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Carotid atherosclerosis and cognitive function in midlife: The beaver dam offspring study

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ABSTRACT

Background: Atherosclerosis may be associated with cognitive function; however the studies are few, especially among midlife adults.
Methods: Participants in the beaver dam offspring study who had cognitive test data and gradable carotid artery ultrasound scans were included ($n = 2794$, mean age: 49 years). Atherosclerosis was measured by carotid intima-media thickness (IMT) and the presence of plaque. Cognitive function was measured by the trail making test (TMT), grooved pegboard test (GPT) and mini-mental state examination (MMSE). Generalized cognitive function was defined by a summary score calculated from the TMT and GPT. Linear regression was used to evaluate the associations between carotid atherosclerosis and cognitive function tests.
Results: Larger IMT was associated with lower GPT, MMSE and the summary score adjusting for multiple factors, the coefficients were: 13.8s ($p < 0.0001$), −0.6 ($p = 0.007$), and 0.47 ($p = 0.01$), respectively for 1 mm increase in IMT. Plaque scores were significantly associated with TMT-B, GPT, MMSE, and the summary score adjusting for age, sex and education. The associations remained statistically significant after further adjustments except for the association with TMT-B, which was attenuated and no longer significant.
Conclusions: Our results show the significant associations between markers of carotid atherosclerosis and cognitive function in a cohort of persons aged 21–84 years. Longitudinal studies are needed to further examine these associations.

1. Introduction

Recent studies have shown that carotid atherosclerosis may be associated with cognitive function and dementia, but associations have been inconsistent [1–5]. In addition, most studies have been conducted among older adults, and there are few studies of this relationship in younger adults. It has been suggested that carotid atherosclerosis may cause cerebral ischemia and hypo-perfusion, which may contribute to brain atrophy and cause impairment in cognitive function [6]. Though atherosclerosis may begin earlier in life, even in childhood [7], it is not clear when it might begin to affect cognitive function. Therefore, it is important to examine the relationship between atherosclerosis and cognitive function in a relatively younger population.

Our study investigated the associations between carotid atherosclerosis and cognitive function in a large cohort of adults aged 21–84 years. We hypothesize that carotid atherosclerosis measurements are associated with worse cognitive function, although the effect size may be small in middle-aged adults.

2. Methods

2.1. Study population

The beaver dam offspring study (BOSS) is a cohort study of age-related sensory disorders in the adult offspring of the participants in the population-based epidemiology of hearing loss study (EHLS) [8,9]. In brief, the adult children (aged 21 years or older) of EHLS participants were invited to participate in the BOSS examination in 2005–2008. A total of 3285 adults participated in the study, 45% of whom were men. More than 99% of participants were non-hispanic white. Participants with gradable carotid ultrasound images and cognitive test data were included in the analyses ($n = 2794$).

The BOSS was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board, and all participants provided informed consent.

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2.2. Data collection

2.2.1. Carotid atherosclerosis

Carotid artery ultrasound scans were obtained with a Biosound AU4 (Indianapolis, IN, USA) and a 7.5 MHz probe (LA13A) using a slightly modified protocol from the Atherosclerosis Risk in Communities (ARIC) study [10]. The intima-media thickness (IMT) was measured on the left and right sides of the near and far walls of the common carotid artery (CCA), the bifurcation and the internal carotid artery (ICA). The mean IMT of the measurements from 12 sites was calculated.

The presence of plaque at six sites (CCA, ICA and the bifurcation, both sides) was determined. Plaque was assessed as present if: acoustic shadowing was present and there was a change in wall shape, such as a protrusion into the lumen, a change in wall texture (seen as walls echoing brighter than adjacent boundaries), or the IMT at the maximum point in that location was greater than or equal to 1.5 mm; or, in the absence of acoustic shadowing, two of the three wall characteristics (shape, texture and thickness) were observed [11]. The number of sites was counted and a plaque score (0, 1 and 2) was created by categorizing the number of sites with plaque into 3 groups: 0 site (plaque score 0), 1–3 sites (plaque score 1) and 4–6 sites (plaque score 2).

The reproducibility of IMT and plaque assessment was good. In a 10% sample ($n = 280$) of participant scans that were re-graded the mean difference in IMT was 0.0019 mm and kappa statistics for plaque assessment ranged from 0.58 (ICA) to 0.71(bifurcation) with 97.3% agreement within ± 1 for the number of sites with plaque.

