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Higher incidence of mild cognitive impairment in familial hypercholesterolemia

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Abstract

Objective—Hypercholesterolemia is an *early* risk factor for Alzheimer's disease. Low density lipoprotein (LDL) receptors may be involved in this disorder. Our objective was to determine the risk of mild cognitive impairment in a population of patients with heterozygous familial hypercholesterolemia, a condition involving LDL receptors dysfunction and life long hypercholesterolemia.

Methods—Using a cohort study design, patients with (N=47) meeting inclusion criteria and comparison patients without familial hypercholesterolemia (N=70) were consecutively selected from academic specialty and primary care clinics respectively. All patients were older than 50 years. Those with disorders which could impact cognition, including history of stroke or transient ischemic attacks, were excluded from both groups. Thirteen standardized neuropsychological tests were performed in all subjects. Mutational analysis was performed in patients with familial hypercholesterolemia and brain imaging was obtained in those with familial hypercholesterolemia and mild cognitive impairment.

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Results—Patients with familial hypercholesterolemia showed a very high incidence of mild cognitive impairment compared to those without familial hypercholesterolemia (21.3% vs. 2.9%; p = 0.00). This diagnosis was unrelated to structural pathology or white matter disease. There were significant differences between the familial hypercholesterolemia and the no-familial hypercholesterolemia groups in several cognitive measures, all in the direction of worse performance for familial hypercholesterolemia patients, independent of apoE4 or apoE2 status.

Conclusions—Because prior studies have shown that older patients with *sporadic* hypercholesterolemia do not show higher incidence of mild cognitive impairment, the findings presented here suggest that *early* exposure to elevated cholesterol or LDL receptors dysfunction may be risk factors for mild cognitive impairment.

Keywords

Mild cognitive impairment; Alzheimer's disease; Hypercholesterolemia; Lipoprotein receptors

INTRODUCTION

Alzheimer's disease is a progressive neurodegenerative disorder characterized by global deterioration of cognition and behavior (1). Development of dementia in Alzheimer's disease is usually preceded by a prodromal stage of abnormal cognitive performance known as mild cognitive impairment (2). A major neuropathological feature of Alzheimer's disease is the increase in insoluble amyloid fibrils composed of 40–42 amino acid peptides known as the amyloid beta protein (Aβ) (3,4).

Recent studies suggest a connection between cholesterol metabolism and the pathogenesis of Alzheimer's disease (5–9). We reported that hypercholesterolemia accelerates Aβ production in the brain of transgenic mice (7,8) and associates with higher levels of Aβ amyloid in the human brain (10). Based on apparently controversial epidemiological studies (11), some investigators have argued that this relationship may be spurious. However, the discrepancies may be more apparent than real due to the following reasons. Most positive studies have typically measured serum cholesterol levels early in life and then correlated these levels prospectively to development of dementia *later* in life (10–16). In contrast, most negative reports have examined cohorts of *older* patients and for short follow up periods and concluded that there was no association between cognitive decline and higher cholesterolemia (11,16) Taken together, the studies suggest that hypercholesterolemia is only an *early* (not a late) risk factor for Alzheimer's disease. In addition, the negative studies inadvertently missed gradual declines in cholesterolemia that precede by years the development of dementia in most affected patients (15); this phenomenon could obscure abnormalities that may have occurred earlier in life. Lastly, subjects with the highest levels of cholesterolemia generally die at younger ages from cardiovascular events and are lost from the samples of elderly subjects (i.e., comparative studies of Alzheimer's disease patients versus controls), introducing a bias known as survivor effect (17). The hypothesis that hypercholesterolemia represents an early risk factor for Alzheimer's disease was recently tested and substantiated by us in a neuropathological study (10). Hypercholesterolemia strongly correlated with presence of brain amyloid but only in subjects aged 40 to 55 (p=0.00). Interestingly, the differences in cholesterolemia between amyloid-bearing and amyloid-free brains disappeared as the subjects' age increased beyond 55 years. With the foregoing mechanisms in mind, one can also explain most studies negating a role for statins in Alzheimer's disease prevention because they have been conducted in samples of patients older than 65 years, failing to consider the mentioned age-related dynamics in the populations' risk (18–26).

