomia, concentration difficulties and defects in the understanding of complex verbal material. © 2000 National Academy of Neuropsychology. Published by Elsevier Science Ltd*

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Heterogeneity in Alzheimer's disease has been observed (Cummings & Benson, 1992; Mayeux, 1985). Genetic factors have long been recognized in Alzheimer's disease, which, in a minority of the cases, exhibit an autosomal dominant familial pattern (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, Tuokko, Horton, Baird, & Beattie, 1988). Interestingly, patients with familial Alzheimer's disease (FAD) may present an earlier onset of symptoms and more rapid decline in cognition than patients with sporadic Alzheimer's disease (SAD) (Farrer et al., 1990; Jacobs et al., 1994; Lehtovirta et al., 1996; Richard et al., 1993). Furthermore, in addition to the memory deficits that are typical of SAD, aphasia and apraxia have been noted in FAD (Chui, Teng, Henderson, & May, 1985; Feldman, Chandler, Lewy, & Glaser, 1963; Frommelt et al., 1991; Karlinsky et al., 1992; Lampe et al., 1994; Martin et al., 1991).

The distinction between familial and sporadic disease, nonetheless, has over the years proven to be relatively arbitrary with the discovery of susceptibility genes that likely provoke sporadic forms of the illness. Mutations in chromosomes 1, 14, and 21 account for only a fraction of the disease (about 5–10%). Most AD patients suffer a late onset form likely related with some genetic or familial basis, although not autosomal dominant in nature. Some factors may result in increased vulnerability to the disease. Differences in the age of onset in the very same family carrying the very same mutation indicates that there are some other nongenetic and/or other genetic factors capable to modify the onset of the disease (Corder et al., 1993; Kehoe et al., 1999; Liao et al., 1998). Hence, even the sporadic forms of AD may have a familial basis, although not autosomal dominant in nature.

Recently, a large kindred of FAD was found in Colombia (South America). An initial clinical, epidemiological, genetic, and pathological description of this group have been presented elsewhere (Alzheimer's Disease Collaborative Group, 1995; Lopera et al., 1994, 1997). In this study the question about which is the phenotype of AD in families with PS1 mutation was raised.

We asked whether early preclinical signs of dementia could be found in asymptomatic subjects carrying a mutation in the presenilin-1 (PS1) gene. We hypothesized that subjective memory complaints predict the onset of the dementia. Thus, it was assumed that those otherwise normal subjects complaining of memory defects were indeed pre-

senting a wide array of subtle cognitive defects. It was proposed that subjective memory complaints, in consequence, represent the earliest sign of dementia in carriers of the PS1 mutation.

## METHOD

### *Subjects*

An initial 125-subject sample, further reduced to 122 participants, was used in this study. All of the subjects were analyzed for the presence of a mutation in the PS1 gene. Forty of them were found to be positive for the mutation in the PS1 gene (E280A, substitution of glutamic acid for alanine) (Alzheimer's Disease Collaborative Group, 1995) (mutation-positive group, MP), whereas 82 showed negative results (mutation-negative group, MN). All the 122 participants were evaluated by neurologic and neuropsychological testing. The clinical diagnostic criteria used to rule out dementia were the National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984) and the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (American Psychiatric Association, 1994). Subjects were active, functionally normal, even though some of them complained of memory difficulties. In a secondary analysis, the MP group (40 subjects) was subdivided into two subgroups: Without memory difficulty (MP-1) (30 subjects) and with memory difficulty (MP-2) (10 subjects). A 15-question checklist was used to screen memory complaints. In order to avoid the potential effect of uncontrolled confounding variables, three MN subjects presenting significant memory complaints according to the checklist criteria were not used in further analyses. Therefore, the final sample included 122 participants.

Both groups (MP and MN) were matched by sociocultural conditions and educational level. MN subjects were blood relatives (i.e., siblings and other blood-related kin) of the MP participants. Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) scores were between 24 and 30. Twenty-three points has been shown to be an appropriate MMSE cutoff score among subjects with minimal education (Ardila, Rosselli, & Puente, 1994). The neurological exam of all subjects was within normal limits. They were living in the highlands of the state of Antioquia in Colombia, and belonged to 12 different families dwelling in relatively close areas (Angostura, Yarumal, Santa Rosa de Osos, Ituango, San José de la Montaña, Dadeiba, Sopetrán, Cedeno, Sabanalarga, Medellín, and Belmira).

The demographic characteristics of the three groups can be observed in Table 1. The sample was comprised of 44 males and 78 females. The MP-1 was the youngest group followed by the MP-2. There were no significant differences in the patients' level of education. In all groups there were illiterates or subjects with just 1 year of schooling.

### *Instruments*

Two groups of neuropsychological instruments were individually administered to all the participants:

*The neuropsychological test battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989).* This consists of a Spanish version adapted to the cultural and linguistic idiosyncrasies of the target population. Words included cor-

**TABLE 1**
**Distribution of the Sample**

| | MN | MP-1 | MP-2 | Differences |
|---|---|---|---|---|
| *n* | 82 | 30 | 10 | |
| Gender | | | | |
| Males | 29 | 10 | 5 | |
| Females | 53 | 20 | 5 | |
| Age | | | | |
| *M* | 44.58 | 34.56 | 41.50 | MN vs. MP-1; MP-1 vs. MP-2 |
| *SD* | 12.00 | 7.23 | 4.00 | |
| Range | 23–76 | 23–54 | 37–48 | |
| Education | | | | |
| *M* | 4.19 | 5.50 | 4.10 | |
| *SD* | 3.22 | 3.94 | 2.30 | |
| Range | 0–13 | 0–14 | 1–8 | |

*Note*. MP-1 group was significantly younger than the other two groups. Differences between MN and MP-2 were not significant. MN = mutation negative; MP-1 = mutation positive without memory difficulty; MP-2 = mutation positive with memory difficulty.

responded to the usual Spanish spoken in Antioquia state. Spelling backwards was not used in the MMSE because to spell is extremely unusual in Spanish language. Instead, subtracting by three was included. This neuropsychological test battery has the following sections:

