

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 might 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 receptor dysfunction and lifelong hypercholesterolemia.

METHODS: By using a cohort study design, patients with familial hypercholesterolemia (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 that could affect cognition, including history of stroke or transient ischemic attacks, were excluded from both groups. Thirteen standardized neuropsychologic 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.

RESULTS: Patients with familial hypercholesterolemia showed a high incidence of mild cognitive impairment compared with those without familial hypercholesterolemia (21.3% vs 2.9%; $P = .00$). This diagnosis was unrelated to structural pathology or white matter disease. There were significant differences, independent of apolipoprotein E4 or E2 status, between those with familial hypercholesterolemia and those with no familial hypercholesterolemia in several cognitive measures, all in the direction of worse performance for those with familial hypercholesterolemia.

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

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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 neuropathologic 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.^{3,4}

Recent studies suggest a connection between cholesterol metabolism and the pathogenesis of Alzheimer's disease.⁵⁻⁹ We reported that hypercholesterolemia accelerates amyloid beta protein production in the brain of transgenic mice^{7,8} and

associates with higher levels of amyloid beta protein amyloid in the human brain.¹⁰ On the basis of apparently controversial epidemiologic studies,¹¹ some investigators have argued that this relationship might be spurious. However, the discrepancies might be more apparent than real for 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 might have occurred earlier in life. Last, subjects with the highest levels of cholesterolemia generally die of cardiovascular events at younger ages and are lost from the samples of elderly subjects (ie, comparative studies of patients with Alzheimer's disease vs 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 neuropathologic study.¹⁰ Hypercholesterolemia was strongly correlated with the presence of brain amyloid but only in subjects aged 40 to 55 years ($P = .00$). 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 also can 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 who have 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 low-density lipoprotein (LDL) receptors. Members of the LDL receptor family, including LDL receptors themselves, have been implicated in synaptic function and Alzheimer's disease pathogenesis.¹⁸ There are no studies examining cognition in this population, indepen-

dently of cerebrovascular disease, because statins have only been widely available since the early 1990s.

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 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 of ≥ 8 were included in the familial hypercholesterolemia group.

Patients with clinical familial hypercholesterolemia were then recruited into the Spanish Familial Hypercholesterolemia Register²² and subjected to DNA testing for identification of LDL receptor mutations and the apolipoprotein B 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 and colleagues.²³ By these methods (microarray and sequencing), LDL receptor 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, aged more than 50 years, and without history of stroke or transient ischemic

CLINICAL SIGNIFICANCE

- A high incidence of mild cognitive impairment is observed in patients with familial hypercholesterolemia.
- Early exposure to elevated cholesterol or dysfunction of lipoprotein receptors might be risk factors for mild cognitive impairment.
- Symptoms of memory deficits in patients with familial hypercholesterolemia might represent a marker of mild cognitive impairment.
- Impaired cognition is unrelated to white matter disease and independent of apolipoprotein E4 or E2 status.

attacks were recruited from 2 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 self-referred or referred for neurologically unrelated conditions for lipid management or to establish primary care. Patients with clinical evidence of psychiatric or neurologic disorders (including history of stroke or transient ischemic attack), any metabolic disease that could affect cognitive performance, illiteracy, history of excessive alcohol use (consumption > 50 g/d), or drug abuse were excluded from the study. In addition, patients with history of hypertension, diabetes, or prior coronary artery bypass graft surgery also were excluded from both the familial hypercholesterolemia and the no-familial hypercholesterolemia groups because these conditions might adversely affect cognitive performance and potentially bias the results. Comprehensive medical histories and neurologic examinations were obtained from all participating subjects, including 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 also was conditioned on the absence of hypercholesterolemia (LDL cholesterol level < 160 mg/dL). The latter was necessary to avoid inadvertent inclusion of patients with familial hypercholesterolemia into the comparison group because not all mutations associated with familial hypercholesterolemia are known and the genetic screen detects only approximately 50% of the mutations. All study participants underwent detailed neuropsychologic 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; 2 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 was clinically assessed for family history of early coronary heart disease (<55 years for men and <60 years 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-cholesterol was estimated with the Friedewald equation.²⁵ Baseline lipid profiles were obtained from patients who had not received hypolipemic therapy for at least 4 weeks before drawing fasting glucose samples. Apolipoprotein E 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

Neuropsychologic Evaluation

The neuropsychologic examination was conducted by 2 experienced neuropsychologists blinded to the patients' diagnosis. We selected 13 well-established neuropsychologic instruments for screening of all cognitive domains.²⁷ The tests selected included the Mini-Mental State Examination, Buschke Memory Impairment Screen, semantic verbal category fluency for animals, Benton temporal orientation, clock drawing test (copy and command forms), Rey Auditory Verbal Learning test, Verbal Paired Associates, Boston Naming Test, digit span (forward and backward), Digit Symbol Substitution Test, Trail Making Test (Parts A and B), and Stroop test. Other measures incorporated in the assessment were the Global Dementia Scale and Hamilton Depression Rating Scale.