The aim of the current study was to determine whether patients afflicted with familial hypercholesterolemia exhibit cognitive abnormalities. Patients with familial hypercholesterolemia offer a unique window into the role of cholesterol metabolism in cognition because the afflicted patients are exposed to hypercholesterolemia from early in life and also carry a dysfunction of LDL receptors. Members of the LDL receptors family, including LDL receptors themselves, have been implicated in synaptic function and in Alzheimer's disease pathogenesis (18). There are no studies examining cognition in this population, independent of cerebrovascular disease, as statins have only been widely available since the early 1990's.

Familial hypercholesterolemia is characterized by hypercholesterolemia since birth and is caused by inherited genetic abnormalities that directly or indirectly affect the function of the LDL receptors (19). The resulting condition carries a high risk of early-onset coronary heart disease and decreased survival if untreated (19).

METHODS

Diagnosis of Familial Hypercholesterolemia

We used the Dutch Lipid Clinic Network criteria (20). Briefly, these criteria are based on LDL-cholesterol levels above the age- and gender-specific 95th percentiles of a reference population, vertical transmission of hypercholesterolemia, early-onset coronary heart disease in the index case and/or first-degree relatives, and presence of tendon xanthomas (21). Each of these variables was scored, and an overall score was constructed to indicate the diagnostic probability of familial hypercholesterolemia (possible 3–5, probable 6–7, and certain ≥8). Only individuals with a score ≥8 were included in the familial hypercholesterolemia group.

Patients with clinical familial hypercholesterolemia were then recruited into the Spanish familial hypercholesterolemia Register (22) and subjected to DNA testing for identification of LDL receptors mutations and the apoB R3500G mutation following standard protocols. Briefly, genomic DNA was screened by a microarray system (Lipochip, Progenika Biopharma, Derio, Spain) (23,24). DNA samples from those patients in whom no mutation was identified by the microarray method were further sequenced after polymerase chain reaction amplification of the promoter region, the translated exon sequences, and the exon-intron boundaries of the LDL receptors gene. Large rearrangements were analyzed using a method based on quantitative fluorescent multiplex polymerase chain reaction. Nucleotide positions were numbered as suggested by Yamamoto (23). By these methods (microarray and sequencing), LDL receptors gene mutations were identified in 24 patients (~50% of patients), a proportion that is in agreement with other studies (29,31–33).

Subjects and Design

Between August 2005 and May 2007, 47 patients with a diagnosis of familial hypercholesterolemia, older than 50 years without history of stroke or transient ischemic attacks (TIA) were recruited from two Lipid Clinics (University of Barcelona and the Spanish Familial Hypercholesterolemia Foundation, Madrid, Spain). Patients without familial hypercholesterolemia were recruited from the Internal Medicine Service of the University of Barcelona. None of the patients were referred to any of these clinics for cognitive problems. The patients with familial hypercholesterolemia were either self referred, referred for neurologically unrelated conditions for lipid management or to establish primary care. Patients with clinical evidence of psychiatric or neurological disorders (including history of stroke or TIA), any metabolic disease which could impact cognitive performance, illiteracy, history of excessive alcohol use (consumption > 50g/day) or drug abuse were excluded from the study. In addition, patients with history of hypertension, diabetes, or prior coronary artery bypass