1. Verbal Fluency. Subjects are asked to name as many animals as possible in 1 minute. The score was the total number of animals named.
2. Naming. Subjects are asked to name 15 objects presented as line drawings. Three groups of five items were used, the names having high-, middle-, and low-frequency everyday language.
3. Mini-Mental State Exam (MMSE; Folstein et al., 1975). This is a brief standardized neuropsychological test battery that includes orientation, immediate and delayed memory, concentration, language (oral and written), and constructional praxis.
4. Memory of Words. Ten words are read and recalled three times. Maximum score is 30 for the three trials. Intrusions are also scored.
5. Constructional Praxis. Four line-drawings of figures with an increasing complexity (circle, diamond, rectangles, and cube) are presented for copying; maximum score is 11.
6. Recall of Words. Recall of words from test 4. A maximum of 90 seconds is allowed, and the maximum score is 10.
7. Recognition of Words. Recognition of the 10 words from test 4; 10 correct and 10 wrong words are included in a list; maximum correct (correct "yes") recognition is 10; maximum correct "was not there" answer is 10.
8. Recall of Line-Drawings. Recall from the four drawing in test 5. Maximum score is 11.

*Additional neuropsychological tests administered to extend the neuropsychological evaluation.*

1. Raven Test (Raven, 1982). Only Part A and B were included.
2. Wechsler Memory Scale (Wechsler, 1945).

3. Praxis Ability Test. Twenty buccofacial movements and 20 movements for each the left hand under verbal command were included. Each movement was scored from 1 (failure) to 5 (normal). Maximum score was 100 for each condition (buccofacial and left hand).
4. Rey-Osterrieth Complex Figure (Osterrieth, 1944), copy, and immediate reproduction. The scoring system proposed by Taylor (1959) was used. The maximum score was 36.
5. Phonological Verbal Fluency: The average number of words beginning with "f," "a," and "s" produced in 1 minute.
6. Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983).
7. Naming of Categories (Lopera, 1991). Ninety-two figures corresponding to 11 semantic categories (10 house items, 10 current use objects, 5 flowers, 5 transportation vehicles, 10 tools, 7 professional activities, 10 animals, 10 foods, 10 body parts, 10 colors, and 5 actions) were used. Figures are presented one by one asking the subject to name them. If the subject fails, a semantic cue is presented. If the subject fails again, a phonological cue is used. Finally, four answer options are used (the correct word, a nonrelated word, a semantic and a phonological related word). Each correct answer is scored 1. Maximum score is 92.
8. Boston Diagnostic Aphasia Examination, Spanish version (Goodglass & Kaplan, 1983).
9. Memory of Three Phrases. The subject repeats three sentences one at the time. After repeating the last one he/she is required to recall all three. One a point is given for each correct recalled sentence. Maximum score 3.
10. Serial Verbal Learning (Ardila et al., 1994). A list of 10 common nouns is read to the subject, who has to recall as many words as he/she can in any given order. The words are repeated up to 10 trails or until the subject recalls the 10 words. Three scores were used: number of words recalled in the first trial, maximum number of words retrieved in the last trial, and number of words recalled in a delayed condition (15–20 minutes later).
11. Knopman Test (Knopman & Ryberg, 1989). Ten written words are used. The subject must make a sentence with each one. Each word is presented twice. If the subject has difficulties, examiner suggests a sentence in the first presentation. In the second trial the subject can make a new sentence or to repeat the sentence suggested by the examiner. Five minutes later, the subject is requested to recall the 10 words used. Two scores are used: sentences made in the first trial (maximum score = 10), and recalled words (maximum score = 10).
12. Digit Symbol from the WMS (Wechsler, 1974).
13. Visual "A" Cancellation Test (Ardila et al., 1994).

Wechsler Memory Scale, Rey-Osterrieth Complex Figure, Verbal fluency, Boston Naming Test, Naming of Categories, Boston Diagnostic Aphasia Examination, Serial Verbal Learning and Visual "A" Cancellation Test have been previously normalized in Colombia in different age and education groups (Ardila & Rosselli, 1989, 1994; Ardila et al., 1994; Rosselli, Ardila, Flórez, & Castro, 1990; Rosselli & Ardila, 1991). It is important to note that most of the subjects had a very limited education and some were completely illiterate. Neuropsychological tests are highly sensitive to educational variables (Lezak, 1995), and illiteracy has been correlated with an extremely low performance in most neuropsychological tests (Ardila, Rosselli, & Rosas, 1989; Rosselli, Ardila, & Rosas, 1990). Moreover, a significant association between school attendance and cognitive decline during aging has been suggested (Caramelli et al., 1997; Stern et al., 1994; Stern,

Ming, Denaro, & Mayeaux, 1995). In consequence, neuropsychological test scores in illiterates and people with very low levels of education have to be treated with extreme caution.

In addition, a Subjective Memory Complaints Checklist (Matallana & Montañez, 1995) was used. This checklist was administered to all the participants. The Subjective Memory Complaints Checklist includes 15 questions (e.g., difficulties remembering recent national events, following a televison program or movie, finding people or places names, etc.). Each question is scored in a 0–3-point scale (0 = Never; 1 = Seldom; 2 = Sometimes; 3 = Almost always). Therefore, maximum score is 45 points. When memory difficulties (i.e., a decrease in memory ability with regard his/her previous level of functioning) not severe enough to interfere with working and social life were reported, it was considered as an "isolated memory complaint." Based on previous exploratory studies, a cutoff of 18 points was used. Ten MP subjects and three MN participants obtained fulfilled the criterion for "isolated memory complaint." The later three subjects were excluded from the sample.

The purpose of the evaluation was explained to all the participants following an uniform protocol. Consent for evaluation was obtained from all subjects according to a protocol approved by the Human Subjects Committee of the University of Antioquia.

Professional psychologists and graduate neuropsychology students, under the supervision of a professor, performed testing. Examiners were blind to the genetic testing results. In all the cases, the CERAD neuropsychological test battery was administered initially, followed by the administration of the other neuropsychological tests. Testing took 4 to 5 hours, depending upon the group. Testing was divided into several 45- to 60-minute sessions.

### *Statistical Procedure*

Differences between groups were analyzed for significance using Student's $t$ test. Two-tailed probabilities are reported, and $p > .05$ was considered nonsignificant.

