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Cardiovascular risk and memory in non-demented elderly women

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Abstract

Objective—To determine whether cardiovascular (CV) risk is associated with subtle memory deficits in non-demented, healthy older women with a family history of Alzheimer disease (AD).

Methods—Baseline data of 375 participants from a randomized, double-blind placebo-controlled primary prevention trial to test the efficacy of hormone replacement therapy in delaying AD and cognitive decline were analyzed. All subjects were women over 65 with a family history of AD who had normal cognition and no active heart disease at baseline. A baseline memory composite score was calculated, consisting of immediate and delayed recall of verbal and nonverbal material. Multiple linear regression was performed to examine the association of relative CV risk with memory functioning; age, ethnicity and education level were included as covariates.

Results—Mean baseline memory composite score was significantly higher in those with low relative CHD risk than those with high relative CHD risk.

Conclusion—These findings suggest that subtle elevation of CHD risk may negatively affect memory functioning even in otherwise healthy, non-demented older women without a history of heart disease.

Keywords

cognitive aging; memory; neuropsychological assessment; cardiac

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Disclosure statement

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1. Introduction

Vascular risk factors may play a role in memory dysfunction and progression to dementia.[1,7] Studies have shown inconsistent evidence for an association between poorer cognitive performance in the non-demented elderly and individual cardiovascular risk factors.[1–3,7] About 25% of Americans have at least three cardiovascular risk factors,4 and in the Cardiovascular Health Study, 60% of subjects 65 or over had at least two risk factors and over 10% had four or more.5 The cumulative burden of vascular disease may have an important effect on cognition similar to that seen in coronary heart disease (CHD).[7] Previous studies suggest that higher vascular risk may contribute to poorer cognitive status. Clustering of vascular risk factors has been associated with an increased risk of Alzheimer disease (AD),3 and in the Framingham Offspring Study, dementia and stroke-free subjects with higher cerebrovascular risk had lower cognitive performance. 2 We examined whether higher CHD risk is associated with cognitive deficits in non-demented, healthy elderly women with a family history of AD.

2. Methods

We examined baseline data from a multicenter trial for the primary prevention trial of AD and memory loss in 477 non-demented women age 65 and older who have a family history of AD. All protocols were approved by each site's Institutional Review Board (IRB). Recruitment strategy was individualized to each site and pre-approved by its IRB. All subjects signed informed consent. The entry criteria were no memory complaints, normal scores on immediate and delayed verbal recall, a score less than 16 on the Beck Depression Inventory, no serious medical, neurological (including stroke or transient ischemic attack) or psychiatric conditions, and no use of cognitive enhancing or experimental drugs. The LDL-based approach of the Framingham algorithm was used to calculate absolute 10 year CHD risk.10 Since CHD risk as compared to an age and gender-matched, low-risk subject is a more accurate estimate of CHD risk in the elderly, we then calculated each subject's relative CHD risk as per NHBLI guidelines.6 Since our population was skewed towards the healthy elderly, for purposes of comparison, subjects were divided into a low CHD risk group (those below the study population's median) and a high CHD risk group (those at or above the median); the median relative CHD risk was 1.125 or an absolute risk of 9%. Subjects were similarly dichotomized for each continuous CHD risk factor. Analyses focused on tests of memory, the pre-stated primary outcome of the original study, namely the Selective Reminding Test (SRT), which measures the acquisition of verbal material by asking subjects to learn a list of twelve unrelated items after six trials and testing retention after fifteen minutes; the Visual Reproduction Test (VRT) for the Wechsler Memory Scale-Revised, which measures the acquisition of nonverbal material by asking subjects to draw five line drawings from memory and testing retention after thirty minutes; and the Mini-Mental State Examination (MMSE). The *a priori* primary outcome measure of the planned clinical trial, the memory composite score, was calculated as the sum of the immediate and delayed recall scores for SRT and VRT.