graft surgery (CABG) were also excluded from both the familial hypercholesterolemia and the no-familial hypercholesterolemia groups as these conditions may adversely affect cognitive performance and potentially bias the results. Comprehensive medical histories and neurological examinations were obtained from all participating subjects that included visual capacity, history of alcohol consumption and administration of the Hamilton depression rating scale (24). All subjects were outpatients. Comparison subjects without familial hypercholesterolemia underwent a similar screening process as detailed above, however, the criteria for inclusion of control subjects was also conditioned on the absence of hypercholesterolemia (LDL cholesterol level <160 mg/dL). The latter was necessary to avoid inadvertent inclusion of familial hypercholesterolemia patients into the comparison group as not all mutations associated with familial hypercholesterolemia are known and the genetic screen detects only about 50% of the mutations. All study participants underwent detailed neuropsychological studies and laboratory investigations. Brain magnetic resonance imaging (MRI) was performed in all patients meeting criteria for mild cognitive impairment in the familial hypercholesterolemia group, two patients with mild cognitive impairment in the no-familial hypercholesterolemia group refused the MRI study. All subjects provided informed consent to a protocol approved by the Institutional Review Boards at each location.

Clinical and Laboratory Determinations

All subjects' medical records were thoroughly reviewed and each patient clinically assessed for family history of early coronary heart disease (<55 yr for men and <60 yr for women), medication use, demographic characteristics, standard cardiovascular risk factors, and presence of tendon xanthomas (21). Serum glucose, cholesterol and triglycerides were measured by standard automated enzymatic procedures. LDL-c was estimated with the Friedewald equation (25). Baseline lipid profiles were obtained from patients who had remained off hypolipemic therapy for at least four weeks prior to drawing fasting blood samples. ApoE genotyping was performed by the polymerase chain reaction followed by restriction digestion with 5 U of *Hha I*. Digested products were separated by electrophoresis as described (26).

Neuropsychological Evaluation

The neuropsychological examination was conducted by 2 experienced Neuropsychologists blinded to the patients' diagnosis. We selected 13 well established neuropsychological instruments for screening of all cognitive domains (27). The tests selected included the Mini-Mental State Examination (MMSE), the Buschke memory impairment screen (B-MIS), the semantic verbal category fluency for animals, the Benton temporal orientation, the clock drawing test (copy and command forms), the Rey auditory verbal learning test (RAVLT), the verbal paired associates (VPA), the Boston naming test (BNT), the digit span (forward and backward), the digit symbol substitution test (DSST), the trail making test (TMT, parts A and B), the Stroop test. Other measures incorporated in the assessment were the Global Dementia Scale (GDS) and the Hamilton Depression Rating Scale (HDRS).

Definitions of Cognitive Abnormalities and Mild Cognitive Impairment

The diagnosis of mild cognitive impairment was made using the criteria outlined by Petersen et al (2), recently endorsed by USA (28) and European expert groups (29). Briefly, amnestic mild cognitive impairment was defined as having a positive history of memory complaints and abnormal memory function on at least two neuropsychological instruments tapping on the memory domain and normal performance on instruments tapping mainly on domains other than memory. However, patients with abnormal memory performance on two instruments plus *only* isolated deficits in a *single* instrument tapping on another domain were also classified as having amnestic mild cognitive impairment. Mild cognitive impairment patients were also required to have intact activities of daily living and not to be demented. For the results to be

considered abnormal, the scores were required to be below 1.5 standard deviations of the controls. Patients were classified as affected with the multiple-domain form of mild cognitive impairment if they exhibited memory complains and abnormal memory on neuropsychological testing as defined above plus abnormal scores (below 1.5 SD of the controls) in at least two additional instruments tapping on cognitive domains other than memory. Patients with deficits in other cognitive domains as identified by poor performance on two instruments (tapping primarily in such domains) were considered for the diagnosis of non-amnestic mild cognitive impairment (i.e., dysexecutive syndrome) (2) but these subtypes were not encountered in our cohorts.

Imaging Studies

Brain MRI was carried out in patients with mild cognitive impairment. The scans were performed by using a 1.5 Tesla Sigma apparatus (General Electric), according to a pre-established protocol that included coronal T1, axial T1, Fast Spin Echo, Diffusion – T2 and Flair and coronal Fast Spin Gradient. All scans were read by an experienced Neuroradiologist.