## RESULTS

Initially, MN and MP groups were compared in the different neuropsychological tests. Table 2 presents the results obtained in the CERAD neuropsychological test battery. Statistically significant differences were observed in just a few test scores: Memory of Words (Intrusions in trial 2 and total intrusions), Recall of Words (intrusions), and Recognition of Words (correct "no"). Test scores were quite similar, even though the MN group in general obtained slightly higher scores than the MP group. Scores in the MMSE as a measure of general cognitive activity were 27.64 and 26.78 respectively ($p < .105$).

Table 3 presents the mean scores and standard deviations in the other neuropsychological tests. Performance in both groups was quite similar. Only some few test scores established statistically significant differences: Digits Backward, Memory Three Phrases and Visual "A" Cancellation Test. Difference in the Memory of Three Phrases Tests was particularly robust ($p < .003$).

The MP was further subdivided in two subgroups: Those subjects without memory complaints (MP-1) and those participants with memory complaints (MP-2). When comparing both subgroups (MP-1 and MP-2) an MP-1 subgroup better performance was found throughout the different subtests. Nonetheless, only in some subtests, differences

**TABLE 2**
**Mean Score and Standard Deviations (in parentheses) in the CERAD Neuropsychological Test Battery**

| Tests | MN ($n$ = 82) | MP ($n$ = 40) | $t$ | $p$ |
|---|---|---|---|---|
| Verbal Fluency | | | | |
| 0–15 seconds | 5.42 (1.64) | 5.30 (1.60) | 0.40 | .687 |
| 16–30 seconds | 4.19 (1.30) | 3.72 (1.33) | 1.85 | .066 |
| 31–45 seconds | 3.59 (1.53) | 3.30 (1.22) | 1.07 | .285 |
| 46–60 seconds | 3.15 (1.40) | 3.10 (1.28) | 0.22 | .825 |
| Total | 16.34 (4.27) | 15.43 (4.31) | 1.10 | .270 |
| Naming | | | | |
| High Frequency | 4.79 (0.40) | 4.85 (0.36) | 0.75 | .452 |
| Middle frequency | 4.09 (0.91) | 4.33 (1.05) | 0.23 | .220 |
| Low frequency | 3.74 (1.29) | 3.85 (1.23) | 0.43 | .667 |
| Total | 12.56 (2.14) | 13.03 (2.26) | 1.10 | .273 |
| Time | 88.03 (34.88) | 83.28 (27.72) | 0.75 | .452 |
| MMSE | 27.64 (6.29) | 26.78 (3.23) | 1.63 | .105 |
| Memory Words | | | | |
| Reading | 9.39 (2.40) | 9.50 (2.21) | 0.24 | .809 |
| Trial 1 | 3.82 (1.14) | 3.45 (1.13) | 1.72 | .083 |
| Intrusions | 0.43 (0.83) | 0.73 (0.91) | 1.73 | .086 |
| Trial 2 | 5.43 (1.14) | 5.08 (1.49) | 1.48 | .139 |
| Intrusions | 0.12 (0.32) | 0.30 (0.56) | 2.19 | .030 |
| Trial 3 | 6.68 (1.58) | 6.30 (1.77) | 1.20 | .231 |
| Intrusions | 0.23 (0.79) | 0.55 (1.20) | 1.75 | .082 |
| Total Correct | 16.00 (2.90) | 14.88 (3.88) | 1.79 | .076 |
| Total Intrusions | 0.67 (1.12) | 1.48 (1.72) | 3.09 | .002 |
| Constructional Praxis | | | | |
| Circle | 1.96 (0.18) | 1.88 (0.33) | 1.86 | .065 |
| Diamond | 2.60 (0.73) | 2.63 (0.81) | 0.10 | .917 |
| Rectangles | 1.97 (0.22) | 1.98 (0.16) | 0.01 | .988 |
| Cube | 3.18 (1.33) | 3.48 (1.01) | 1.22 | .224 |
| Total | 9.74 (1.91) | 9.95 (1.80) | 0.57 | .570 |
| Recall of Words | | | | |
| Total Correct | 5.36 (1.54) | 4.90 (2.34) | 1.31 | .192 |
| Intrusions | 0.36 (0.69) | 1.05 (1.58) | 3.32 | .001 |
| Recognition of Words | | | | |
| Correct “yes” | 9.68 (0.94) | 9.28 (1.52) | 1.82 | .071 |
| Correct “no” | 9.73 (0.93) | 9.28 (1.72) | 1.97 | .050 |
| Recall of Drawings | | | | |
| Circle | 1.58 (0.88) | 1.50 (0.85) | 0.50 | .614 |
| Diamond | 1.74 (1.35) | 1.38 (1.39) | 1.40 | .163 |
| Rectangles | 1.57 (0.84) | 1.20 (0.99) | 2.15 | .330 |
| Cube | 1.91 (1.64) | 1.78 (1.58) | 0.44 | .656 |
| Total | 6.76 (2.89) | 5.80 (2.95) | 1.72 | .087 |

*Note*. Significant differences are presented. CERAD = Consortium to Establish a Registry for Alzheimer’s disease; MN = mutation negative; MP = mutation positive; MMSE = Mini-Mental State Examination.

were statistically significant (Table 4). In the MMSE as a measure of general cognition, statistically significant differences were observed between the scores in group MP-1 (28.03) and MP-2 (23.00) ($p < .001$). Verbal Fluency and Constructional Praxis scores did not establish statistically significant differences between both subgroups. In the Naming Test, differences were found only in finding low-frequency, not high- or middle-frequency words. In the Memory of Words test, statistically significant differences were observed across the different trials and also in the total score. Differences were also observed in the Intrusions score in the second trial and in the total number of intrusions. In the Recall of Words test, both scores (total correct and intrusions) were significantly dif-