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 US²⁸ and European expert groups.²⁹ Briefly, amnesic mild cognitive impairment was defined as having a positive history of memory complaints and abnormal memory function on at least 2 neuropsychologic 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 2 instruments plus *only* isolated deficits in a *single* instrument tapping on another domain also were classified as having amnesic mild cognitive impairment. Patients with mild cognitive impairment also were 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 less than 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 complaints and abnormal memory on neuropsychologic testing as defined above plus abnormal scores (<1.5 standard deviations of the controls) in at least 2 additional instruments tapping on cognitive domains other than memory. Patients with deficits in other cognitive domains as identified by poor performance on 2 instruments (tapping primarily in such domains) were considered for the diagnosis of non-amnesic mild cognitive impairment (ie, 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, Fairfield, Conn), 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 neuropsychologic test scores were compared between familial hypercholesterolemia and control (no-familial hypercholesterolemia) groups using independent sample *t* tests for continuous variables and chi-square tests for categorical values. All tests were 2-sided using *P* less than .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 patients with familial hypercholesterolemia, 70 patients with no familial hypercholesterolemia) 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 Mini-Mental State Examination, Verbal Paired Associates, Rey Auditory Verbal Learning, and Trail Making Test. 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, 1.71-32.47). Ten subjects (21.3%) from the familial hypercholesterolemia group met criteria for mild cognitive impairment and exhibited neuropsychologic findings supporting this diagnosis. Of these patients, 7 were classified as having amnesic mild cognitive impairment and 3 were classified as having the multiple-domain form. On the other hand, only 2 subjects (2.9%) from the no-familial hypercholesterolemia group met the criteria for mild cognitive impairment (1 patient had the amnesic type, and 1 patient had 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 those with familial hypercholesterolemia, as summarized in [Table 2](#).

Factors associated with cognitive functioning were explored using stepwise linear regression separately for each

Table 1 Participant Characteristics

	FH N = 47	No FH N = 70	<i>P</i> Value
Men (No., %)	21 (44.7)	32 (45.7)	1.00
Age, y (mean, SD)	60.1 (6.7)	61.0 (7.0)	.49
Education, y (mean, SD)	10.1 (5.2)	9.7 (5.2)	.65
Family history of premature CHD (No., %)	15 (31.9)	7 (10.0)	.00
Ever smoked (No., %)	14 (29.8)	35 (50.0)	.04
Body mass index, kg/m ² (mean, SD)	26.5 (3.5)	25.6 (3.2)	.15
Baseline glucose (mean, SD)	91.5 (8.7)	91.5 (10.3)	1.00
Mild cognitive impairment (No., %)	10 (21.3)	2 (2.9)	.00
Baseline lipid profile, mg/dL			
Total cholesterol (mean, SD)	386.3 (65.7)	214.8 (23.3)	.00
LDL cholesterol (mean, SD)	300.4 (66.9)	136.1 (17.8)	.00
HDL cholesterol (mean, SD)	60.7 (12.8)	61.7 (13.1)	.70
Triglycerides, (mean, SD)	128.2 (40.3)	84.5 (29.2)	.00
Apolipoprotein E status (FH n = 46, Comp n = 63)			
ε4 carrier (No., %)	9 (19.6)	11 (17.5)	.81
ε2 carrier (No., %)	0 (0.0)	9 (14.3)	.01

CHD = coronary heart disease; FH = familial hypercholesterolemia; SD = standard deviation; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

Demographic and clinical characteristics of the study subjects.

Table 2 Neuropsychologic Test Results

Neuropsychologic Tests	FH	No FH	P Value
MMSE ^a	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
RAVL 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
VPA			
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
TMT			
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

FH = Familial hypercholesterolemia; MMSE = Mini-Mental State Examination; RAVL = Rey Auditory Verbal Learning; TMT = Trail Making Test; VPA = Verbal Paired Associates.

Neuropsychologic assessment: standardized tests scores for FH and No-FH groups. Data are expressed as mean and SD.