Data Analysis

Demographics, clinical features, apolipoprotein E status, and neuropsychological test scores were compared between familial hypercholesterolemia and control (no-familial hypercholesterolemia) groups using independent samples t-tests for continuous variables and chi-square tests for categorical values. All tests were 2-sided using $p<0.05$ as the threshold for statistical significance. Of primary interest was the difference between familial hypercholesterolemia and no-familial hypercholesterolemia groups in the proportion of patients with mild cognitive impairment. Power calculations for the chi-square test (2-sided, alpha=0.05, 45 familial hypercholesterolemia patients, 70 no-familial hypercholesterolemia patients) yielded 80% power to detect a difference in mild cognitive impairment proportions of 3% in the no-familial hypercholesterolemia group (lowest reported proportion) and 20% in the familial hypercholesterolemia group.

In addition to direct familial hypercholesterolemia versus no-familial hypercholesterolemia group comparisons, factors associated with cognitive test scores were explored using separate stepwise multiple linear regression models for the MMSE, VPA, RAVL, and trail making tests. The dependent variable in each model was the test score, with the following independent variables allowed to enter: familial hypercholesterolemia group, age per 10 years, gender, education per 5 years, family history of premature coronary heart disease, ever tobacco use, body mass index, total cholesterol, and presence of apolipoprotein E4 and E2 alleles. SPSS software, version 12.0 (SPSS Inc, Chicago, Ill), was used for all analyses.

RESULTS

Participant Characteristics

Participant characteristics are presented in Table 1.

Cognitive Function

None of the patients with familial hypercholesterolemia and mild cognitive impairment had a history of coronary events—Patients in the familial hypercholesterolemia group were significantly more likely than those in the no-familial hypercholesterolemia group to have developed mild cognitive impairment (relative risk 7.45, 95% confidence interval 1.71 to 32.47). Ten subjects (21.3%) from the familial hypercholesterolemia group met criteria for mild cognitive impairment and exhibited neuropsychological findings supporting this diagnosis. Of these patients, 7 were classified as

having amnestic mild cognitive impairment and 3 the multiple-domain form. On the other hand, only two subjects (2.9%) from the no-familial hypercholesterolemia group met the criteria for mild cognitive impairment (one patient had the amnestic type and one the multiple-domain form).

There were significant differences between the familial hypercholesterolemia and the no-familial hypercholesterolemia groups in a number of individual cognitive measures, all in the direction of worse cognitive performance for familial hypercholesterolemia patients, as summarized in Table 2.

Factors associated with cognitive functioning were explored using stepwise linear regression separately for each test (Table 3). Membership in the familial hypercholesterolemia group was independently associated with worse scores on the MMSE (p=0.01), VPA (p=0.00), and RAVL Interference (p=0.049) tests. Surprisingly, cholesterol level was independently associated *only* with worse scores in the TMT part B test (p=0.01). As expected, younger age and higher education years were independent predictors of better scores in several neuropsychological measures. Finally, women scored significantly better than men in the RAVL Total (p=0.049) and Delayed Recall (p=0.01) tests. In the familial hypercholesterolemia group, the presence of memory complaints was associated with significantly decreased performance on neuropsychological testing (table 4). However, whether this clinical subjective marker of such lower performance will extend to larger samples is unknown.

Imaging Studies

Brain MRI studies were obtained from 10 patients with familial hypercholesterolemia and mild cognitive impairment and in none of the 2 no-familial hypercholesterolemia subjects with mild cognitive impairment. None of the scans showed significant vascular lesions. A small lacunar pontine infarction was present in two of the familial hypercholesterolemia patients; one patient had a small T2 hyperintense area in the subcortical parieto-occipital white matter. Surprisingly, no areas of leukoariosis, T2 hyperintense white matter lesions (except for few minute T2 hyperintense periventricular white matter lesions in 2 patients) or other significant structural abnormalities were identified.