**TABLE 3**
**Results in Several Neuropsychological Tests**

| Tests | MN ($n$ = 82) | MP ($n$ = 40) | $t$ | $p$ |
|---|---|---|---|---|
| Raven Test | | | | |
| A | 7.88 (3.61) | 7.27 (2.21) | 0.91 | .365 |
| B | 4.29 (2.25) | 4.44 (2.04) | 0.35 | .725 |
| Wechsler Memory Scale | | | | |
| Information | 4.74 (1.09) | 4.80 (1.43) | 0.25 | .798 |
| Orientation | 4.95 (0.28) | 4.91 (0.51) | 0.44 | .658 |
| Mental Control | 4.71 (2.08) | 5.58 (2.59) | 1.90 | .060 |
| Logical Memory | 7.97 (3.44) | 7.92 (3.10) | 0.05 | .955 |
| Digits: Forward | 4.80 (1.11) | 5.02 (1.27) | 0.95 | .341 |
| Backward | 2.57 (1.81) | 3.27 (1.36) | 2.09 | .039 |
| Associative Learning | 12.76 (4.34) | 12.22 (5.24) | 0.54 | .585 |
| Visual Reproduction | 5.88 (3.28) | 6.76 (3.46) | 1.28 | .203 |
| Total Score | 48.36 (12.91) | 50.65 (13.50) | 0.83 | .404 |
| Praxis | | | | |
| Left Hand | 89.82 (7.83) | 90.05 (6.44) | 0.15 | .876 |
| Buccofacial | 96.49 (3.41) | 95.82 (4.50) | 0.83 | .403 |
| Rey-Osterrieth Complex Figure | | | | |
| Copy | 22.46 (8.48) | 24.61 (9.26) | 1.28 | .203 |
| Immediate Recall | 10.01 (5.96) | 9.72 (6.48) | 0.29 | .772 |
| Verbal Fluency | | | | |
| FAS | 8.58 (2.90) | 9.47 (3.46) | 1.36 | .174 |
| Boston Naming Test | 38.96 (8.94) | 37.81 (8.31) | 0.70 | .485 |
| Naming of Categories | | | | |
| Spontaneous | 81.78 (13.83) | 82.82 (9.89) | 0.13 | .698 |
| Semantic Cueing | 6.75 (10.02) | 5.44 (5.87) | 0.70 | .484 |
| Phonological Cueing | 3.82 (10.11) | 2.70 (3.36) | 0.62 | .536 |
| Recognition | 0.35 (0.98) | 0.41 (0.60) | 0.31 | .753 |
| Total | 90.26 (11.27) | 91.38 (1.30) | 0.57 | .566 |
| Token Test | 30.91 (5.02) | 30.85 (5.48) | 0.05 | .959 |
| Boston Diagnostic Aphasia Examination | | | | |
| Auditory Comprehension | | | | |
| Word Discrimination | 69.18 (3.75) | 68.44 (4.72) | 0.85 | .395 |
| Body part | 18.94 (4.34) | 18.26 (1.63) | 0.87 | .386 |
| Commands | 14.48 (0.99) | 14.26 (1.37) | 0.88 | .369 |
| Complex Material | 9.06 (2.24) | 9.17 (2.06) | 0.24 | .804 |
| Naming | | | | |
| Responsive | 30.00 (0.00) | 29.79 (0.84) | 1.97 | .054 |
| Confrontation | 92.82 (4.93) | 92.45 (5.59) | 0.32 | .744 |
| Body Part Naming | 26.02 (3.30) | 25.12 (2.88) | 1.32 | .190 |
| Reading | | | | |
| Word Reading | 29.28 (2.17) | 28.96 (4.06) | 0.49 | .623 |
| Reading Sentences | 6.86 (2.76) | 7.35 (2.52) | 0.86 | .388 |
| Repetition | | | | |
| High probability | 7.94 (0.24) | 7.90 (0.38) | 0.46 | .645 |
| Low probability | 7.82 (0.70) | 7.81 (0.53) | 0.02 | .984 |
| Automatic Series | 7.37 (0.72) | 7.54 (0.71) | 1.15 | .253 |
| Writing | | | | |
| Narrative | 4.73 (1.01) | 4.75 (0.90) | 0.11 | .902 |
| Primer Level | 13.91 (2.49) | 14.33 (2.35) | 0.81 | .412 |
| Sentence Dictation | 11.44 (2.35) | 11.54 (2.26) | 0.21 | .829 |
| Memory Three Phases | | | | |
| First Trial | 1.82 (1.28) | 1.07 (1.07) | 3.06 | .003 |
| Serial Verbal Learning | | | | |
| First Trial | 5.15 (1.25) | 5.45 (1.42) | 1.13 | .258 |
| Maximum | 9.36 (1.16) | 9.31 (1.62) | 0.15 | .878 |
| Delayed Recall | 7.37 (1.82) | 6.71 (2.75) | 1.47 | .143 |
| Knopman Test | | | | |
| First Trial | 6.35 (2.50) | 6.38 (2.32) | 0.06 | .948 |
| Second Trial | 7.86 (1.86) | 7.87 (1.65) | 0.05 | .960 |
| Recall After 5 minutes | 5.80 (2.11) | 6.05 (2.24) | 0.56 | .576 |

(*continued on next page*)

**TABLE 3**
**(Continued)**

| Tests | MN ($n$ = 82) | MP ($n$ = 40) | $t$ | $p$ |
|---|---|---|---|---|
| Intrusions | 0.65 (1.00) | 0.67 (1.09) | 0.11 | .909 |
| Perseverations | 0.62 (1.02) | 0.61 (1.01) | 0.01 | .987 |
| Sentence construction | | | | |
| First Trial | 9.11 (1.17) | 9.33 | 0.97 | .330 |
| Second Trial | 9.64 (0.72) | 9.57 (0.45) | 0.43 | .667 |
| Digit Symbol | 22.39 (15.12) | 22.85 (12.78) | 0.15 | .879 |
| Visual "A" Cancellation Test | | | | |
| Score | 14.88 (2.46) | 15.29 (1.03) | 0.94 | .345 |
| Omissions | 1.55 (2.31) | 0.70 (1.03) | 2.01 | .047 |
| Additions | 0.16 (0.80) | 0.08 (0.37) | 0.46 | .641 |
| Time in seconds | 59.68 (28.82) | 50.55 (27.84) | 0.02 | .984 |

ferent. In Recognition of Words as well, both scores (correct "yes" and correct "no") were different with a statistical level of significance between groups. By the same token, in the Recall of Drawings, differences were established for the Diamond, Rectangles, and total score.