102 participants (21.3%) were excluded because they were on a lipid-lowering agent or antihypertensive ($n = 56$) or were missing relevant data ($n = 46$). Since the percentage of smokers was low (10.0%), the 145 subjects with unknown smoking status were assumed to be non-smokers and were evenly divided between both CHD risk groups. All statistical analyses were performed with our cohort of 375 subjects except for 1 subject missing a Beck Depression Inventory Score, 17 subjects missing *APOE* genotyping data, and 2 subjects missing MMSE scores. Comparisons between the CHD risk groups were done using *t*-test and χ^2 tests as appropriate. We then performed multiple linear regression analyses with each cognitive measure as the dependent variable and with CHD risk group or risk factor with age, ethnicity,

education and *APOE* ε4 status as the covariates. The level of significance was $p < 0.05$. All statistical analyses were done using SPSS v. 15.0.

3. Results

375 subjects were available for analyses. Table 1 presents the clinical characteristics and cognitive measures at baseline for the study's entire population and each of the CHD risk groups. The low CHD risk group had more optimal CHD measurements (except for smoking status which was borderline significant), more Caucasians, and higher education than the high CHD risk group did. Average ages did not differ between the two groups because the Framingham algorithm awards the same number of points for age over 60. The low CHD risk group also had higher unadjusted mean raw scores on the MMSE and measures of memory than the high CHD risk group. Both groups, however, had normal MMSE scores, which confirmed that all participants were cognitively intact. *APOE* ε4 carriers did not have a significantly higher risk than non-carriers for having any CHD risk factor in the Framingham algorithm.

Table 2 presents the β values and 95% CI's for the multiple linear regression model in which the memory composite score was the dependent variable and CHD risk group, age, education and ethnicity were covariates. The *R* value for this model was 0.466. Higher CHD risk, higher age, lower education and non-Caucasian ethnicity were associated with lower memory composite scores. Inclusion of *APOE* ε4 status as a covariate did not change these results ($p = 0.139$). Multiple linear regression models also demonstrated that none of the other cognitive measures was significantly associated with CHD risk after controlling for age, education and ethnicity. Likewise, none of the CHD risk factors (hypertension, LDL levels, HDL levels smoking or diabetes) or *APOE* ε4 status was significantly associated with any of the cognitive measures.

4. Discussion

In our cohort of healthy, non-demented elderly women with a family history of AD, lower CHD risk correlated with higher memory composite scores. The high CHD risk group also had lower scores on the individual component scores of the composite in the unadjusted analyses. These results suggest that even in healthy, non-demented subjects with no known heart disease, elevated cumulative CHD risk is correlated with poorer global memory functioning.

The literature for vascular risk factors and their effects on cognitive performance has focused mostly on certain individual CHD risk factors such as type 2 diabetes, hypertension or dyslipidemia, but the data for such associations have been variable.[1–3,7] We observe a trend toward an association between each of the risk factors and measures of memory, although it did not reach statistical significance. Perhaps the very healthy nature of our population minimized the range of risk as well as the opportunity to observe a stronger association. The long-term effects of cumulative vascular risk and cognitive changes have been reported by others. In stroke and dementia free subjects in the Framingham Offspring Study, cumulative stroke risk correlated with cognitive deficits consistent with vascular injury[2] and brain atrophy on quantitative MRI in the context of modest cognitive decline.[8] In general, these findings often are on tests of attention and planning and are less likely to be on tests of attention. However, these results speak to memory deficits which are thought to be the most common indicators of future decline.

There are several limitations to our work. First, this is a cross-sectional study of a carefully selected cohort of healthy women with a family history of AD. We will examine whether our longitudinal data support the hypothesis that CHD risk is a prognostic indicator for cognitive

decline in our population. Second, the pathophysiology of these differences cannot be determined. In verbal and visual memory, we see differences in both consolidation (total recall) and retrieval (delayed recall). While this pattern might be considered more consistent with primary dementia as opposed to a vascular effect, the difference is too small and not in the impaired range. The presence of CHD risk factors suggest a possible vascular or even a cerebrovascular burden. On the other hand, the presence of a family history of AD supports a hypothesis of a prodrome with early amyloid accumulation having a more apparent impact on memory, particularly when combined with another risk factor. Longitudinal studies of these subjects will help determine the progression in memory and other cognitive changes that may support a specific etiology. A third limitation is that our sample consisted of women; whether our findings extend to men will need to be tested. Our entry criteria excluded subjects with clinical vascular disease so we are unable to assess the effect in such a group. Should the subjects in follow-up group develop more pronounced vascular disease, we may have an opportunity to determine if the cognitive difference is enhanced.