2.2.2. Cognitive function tests

The trail making test, part A (TMT-A) and part-B (TMT-B), and the grooved pegboard test (GPT) were administered to the participants [12]. The TMT measures executive, attention and psychomotor function, and the GPT measures executive, and psychomotor function (eye-hand coordination and motor speed). The TMT requires a subject to connect 25 consecutive targets as fast as possible on a sheet of paper, within 5 min. Two versions were used: TMT-A, in which the targets are all numbers (1, 2, 3, etc.), and TMT-B, in which the subject alternates between numbers and letters (1, A, 2, B, etc.). The GPT consists of a metal board with a matrix of 25 holes with randomly positioned slots. Pegs have a ridge along one side and must be rotated to match the hole before they can be inserted. The subject's task is to insert metal pegs as quickly as possible into the slots in sequence within 5 min. The score for each task is the time (s) taken to complete the test within 5 min, and a score of 301 was given if the subject had not completed the task within 5 min. The mini-mental state examination (MMSE) is a measure of general cognitive function which measures orientation to time and place, attention and calculation, language, and memory [13]. The test was only administered to participants aged 50 years or older, as it was suggested to be relatively insensitive in younger persons [14]. The MMSE score was used as the outcome in our analyses in individuals aged 50 years or older.

2.3. Covariates

Data on demographics, current medications, lifestyle and the SF-36 mental score were obtained during the interview. Height, weight and seated blood pressures were measured. Blood samples were obtained and assayed for the glycated hemoglobin A1C, serum total cholesterol and high density lipoprotein (HDL) levels. APOE genotyping was performed at the Center for Applied Genomics, the Children's Hospital of Philadelphia among participants 45 years and older.

Besides age, sex and education, other CVD factors were considered as potential confounders if they were found to be associated with carotid atherosclerosis and cognitive function, and if their inclusion in the statistical models resulted in a moderate change in the estimates of the effect of atherosclerosis.

2.4. Statistical analysis

Ordinary linear regression models were used with each original individual test score as an outcome in separate models. Because participants who did not complete the TMT or GPT in the allotted time were older, had lower income and less education than those who did complete the tasks (data not shown), a sensitivity analysis was conducted excluding those participants. Analyses with the TMT and GPT were repeated among participants <60 years old.

A principal component analysis (PCA) was performed for the three tests (TMT-A, TMT-B and GPT) to get a summary score, which combines information from the three individual tests and measures the common aspect of cognition that was captured by each test. Analysis with this score reduces multiple testing for each individual test score, and it also provides an answer to whether there is an association between atherosclerosis and the common aspect of cognitive function measured by these tests, in addition to the results from individual tests. All the analyses were conducted with SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

Among the 2794 participants, 46% were men. The mean age was 49 years (s.d.: 9.8 years), and the quartiles of age distribution were 42, 48, and 56 years for the 25th, 50th and 75th percentile, respectively. The mean carotid IMT was 0.65 mm (s.d.: 0.15 mm), and the quartiles of IMT distribution were 0.56, 0.62, and 0.70 mm for the 25th, 50th and 75th percentile, respectively. Two percent of the cohort had a plaque score of 2 (plaque presented in 4–6 sites), and 22% had a plaque score of 1 (plaque presented in 1–3 sites). Fourteen participants and two participants failed to complete the TMT-B and the GPT in 5 min. The characteristics of the study population are presented in Table 1.

The associations between carotid atherosclerosis and TMT and GPT are shown in Table 2. After adjusting for multiple potential confounders, carotid IMT was associated with the GPT performance. Plaque scores were associated with TMT-A, TMT-B and GPT after adjusting for age, sex and education. The associations between plaque score and TMT were attenuated and lost significance in the multivariable model. However, in the sensitivity analysis (excluding those who scored 301s), plaque score was significantly associated with TMT-B after multiple adjustments, with coefficients 1.7s (s.e.: 1.3, $p = 0.2$) and 7.4s (s.e.: 3.6, $p = 0.04$) for plaque score 1 and 2, respectively.

The analyses with TMT and GPT were repeated among participants less than 60 years old. In these relatively younger participants, IMT remained associated with GPT in the multivariable model, and plaque score was significantly associated with TMT-A, TMT-B and GPT in the multivariable models (data not shown).

The PCA yielded one eigenvalue greater than 1 which accounted for 67% of the variance of the three tests. This component was retained as the summary score. The coefficients of this score for TMT-A, TMT-B and GPT were 0.60, 0.60, and 0.54, respectively. Carotid IMT and plaque score were both associated with this summary score after multiple adjustments, and the coefficients were 0.47 (s.e.: 0.19, $p = 0.01$) for 1 mm IMT, and 0.11 (s.e.: 0.06, $p = 0.04$), 0.37 (s.e.: 0.15, $p = 0.02$) for plaque score 1 and 2, respectively.

Of the 1262 participants (mean age: 57.6 years) who completed the MMSE, 9 were cognitively impaired (total score <24 out of 30).