DISCUSSION

In this study, we found an association between familial hypercholesterolemia and mild cognitive impairment. The proportion of familial hypercholesterolemia patients exhibiting abnormal cognitive function and meeting criteria for mild cognitive impairment (21.3%) was significantly higher than that observed in the control group (2.9%; p = 0.00) and far exceeded the age-specific prevalence predicted from either epidemiological studies in the general population or the prevalence observed in follow-up of large cohorts with milder *sporadic* hypercholesterolemia (2,30–32).. All 10 patients from the mild cognitive impairment group had history of memory complaints and all of them had neuropsychological profiles meeting the criteria for mild cognitive impairment. Therefore, the clinical presence of a memory complaint appeared to be (at least in this small sample) an important marker for mild cognitive impairment. In the non-familial hypercholesterolemia control group, however, there were 4 patients with memory complaints. The diagnosis of mild cognitive impairment, however, could be confirmed in only 2 of these 4 patients in the non-familial hypercholesterolemia group by neuropsychological examination. When comparing the familial hypercholesterolemia with the non-familial hypercholesterolemia groups, score differences were more conspicuous with the MMSE (p=0.03), clock test (order: p=0.01), VPA (p=0.00) and RAVL (A3: p=0.048; A5: p=0.01; interference: p=0.02). The TMT part B was almost significant at p = .053. There were also significant differences in the Global Deterioration Scale (p=.03). Our findings can not be explained solely by large vessel cerebrovascular disease as this possibility was excluded

clinically and by imaging. We were surprised however, by the relative lack of white matter disease in patients with mild cognitive impairment.

The term mild cognitive impairment is generally used to define a transitional stage between normal cognitive function and dementia (2, 39–41). Estimates of its progression rate to Alzheimer's disease range from 10 to 15% per year compared to 1–2% for cognitively intact subjects (2). There are disagreements on which tests are most accurate for the diagnosis of mild cognitive impairment; however, instruments that assess learning and retention of information appear to be best as predictors for progression to Alzheimer's disease (33).

We became interested in familial hypercholesterolemia because this condition may offer a unique window into the role of cholesterol metabolism in cognition. Two aspects of familial hypercholesterolemia may be of particular relevance to Alzheimer's disease. The first is that patients afflicted with this disorder are exposed to higher cholesterol levels from early in life. This is important because as mentioned, hypercholesterolemia may be an early risk factor for Alzheimer's disease (10,15). The second feature is the involvement of LDL receptors in familial hypercholesterolemia. LDL receptors have been implicated in synaptic maintenance and in Alzheimer's disease pathogenesis. Members of the LDL receptors family are involved in Aβ clearance (18,34) and synaptic plasticity from the brain as supported by a growing body of literature (18). One study showed that when an Alzheimer's disease mouse model of amyloidosis was crossed into an LDL receptors-deficient background, the mice not only developed exacerbated age-dependent cerebral beta-amyloidosis but also, more severe behavioral abnormalities than observed in LDL receptors-intact Alzheimer's disease mice (34).

Based on the results of the current study, we propose the hypotheses that either early exposure to cholesterol or dysfunction of LDL receptors contribute to cognitive dysfunction in patients with familial hypercholesterolemia and it is possible that similar mechanisms may be involved in mild cognitive impairment not associated with familial hypercholesterolemia. These hypotheses may also explain the apparently divergent results between our data and those from longitudinal studies of patients older than 65 years of age in whom (sporadic) hypercholesterolemia was not associated with increased risk of developing incident mild cognitive impairment (44, 49). Presumably, these patients were neither exposed to high cholesterol levels early in life nor affected by LDL receptors mutations.