Results in other neuropsychological tests are presented in Table 5. MP-1 outperformed MP-2 across the different test scores. MP subjects without memory complaints significantly outscored MP participants with memory complaints in the following test scores: WMS (Logical Memory, Associative Learning, and Total score), Rey-Osterrieth Complex Figure (Immediate Recall Condition), Boston Diagnostic Aphasia Examination (Complex Ideational Material subtest), Memory Three Phrases test, Serial Verbal Learning (maximum score and Delayed Recall), Knopman Test (First trial, Second trial and Recall after 5 Minutes), and Digit Symbol, Visual "A" Cancellation Test (Additions).

## DISCUSSION

The hypothesis that early preclinical signs of dementia could be found in asymptomatic subjects carrying a mutation in the PS1 gene (E280A) was supported. Functionally normal subjects complaining of memory difficulties presented cognitive defects in several domains. Our results corroborate that in AD, specific memory deficits may serve as preclinical cognitive markers, especially in individuals with risk factors for AD such as a positive family history (Bondi et al., 1994). Because the PS1 mutation is completely penetrant, all subjects in the MP group will eventually develop AD.

Otherwise normal subjects with subjective complaints of memory difficulties may have the initial symptoms of dementia. These subjects in our study presented significantly decreased scores in several neuropsychological memory tests: Memory of Words, Recall of Words, Recall of Drawings, Rey-Osterrieth Complex Figure-Immediate Recall, Memory of Three Phrases, and Knopman Test. Thus, subjective memory complaints were objectively documented. In addition to the memory difficulties, other minor cognitive impairments were also found.

Thus, memory complaints appeared to be the earliest symptoms of dementia in FAD. These memory difficulties were associated with mild anomia, concentration difficulties, and defects in the understanding of complex verbal material. Noteworthy, neither constructional defects, nor verbal fluency defects, or word-finding difficulties (excepting for low-frequency words) were observed.

**TABLE 4**
**Mean Score and Standard Deviations (in parentheses) in the CERAD Neuropsychological Test Battery**

| Tests | MP-1 ($n$ = 30) | MP-2 ($n$ = 10) | $t$ | $p$ |
|---|---|---|---|---|
| Verbal Fluency | | | | |
| 0–15 seconds | 5.46 (1.65) | 4.80 (1.39) | 1.14 | .269 |
| 16–30 seconds | 3.86 (1.30) | 3.30 (1.41) | 1.16 | .252 |
| 31–45 Seconds | 3.36 (1.18) | 3.10 (1.37) | 0.59 | .557 |
| 46–60 Seconds | 3.30 (1.29) | 2.50 (1.08) | 1.76 | .086 |
| Total | 16.00 (4.51) | 13.70 (3.19) | 1.48 | .146 |
| Naming | | | | |
| High Frequency | 4.86 (0.34) | 4.80 (0.42) | 0.50 | .620 |
| Middle Frequency | 4.40 (1.03) | 4.10 (1.10) | 0.78 | .441 |
| Low Frequency | 4.13 (0.97) | 3.00 (1.56) | 2.72 | .010 |
| Total | 13.40 (2.02) | 11.90 (2.64) | 1.87 | .078 |
| Time | 79.46 (27.29) | 94.70 (26.67) | 1,53 | .133 |
| MMSE | 28.03 (1.92) | 23.00 (3.49) | 5.76 | .001 |
| Memory Words | | | | |
| Reading | 9.66 (1.82) | 9.00 (3.16) | 0.82 | .415 |
| Trial 1 | 3.80 (0.96) | 2.40 (0.96) | 3.98 | .001 |
| Intrusions | 0.60 (0.77) | 1.10 (1.19) | 1.53 | .132 |
| Trial 2 | 5.53 (1.40) | 3.70 (0.67) | 3.94 | .001 |
| Intrusions | 0.16 (0.37) | 0.70 (0.82) | 2.81 | .008 |
| Trial 3 | 6.86 (1.65) | 4.60 (0.69) | 4.17 | .001 |
| Intrusions | 0.46 (1.22) | 0.80 (1.13) | 0.75 | .453 |
| Total Correct | 16.26 (3.37) | 10.70 (1.70) | 4.98 | .001 |
| Total Intrusions | 1.06 (1.14) | 2.70 (2.54) | 2.81 | .008 |
| Constructional Praxis | | | | |
| Circle | 1.86 (0.34) | 1.90 (0.31) | 0.26 | .789 |
| Diamond | 2.73 (0.69) | 2.30 (1.05) | 1.49 | .143 |
| Rectangles | 2.00 (0.00) | 1.90 (0.31) | 1.78 | .083 |
| Cube | 3.50 (1.00) | 3.40 (1.07) | 0.26 | .791 |
| Total | 10.10 (1.60) | 9.50 (2.32) | 0.91 | .367 |
| Recall of Words | | | | |
| Total Correct | 5.66 (2.07) | 2.60 (1.43) | 4.32 | .001 |
| Intrusions | 0.70 (1.31) | 2.10 (1.91) | 2.59 | .013 |
| Recognition of Words | | | | |
| Correct “yes” | 9.76 (1.10) | 7.80 (1.68) | 4.25 | .001 |
| Correct “no” | 9.73 (1.28) | 7.90 (1.79) | 3.53 | .001 |
| Recall of Drawings | | | | |
| Circle | 1.60 (0.77) | 1.20 (1.03) | 1.30 | .200 |
| Diamond | 1.73 (1.33) | 0.30 (0.94) | 3.12 | .003 |
| Rectangles | 1.43 (0.93) | 0.50 (0.85) | 2.79 | .008 |
| Cube | 1.86 (1.61) | 1.50 (1.50) | 0.63 | .531 |
| Total | 6.56 (2.66) | 3.50 (2.63) | 3.16 | .003 |

*Note*. Significant differences are presented. CERAD = Consortium to Establish a Registry for Alzheimer’s Disease; MP-1 = mutation positive without memory difficulty; MP-2 = mutation positive with memory difficulty; MMSE = Mini-Mental State Examination.