^aCorrected for age and education.

test (Table 3). Membership in the familial hypercholesterolemia group was independently associated with worse scores on the Mini-Mental State Examination ($P = .01$), Verbal Paired Associates ($P = .00$), and Rey Auditory Verbal Learning Interference ($P = .049$) tests. Cholesterol level was independently associated *only* with worse scores in the Trail Making Test Part B ($P = .01$). As expected, younger age and higher education years were independent predictors of better scores in several neuropsychologic measures. Finally, women scored significantly better than men in the Rey Auditory Verbal Learning Total ($P = .049$) and Delayed Recall ($P = .01$) tests. In the familial hypercholesterolemia group, the presence of memory complaints was associated with significantly decreased performance on neuropsychologic testing (Table 4). However, whether this clin-

ical 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 neither of the 2 subjects with no familial hypercholesterolemia with mild cognitive impairment. None of the scans showed significant vascular lesions. A small lacunar pontine infarction was present in 2 of the patients with familial hypercholesterolemia; 1 patient had a small T2 hyperintense area in the subcortical parieto-occipital white matter. No areas of leukoaraiosis, 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 patients with familial hypercholesterolemia 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%; $P = .00$) and far exceeded the age-specific prevalence predicted from either epidemiologic 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 neuropsychologic profiles meeting the criteria for mild cognitive impairment. Therefore, the clinical presence of a memory complaint seemed 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 neuropsychologic examination. When comparing the familial hypercholesterolemia group with the non-familial hypercholesterolemia group, score differences were more conspicuous with the Mini-Mental State Examination ($P = .03$), clock test (order: $P = .01$), Verbal Paired Associates ($P = .00$), and Rey Auditory Verbal Learning (A3: $P = .048$; A5: $P = .01$; interference: $P = .02$). The Trail Making Test Part B was almost significant at $P = .053$. There also were significant differences in the Global Deterioration Scale ($P = .03$). Our findings cannot be explained solely by large vessel cerebrovascular disease because 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 Alz-

Table 3 Independent Determinants of Cognitive Test Scores by Stepwise Multiple Linear Regression Analysis^a

Cognitive Tests	Independent Variables	Regression Coefficient B	Standardized Coefficient Beta	R ² for Model	Coefficient P Value
MMSE ^b	Constant	29.383	—	0.072	—
	FH group	-0.731	-0.269	—	.005
VPA	Constant	16.700	—	0.408	—
	Education per 5 y	0.709	0.221	—	.016
	FH group	-2.339	-0.355	—	<.001
RAVL	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	-0.991	-0.192	—	.049
Delayed recall	Constant	12.611	—	0.093	—
	Age per 10 y	-0.942	-0.237	—	.018
	Gender (female)	1.436	0.273	—	.006
TMT 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	0.072	0.206	—	.013

MMSE = Mini Mental State Examination; RAVL = Rey Auditory Verbal Learning; FH = familial hypercholesterolemia; VPA = Verbal Paired Associates; TMT = Trail Making Test.

^aVariables allowed to enter the model were FH group, age per 10 years, gender, education per 5 years, family history of premature CHD, tobacco use, body mass index, total cholesterol, and presence of $\epsilon 4$ and $\epsilon 2$ alleles.

^bScore already adjusted for age and education years.

heimer's disease range from 10% to 15% per year compared with 1% to 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 seem 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

Table 4 Group Statistics within the Familial Hypercholesterolemia Group: Mild Cognitive Impairment versus No Mild Cognitive Impairment

	MCI	N	Mean	SD	P
MMSE ^a	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	

FH = familial hypercholesterolemia; MCI = mild cognitive impairment; SD = standard deviation; MMSE = Mini Mental State Examination; VPA = Verbal Paired Associates; AVLT = Auditory Verbal Learning Test; TMT B = Trail Making Test Part B.

Intra-group comparison of neuropsychologic 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.

^aCorrected for age and education.

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 who have 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 Alzheimer's disease pathogenesis. Members of the LDL receptors family are involved in amyloid beta 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 receptor-deficient background, the mice not only developed exacerbated age-dependent cerebral beta-amyloidosis but also developed more severe behavioral abnormalities than observed in mice with LDL receptor-intact Alzheimer's disease.³⁴

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

As in other populations with familial hypercholesterolemia who have been studied, only 50% of our patients had detectable LDL receptor mutations. Although this rate was higher among patients with familial hypercholesterolemia with mild cognitive impairment, it would be premature to make conclusions on this finding because of the small sample size. The possibility still stands, however, that in association with or independently of 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 also was insufficient to dissect the effect of cholesterol from the effect of the LDL receptor mutations or their subtypes. Likewise, additional effects of lipoprotein E isoforms could not be fully assessed, although stepwise linear regression analysis suggested that the apolipoprotein E2 or E4 status did not affect cognitive performance (Table 3).

CONCLUSIONS

Cognitive impairment in familial hypercholesterolemia was unrecognized before this report probably because statins became widely available only in the early 1990s. Before that

time, many patients with familial hypercholesterolemia would die of cardiovascular disease early before cognitive impairment could become manifest. Studies of larger samples of patients with familial hypercholesterolemia will allow further insights into the mechanisms and rates of conversion to dementia in this disorder.

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