As in other familial hypercholesterolemia populations studied, only 50% of our patients had detectable LDL receptors mutations. Although this rate was higher among familial hypercholesterolemia patients with mild cognitive impairment, it would be premature to make conclusions on this finding due to the small size of the sample. The possibility still stands however, that in association with or independently from the lipid abnormalities, dysfunctions of LDL receptors or other unknown defects causing the familial hypercholesterolemia phenotype are linked to cognitive decline as patients grow older. The sample size in our study was also insufficient to dissect the effect of cholesterol from the effect of the LDL receptors mutations or their subtypes. Likewise, additional effects of lipoprotein E isoforms could not be fully assessed although stepwise linear regression analysis suggested that the apoE2 or apoE4 status did not affect cognitive performance (Table 3).

Cognitive impairment in familial hypercholesterolemia was unrecognized prior to this report probably because statins became widely available only in the early 1990's. Prior to that time, many patients with familial hypercholesterolemia would succumb early to cardiovascular disease before cognitive impairment could become manifest. Studies of larger samples of patients with familial hypercholesterolemia will allow further insights into the mechanisms and the rates of conversion to dementia in this disorder.

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Table 1

Participant characteristics

	FH N=47	No FH N=70	*P* Value
Men (number, %)	21 (44.7)	32 (45.7)	1.00
Age, y (mean, st dev)	60.1 (6.7)	61.0 (7.0)	0.49
Education, y (mean, st dev)	10.1 (5.2)	9.7 (5.2)	0.65
Family history of premature CHD (number, %)	15 (31.9)	7 (10.0)	0.00
Ever smoked, No. (number, %)	14 (29.8)	35 (50.0)	0.04
Body mass index, kg/m^2 (mean, st dev)	26.5 (3.5)	25.6 (3.2)	0.15
Baseline glucose (mean, st.dev.)	91.5 (8.7)	91.5 (10.3)	1.00
Mild cognitive impairment (number, %)	10 (21.3)	2 (2.9)	0.00
Baseline lipid profile, mg/dL			
Total cholesterol (mean, st dev)	386.3 (65.7)	214.8 (23.3)	0.00
LDL cholesterol (mean, st dev)	300.4 (66.9)	136.1 (17.8)	0.00
HDL cholesterol (mean, st dev)	60.7 (12.8)	61.7 (13.1)	0.70
Triglycerides, (mean, st dev)	128.2 (40.3)	84.5 (29.2)	0.00
Apolipoprotein E status (FH n=46, Comp n=63)			
ε4 carrier, (number, %)	9 (19.6)	11 (17.5)	0.81
ε2 carrier, (number, %)	0 (0.0)	9 (14.3)	0.01

Demographic and clinical characteristics of the study subjects. CHD = coronary heart disease. FH = Familial hypercholesterolemia. N = number of subjects.

Table 2

Neuropsychological test results

Neuropsychological Tests		FH	No FH	*P value*
Mini-Mental State Examination †		28.6 (1.6)	29.2 (1.1)	.027
Benton Temporal Orientation Test		0.38 (2.0)	0.02 (0.1)	.230
Memory Impairment Screen		6.8 (1.6)	7.1 (1.0)	.351
Verbal Category Fluency		19.5 (4.8)	18.9 (4.4)	.548
Clock Drawing Test	Order	9.3 (1.3)	9.9 (0.4)	.005
	Copy	9.9 (0.4)	10.0 (0.2)	.102
Boston Naming Test		50.1 (6.2)	50.9 (6.7)	.528
Rey Auditory Verbal Learning Test	A1	4.9 (1.5)	4.8 (1.5)	.784
	A2	7.2 (1.7)	7.3 (1.5)	.949
	A3	8.4 (2.1)	9.1 (1.5)	.048
	A4	9.4 (2.2)	10.2 (2.1)	.075
	A5	10.0 (2.3)	11.2 (2.0)	.014
	Total	39.9 (8.4)	42.7 (7.1)	.085
	Interference	7.6 (2.9)	8.8 (2.2)	.021
	Delayed Recall	7.3 (2.9)	8.3 (2.4)	.076
Digit span	Forward	5.6 (0.8)	5.8 (0.9)	.268
	Backward	3.9 (1.0)	4.2 (1.0)	.271
Verbal Paired Associated	Easy	16.3 (2.1)	17.6 (0.9)	<.001
	Difficult	6.7 (2.9)	8.9 (2.2)	<.001
	Total	15.8 (3.5)	18.5 (2.7)	<.001
Trail Making Test	Part A	50.9 (21.9)	49.2 (24.1)	.720
	Part B	99.1 (39.7)	84.5 (28.4)	.053
Symbol Digit Modality		49.6 (19.5)	52.8 (20.6)	.456
Stroop Test (Interference)		−2.1 (8.8)	0.1 (7.3)	.218
Global Deterioration Scale		2.13 (0.4)	1.98 (0.1)	.033
Hamilton Depression Rating Scale		2.2 (2.6)	2.8 (3.1)	.329