It can be proposed that minor memory impairment represents the initial dementia symptom of FAD. It can be associated with some concentration defects, difficulties in retrieving low-frequency words, and limitation in understanding complex language. The memory defect includes some amnesia not only for verbal but also for nonverbal information. At this point, however, some minor but significant defects in other cognitive domains are observed. Verbal fluency, visuoconstructive abilities, language, and naming (excepting low-frequency words) remain within normal limits. It may be expected that when advancing the dementia process, constructional difficulties, verbal fluency, and word-finding difficulties will become evident.

**TABLE 5**
**Results in Several Neuropsychological Tests**

| Tests | MP-1 ($n$ = 30) | MP-2 ($n$ = 10) | $t$ | $p$ |
|---|---|---|---|---|
| Raven Test | | | | |
| A | 7.43 (2.03) | 6.75 (2.86) | 0.76 | .452 |
| B | 4.54 (2.12) | 4.12 (1.88) | 0.49 | .624 |
| Wechsler Memory Scale | | | | |
| Information | 4.93 (1.41) | 4.37 (1.50) | 0.95 | .346 |
| Orientation | 5.00 (0.00) | 4.62 (1.02) | 1.90 | .075 |
| Mental Control | 5.50 (2.52) | 5.87 (2.99) | 0.35 | .725 |
| Log Memory | 8.72 (2.84) | 5.25 (2.50) | 3.10 | .004 |
| Digits: Forward | 5.21 (0.99) | 4.37 (1.92) | 1.68 | .101 |
| Backward | 3.18 (1.47) | 3.62 (0.91) | 0.81 | .423 |
| Associative Learning | 13.62 (4.20) | 7.07 (5.79) | 3.37 | .002 |
| Visual Reproduction | 7.33 (3.11) | 4.57 (4.11) | 1.95 | .059 |
| Total Score | 53.60 (11.06) | 39.71 (16.92) | 2.72 | .013 |
| Praxis | | | | |
| Left Hand | 91.00 (5.98) | 85.67 (7.27) | 1.91 | .065 |
| Buccofacial | 95.75 (4.81) | 96.14 (3.29) | 0.20 | .840 |
| Rey-Osterrieth Complex Figure | | | | |
| Copy | 26.04 (7.90) | 19.14 (12.54) | 1.81 | .079 |
| Immediate Recall | 11.41 (6.05) | 3.21 (3.20) | 3.43 | .002 |
| Verbal Fluency | | | | |
| FAS | 9.56 (3.34) | 9.23 (4.04) | 0.23 | .803 |
| Boston Naming Test | 38.96 (8.12) | 34.60 (8.43) | 1.44 | .157 |
| Naming of Categories | | | | |
| Spontaneous | 84.92 (10.06) | 79.25 (8.99) | 1.17 | .249 |
| Semantic Cueing | 4.73 (5.77) | 7.75 (5.99) | 1.28 | .209 |
| Phonological Cueing | 2.54 (3.66) | 3.25 (2.25) | 0.51 | .608 |
| Recognition | 0.38 (0.57) | 0.50 (0.76) | 0.46 | .646 |
| Total | 91.58 (1.06) | 90.75 (1.83) | 1.60 | .118 |
| Token Test | 31.27 (5.36) | 29.50 (6.04) | 0.79 | .433 |
| Boston Diagnostic Aphasia Examination | | | | |
| Auditory Comprehension | | | | |
| Word Discrimination | 68.77 (4.87) | 67.37 (4.30) | 0.72 | .474 |
| Body Part | 18.54 (1.50) | 17.37 (1.84) | 1.81 | .079 |
| Commands | 14.27 (1.51) | 14.25 (0.88) | 0.03 | .973 |
| Complex Material | 9.58 (2.00) | 7.87 (1.80) | 2.14 | .040 |
| Naming | | | | |
| Responsive | 29.88 (0.58) | 29.50 (1.41) | 1.13 | .267 |
| Confrontation | 93.36 (4.87) | 89.62 (7.02) | 1.69 | .101 |
| Body Part Naming | 25.44 (3.01) | 24.12 (2.29) | 1.12 | .268 |
| Reading | | | | |
| Word Reading | 29.12 (4.19) | 28.50 (3.85) | 0.37 | .714 |
| Reading Sentences | 7.31 (2.45) | 7.50 (2.93) | 0.18 | .854 |
| Repetition | | | | |
| High probability | 7.92 (0.40) | 10.00 (0.00) | 0.28 | .778 |
| Low probability | 7.84 (0.47) | 7.75 (0.70) | 0.41 | .681 |
| Automatic Series | 7.56 (0.71) | 7.50 (0.75) | 0.20 | .839 |
| Writing | | | | |
| Narrative | 4.92 (0.28) | 4.25 (1.75) | 1.90 | .067 |
| Primer Level | 14.72 (0.89) | 13.12 (4.51) | 1.71 | .096 |
| Sentence Dictation | 11.88 (0.60) | 10.50 (4.53) | 1.53 | .136 |
| Memory Three Phrases | | | | |
| First Trial | 1.32 (1.02) | 0.40 (0.96) | 2.48 | .018 |
| Serial Verbal Learning | | | | |
| First Trial | 5.59 (1.19) | 5.00 (2.07) | 1.03 | .307 |
| Maximum | 9.88 (0.32) | 7.37 (2.61) | 5.04 | .001 |
| Delayed Recall | 7.63 (1.84) | 3.62 (3.15) | 4.54 | .001 |
| Knopman Test | | | | |
| First Trial | 6.92 (2.19) | 4.62 (1.92) | 2.66 | .012 |
| Second Trial | 8.24 (1.51) | 6.75 (1.66) | 2.37 | .024 |

(*continued on next page*)

**TABLE 5**
**(Continued)**

| Test | MP-1 ($n$ = 30) | MP-2 ($n$ = 10) | $t$ | $p$ |
|---|---|---|---|---|
| Recall After 5 minutes | 6.65 (1.77) | 4.12 (2.64) | 3.14 | .004 |
| Intrusions | 0.58 (0.95) | 1.00 (1.51) | 0.95 | .346 |
| Perseverations | 0.62 (1.02) | 0.62 (1.06) | 0.02 | .982 |
| Sentence Construction | | | | |
| First Trial | 9.40 (0.76) | 9.12 (1.12) | 0.78 | .437 |
| Second Trial | 9.56 (0.71) | 9.62 (0.51) | 0.23 | .814 |
| Digit Symbol | 25.37 (11.89) | 13.14 (12.15) | 2.41 | .022 |
| Visual "A" Cancellation Test | | | | |
| Score | 15.41 (0.89) | 14.86 (1.46) | 1.27 | .213 |
| Omissions | 0.59 (0.89) | 1.14 (1.46) | 1.27 | .203 |
| Additions | 0.00 (0.00) | 0.43 (0.79) | 2.96 | .006 |
| Time in Seconds | 55.37 (21.90) | 75.71 (42.46) | 1.77 | .085 |

## REFERENCES


Alzheimer's Disease Collaborative Group. (1995). The structure of the presenilin 1 (S182) gene and identification of six novel mutations in early onset AD families. *Nature Genetics*, **11**, 219–222.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Ardila, A., & Rosselli, M. (1989). Neuropsychological characteristics of normal aging. *Developmental Neuropsychology*, **5**, 307–320.