Our work highlights that the cumulative CHD risk may be a key to better understanding the connection between cognition in the elderly and cardiovascular disease. It is not clear how this work relates to potential therapeutic interventions. Therapeutic agents that modify only an individual risk factor have not consistently shown cognitive benefit.[1] Given the frequent coexistence of CHD risk factors and the possible effects of beta amyloid on the cerebral microvasculature, a drug cocktail which targets multiple pathways may be needed to increase the likelihood of an improvement of cognitive performance or even the prevention of cognitive decline. Alternatively, these findings could illustrate a common pathway affecting both cardiovascular and brain systems that is not directly modifiable.

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Table 1

Baseline Characteristics of the Entire Cohort and each CHD Risk Group

Variables	Entire (n = 375)	Low risk (n = 170)	High risk (*n* = 205)	*p*[a]
Relative CHD risk	1.37 (0.75)	0.80 (0.22)	1.85 (0.69)	< 0.001
CHD risk components				
Age, y	72.7 (5.3)	72.2 (5.0)	73.1 (5.4)	0.077
LDL, mg/dL	140.4 (36.9)	128.9 (32.5)	150.0 (37.7)	< 0.001
TC, mg/dL	223.7 (39.2)	218.2 (35.8)	228.2 (41.4)	0.014
HDL, mg/dL	56.7 (16.2)	66.7 (13.8)	48.4 (13.0)	< 0.001
Systolic BP, mm Hg	133.8 (17.8)	124.5 (15.3)	141.6 (15.9)	< 0.001
Diastolic BP, mm Hg	78.1 (9.7)	74.9 (9.2)	80.7 (9.4)	< 0.001
Diabetes mellitus, n (%)	26 (6.9)	2 (1.2)	24 (11.7)	< 0.001
Smoking, n (%)	23 (6.1)	6 (3.5)	17 (8.3)	0.056
Additional variables				
Mean educational level, y	14.2 (3.2)	14.9 (3.1)	13.7 (3.1)	< 0.001
Ethnicity, non-Caucasian, n (%)	73 (19.5)	25 (14.7)	48 (23.4)	0.034
Beck Depression Inventory[†]	4.3 (3.6)	4.1 (3.7)	4.6 (3.5)	0.193
APOE ε4 carrier, n (%)[†]	116 (32.4)	50 (30.3)	66 (34.2)	0.433
MMSE (0–30)	28.9 (1.4)	29.1 (1.3)	28.7 (1.5)	0.005
SRT Immediate Recall (0–72)	46.5 (8.7)	47.9 (8.7)	45.3 (8.6)	0.005
SRT Delayed Recall (0–12)	7.5 (2.3)	7.8 (2.3)	7.2 (2.3)	0.020
VRT Immediate Recall (0–41)	29.9 (7.3)	31.2 (7.0)	28.8 (7.4)	0.001
VRT Delayed Recall (0–41)	23.0 (9.8)	24.6 (9.8)	21.7 (9.5)	0.004
Memory Composite (0–166)	106.8 (22.0)	111.4 (21.4)	103.0 (21.7)	< 0.001

CHD = coronary heart disease; LDL = low-density lipoprotein; TC = total cholesterol; HDL = high-density lipoprotein; BP = blood pressure; MMSE = Mini-Mental State Examination; SRT = Selective Reminding Test; VRT = Visual Reproduction Test.

[a] *t*-test or χ^2 test as appropriate.

Table 2

Regression coefficients for covariates in memory composite score model

Variable	Regression coefficient (β) (CI)	*p*
CHD risk group	−4.376 (−8.463, −0.288)	0.036
Age	−1.238 (−1.617, −0.858)	<0.001
Educational level	1.735 (1.089, 2.380)	<0.001
Ethnicity	−8.852 (−13.939, −3.765)	0.001

Values are regression coefficient (95% CI).