Neuropsychological assessment: Standardized tests scores for FH and No-FH groups. Data are expressed as mean and standard deviation (SD). FH = Familial hypercholesterolemia.

† Corrected for age and education

Table 3

Independent Determinants of Cognitive Test Scores by Stepwise Multiple Linear Regression Analysis.*

Cognitive Tests		Independent variables	Regression coefficient B	Standardized coefficient Beta	R^2 for model	Coefficient *P* value
MMSE†		Constant	29.383	-	0.072	-
		FH group	−0.731	−0.269	-	.005
Verbal Paired Associates		Constant	16.700	-	0.408	-
		Education per 5 y	0.709	0.221	-	.016
		FH group	−2.339	−0.355	-	<.001
RAVL	Total (A1 to A5)	Constant	35.288	-	0.304	-
		Education per 5 y	2.128	0.280	-	.004
		Gender (female)	2.979	0.192	-	.049
	Interference	Constant	8.600	-	0.037	-
		FH Group	−.991	−.192		.049
	Delayed Recall	Constant	12.611	-	0.093	-
		Age per 10 y	−0.942	−0.237	-	.018
		Gender (female)	1.436	0.273	-	.006
Trail making Part B		Constant	31.433	-	0.399	-
		Age per 10 y	12.274	0.240	-	.006
		Education per 5 y	−16.541	−0.471	-	<.001
		Cholesterol	.072	.206		.013

Abbreviations: MMSE = Mini Mental State Examination; RAVL = Rey Auditory Verbal Learning. FH = Familial hypercholesterolemia.

*Variables allowed to enter the model were FH group, age per 10 years, gender, education per 5 years, family history of premature coronary heart disease, tobacco use, BMI, total cholesterol, and presence of ε4 and ε2 alleles.

†Score already adjusted for age and education years.

Table 4

Group statistics within the FH group. Mild cognitive impairment versus no mild cognitive impairment.

	MCI	N	Mean	Std. Deviation	p
MMSE*	Normal	37	28.95	1.433	.004
	MCI	10	27.40	1.430	
VPA basal scores	Normal	37	16.8919	2.81152	.000
	MCI	10	11.7500	2.86017	
AVLT basal scores	Normal	37	42.24	7.661	.000
	MCI	10	31.10	3.635	
Interference AVLT scores	Normal	37	8.38	2.649	.000
	MCI	10	4.80	1.687	
AVLT delayed (at 20 min)	Normal	37	8.03	2.619	.000
	MCI	10	4.60	2.011	
TMT B	Normal	35	93.34	39.501	.068
	MCI	10	119.20	34.941	

Intra-group comparison of neuropsychological performance between patients with mild cognitive impairment and without mild cognitive impairment within the FH group analyzed by a 2-sided, 2 group independent samples t-test for equality of means. MCI= mild cognitive impairment, FH = Familial hypercholesterolemia.

*Corrected for age and education.