Ardila, A., & Rosselli, M. (1994). Development of language, memory and visuospatial abilities in 5- to 12-year-old children using a neuropsychological battery. *Developmental Neuropsychology*, **10**, 97–120.

Ardila, A., Rosselli, M., & Puente, A. (1994). *Neuropsychological evaluation of the Spanish speaker.* New York: Plenum Press.

Ardila, A., Rosselli, M., & Rosas, P. (1989). Neuropsychological assessment in illiterates: Visuospatial and memory abilities. *Brain and Cognition*, **11**, 147–166.

Bondi, M. W., Monsch, A. U., Galasko, D., Butters, N., Salmon, D. P., & Delis, D. C. (1994). Preclinical cognitive markers of dementia of the Alzheimer type. *Neuropsychology*, **8**, 374–384.

Caramelli, P., Poissant, A., Gauthier, S., Bellavance, A. L, Gauvreau, D., Lecours, A. R., & Joanette, J. (1997). Educational level and neuropsychological heterogeneity in dementia of the Alzheimer type. *Alzheimer Disease and Associated Disorders*, **11**, 9–15.

Chui, H. C., Teng, E. L., Henderson, V. W., & May, A. C. (1985). Clinical subtypes of dementia of the Alzheimer's type. *Neurology*, **35**, 1544–1550.

Cook, R. H., Bard, B. E., & Austin, J. H. (1979). Studies in aging of the brain: IV. Familial Alzheimer's disease relation to transmissible dementia, aneuploidy, and microtubular defects. *Neurology*, **29**, 1402–1412.

Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., Roses, A. D., Haines, L. L., & Pericak-Vance, M. A. (1993). Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*, **261**, 921–923.

Cummings, J. L., & Benson, D. F. (1992). *Dementia: A clinical approach* (2nd ed.). London: Butterworths.

Farrer, L. A., Myers, R. H., Cupples, L. A., St. George-Hyslop, P. H., Bird, T. D., Rossor, M. N., Mullan, M. J., Polinsky, R., Lee, L., Heston, L., Van Broeckhoven, C., Martin, J., Crapper-McLachlon, D., & Growdon, J. H. (1990). Transmission and age-at-onset patterns in familial Alzheimer disease: Evidence for heterogeneity. *Neurology*, **40**, 395–403.

Feldman, R. G., Chandler, K. A., Lewy, L. L., & Glaser, G. H. (1963). Familial Alzheimer's disease. *Neurology*, **13**, 811–824.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, **12**, 189–198.

Frommelt, P., Schnabel, R., Kuhne, W., & Nee, L. (1991). Familial Alzheimer disease: A large, multigeneration German Kindred. *Alzheimer's Disease Association Disorders*, **5**, 36–43.

Goodglass, H., & Kaplan, H. (1983). *Evaluacin de las afasias y de transtornos similares* (2nd ed.). Buenos Aires: Editorial Médica Panamericana.

Haltia, M., Vitanen, M., Sulkava, R., Ala-Hurula, V., Poyhonen, M., Goldfarb, L., Brown, P., Levy, E., Houlden, H., Crook, R., Goate, A., Clark, R., Koreblat, K., Pandit, S., Keller, H.D., Lilius, L., Liu, L., Axel-

man, K., Forsell, L., Winblad, B., Pannfelt, L., & Hardy, J.(1994). Chromosome 14-encoded Alzheimer's disease: Genetic and clinicopathological description. *Annals of Neurology*, **36**, 362–367.

Jacobs, D., Sano, M., Marder, K., Bell, K., Bylsma, F., Lafleche, G., Albert, M., Brandt, J., & Stern, Y. (1994). Age at onset of Alzheimer's disease: Relation to pattern of cognitive dysfunction and rate of decline. *Neurology*, **44**, 1215–1220.

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *The Boston Naming Test.* Philadelphia: Lea & Febiger.

Karlinsky, H., Vaula, G., Haines, J. L., Ridgley, J., Bergerson, C., Mortilla, M., Tuplar, R. G., Percy, M. E., Robitaille, Y., & Noldy, N. E. (1992). Molecular and prospective phenotypic characterization of a pedigree with familial Alzheimer's disease and a missense mutation in codon 717 of the B-amyloid precursor protein gene. *Neurology*, **42**, 1445–1453.

Kehoe, P. G., Russ, C., Mcllroy, S., Williams, H., Holmans, P., Holmes, C., Liolitsa, D., Vahidassr, D., Powell, J., McGleenan, B., Liddell, M., Plomin, R., Dynan, K., Williams, N., Neal, J., Cairns, N. J., Wilcock, G., Passmore, P., Lovestone, S., Williams, J., & Owen, M. J. (1999). Variation in DCP1, encoding ACE, is associated with susceptibility to Alzheimer disease. *Nature Genetics*, **21**, 71–72.

Knopman, D. S., & Ryberg, S. (1989). A verbal memory test with high predictive accuracy for dementia of the Alzheimer type. *Archives of Neurology*, **46**, 141–146.

Koss, E., Edland, S., Fillenbaum, G., Mohs, R., Clark, C., Galasko, D., & Morris, J. C. (1996). Clinical and neuropsychological differences between patients with earlier and later onset of Alzheimer's disease: A CERAD analysis, Part XII. *Neurology*, **46**, 136–141.

Lampe, T. H., Bird, T. D., Nochlin, D., Nemens, E., Risse, S. C, Sumi, S. M., Koerker, R., Leaird, B., Wier, M., & Raskind, M. A. (1994). Phenotype of chromosome 14-linked familial Alzheimer's disease in a large kindred. *Annals of Neurology*, **36**, 368–378.

Lehtovirta, M., Soininen, H., Helisalmi, S., Mannermaa, A., Helkala, E. L., Hartikainen, P., Hanninen, T., Ryyanen, M., & Riekkinen, P. J. (1996). Clinical and neuropsychological characteristics in familial and sporadic Alzheimer's disease: Relation to apolipoprotein E polymorphism. *Neurology*, **46**, 413–419.

Lezak, M. D. (1995). *Neuropsychological assessment* (3rd ed.). New York: Oxford University Press.

Liao, A., Nitsch, R. M., Greenberg, S. M., Finckh, U., Blacker, D., Albert, M., Rebeck, G. W., Gomez-Isla, T., Clatworthy, A., Binetti, G., Hock, C., Mueller-Thomsen, T., Mann, U., Zuchowski, K., Beisiegel, U., Staehelin, H., Growdon, J. H., Tanzi, R. E., & Hyman, B. T. (1998). Genetic association of an α2- macroglobulin (Val1000Ile) polymorphism and Alzheimer's disease. *Human Molecular Genetics*, **7**, 1953–1956.

Lopera, F., Arcos, M., Madrigal, L., Kosik, K., Cornerjo, W., & Ossa, J. (1994). Demencia de tipo Alzheimer con agregacin familiar en Antioquia, Colombia. *Acta Neurologica Colombiana*, **10**, 173–187.

Lopera, F. (1991). *Prueba de Denominacion Categorial* [*Category Naming Test*]. Unpublished manuscript.

Lopera, F., Ardila, A., Martinez, A. L., Madrigal, L., Arango-Viana, J. C., Lemere, C., Arango-Lasprilla, J. C., Hincapie, L., Arcos, M., Ossa, J. E., Behrens, I. M., Norton, J., Lendon, C., Goates, A., Ruiz-Linares, A., Rosselli, M., & Kosik, K. S. (1997). Clinical features of early-onset Alzheimer's disease in a large kindred with an E280A presenilin-1 mutation *Journal of the American Medical Association*, **277**, 793–799.

Martin, J. J., Gheuens, J., Bruyland, M., Cras, P., Vanderbeerghe, A., Masters, L., Beyreuther, K., Dom, R., Ceuterick, C., Lubke, U., Van Heuverswijn, H., DeWinter, G., & Van Broeckhover, C. (1991). Early-onset Alzheimer's disease in 2 large Belgian families. *Neurology*, **41**, 62–68.

Matallana, D., & Montañez, P. (1995). *Escala Subjetiva de Quejas de Memoria* [*Subjective Memory Complaints Checklist*]. Unpublished manuscript.

Mayeux, R. (1985). Heterogeneity in dementia of the Alzheimer type: Evidence of subgroups. *Neurology*, **35**, 453–458.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D. L., & Stadlan, E. M. (1984). RP] diagnosis of Alzheimer's disease: A report of the NINCDS-ADRDA work group. Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, **34**, 939–944.

Morris, J. C., Heyman, A., Mohs, R. C., Hughes, J. P., van Belle, G., Fillenbaum, G., Mellits, E. D., & Clark, C. (1989). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*, **39**, 1159–1165.

Nee, L. E., Polinsky, R. J., Eldridge, R., Weingartner, H., Smallberg, S., & Ebert, M. (1983). A family with histologically confirmed Alzheimer's disease. *Archives of Neurology*, **40**, 203–208.

Osterrieth, P. A. (1944). Le test de copie d'une figure complexe. *Archives de Psychologie*, **30**, 206–356

Raven, J. C. (1982). *Revised manual for Raven's Progressive Matrices and Vocabulary Scale.* Windson, UK: NFER Nelson.

Richard, M., Folstein, M., Albert, M., & Miller, L. (1993). Multicenter study of predictors of disease course in Alzheimer Disease: II. Neurological, psychiatric and demographic influences on baseline measures of disease severity. *Alzheimer Disease and Associated Disorders*, **7**, 22–32.

Rosselli, M., & Ardila, A. (1991). Effects of age, education and gender on the Rey-Osterrieth Complex Figure. *The Clinical Neuropsychologist*, **5**, 370–376. 1991.

Rosselli, M., Ardila, A., Flórez, A., & Castro, C. (1990). Normative data on the Boston Diagnostic Aphasia Examination in a Spanish-Speaking population. *Journal of Clinical and Experimental Neuropsychology*, **12**, 313–322. 1990.

Rosselli, M., Ardila, A., & Rosas, P. (1990). Neuropsychological assessment in illiterates II: Language and praxic abilities. *Brain and Cognition*, **12**, 281–296.

Sadovnick, A. D., Tuokko, H., Horton, A., Baird, P. A., & Beattie, B. L. (1988). Familial Alzheimer's disease. *Canadian Journal of Neurological Sciences*, **15**, 142–146.

Stern, Y., Gurland, B., Tatemichi, T. K., Ming, X. T., Wilder, D., & Mayeux, R. (1994). Influence of education and occupation on the incidence of Alzheimer's disease. *Journal of the American Medical Association*, **271**, 1004–1010.

Stern, Y., Ming, X. T., Denaro, J., & Mayeaux, R. (1995). Increased risk of mortality in Alzheimer's disease patients with more advanced educational and occupational attainment. *Annals of Neurology*, **37**, 590–595.

St. George-Hyslop, P. H., Tanzi, R. E., Polinsky, R. J., Haines, J. L., Nee, L., & Wakins, P. C. (1987). The genetic defect causing familial Alzheimer's disease maps on chromosome 21. *Science*, **235**, 885–890.

Taylor, E. M. (1959). *The appraisal of children with cerebral deficits.* Cambridge, MA: Harvard University Press.

Wechsler, D. (1945). A standarized memory test for clinical use. *The Journal of Psychology*, **19**, 87–95.

Wechsler, D. (1974). *WAIS: Manual.* New York: Psychological Corporation.