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Effects of vascular risk factors, statins, and antihypertensive drugs on PiB deposition in cognitively normal subjects

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Abstract

Introduction: Hypertension, hypercholesterolemia, and obesity increase the risk of dementia. Although their detection is commonly followed by an introduction of treatment, little is known about how medications frequently used to treat vascular risk affect amyloid deposition.

Methods: A cross-sectional study of 156 subjects who underwent positron emission tomography with PiB. Using linear regression, we tested whether blood pressure, cholesterol, overweight/obese status, angiotensin receptor blockers (ARBs), beta-blockers, diuretics, angiotensin converting enzyme inhibitors, and statins predicted amyloid deposition.

Results: The use of ARBs ($\beta = -.15$, $P = .044$) and diuretics ($\beta = -.20$, $P = .006$) predicted less amyloid accumulation; older age ($\beta = .29$, $P < .001$) and statins ($\beta = .23$, $P = .004$) were related to greater amyloid deposition. Overweight and/or obese women had more cortical amyloid than their peers.

Discussion: Prospective studies should confirm effects of drugs and increased body weight on amyloid accumulation and establish whether they translate into measurable clinical outcomes. Women may be more susceptible to harmful effects of obesity.

Keywords: Amyloid; PET-PiB; Vascular risk factors; Antihypertensive medications; Statins angiotensin receptor blockers; Diuretics; Brain; Healthy elderly

1. Introduction

Alzheimer's disease (AD) and vascular conditions are increasingly common with age. Vascular disease contributes to AD neurodegeneration [1–3] and may even initiate it [4]. This notion is supported both by epidemiologic studies showing that atherosclerosis risk factors like hypertension, high cholesterol, and obesity are associated with higher incidence of cognitive impairment and AD [5], and by neuropathology studies showing that indices of atherosclerosis correlate with AD markers [6].

Amyloid ß deposition in extracellular plaques [7] and vessel walls [4] is a key feature of AD. In animal studies, hypoperfusion and ischemia-activated gamma-secretase [8], increased *BACE1* gene transcription and expression, and augmented Aß accumulation [9]. These observations suggest that the association between vascular disorders and AD could be mediated by changes in amyloid metabolism.

L.M., M.d.L., and W.T. have an imaging patent which belongs to NYU. Other authors report no conflict of interest.

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Recent years have brought evidence that higher brain amyloid deposition, measured with Pittsburgh compound B (PET-PiB), is related to high blood pressure [10–12] and abnormal markers of lipid metabolism [13,14]. Interestingly, studies reporting on body mass index (BMI) and PiB found an inverse relationship, with low BMI related to greater PiB uptake [12,15]. Both of these observations were based on subjects in their seventies or older, and the results might have reflected weight loss in preclinical stages of the disease.

The detection of vascular risk is commonly followed by the introduction of appropriate treatment aimed at risk modification. The treatment itself may affect PET measures of brain amyloid accumulation, but this is largely unknown. In a group of cognitively healthy adults and elderly, we examined cross-sectionally the relationships between the most common vascular risk factors: blood pressure, cholesterol, and body weight, as well as frequently used antihypertensive medications and statins, and brain amyloid deposition measured with PET-PiB.

As women are more likely to suffer from AD than men [16], and sex differences in risk factors for conversion to AD [17] and in the associations between lipid levels and dementia [18] have been reported, we also conducted exploratory analyses to examine whether the relationships between vascular risk factors and PiB deposition differed by gender.

2. Methods

2.1. Subjects

We studied 156 cognitively healthy subjects (mean ± standard deviation, age 60.4 ± 10.4 years; education 16.6 ± 2.0 years; 67% women). Eighty-eight percent of the group was Caucasian, 9% African American, 2.5% Asian, and 0.5% Hispanic. All subjects were recruited by the Center for Brain Health at the NYU School of Medicine for longitudinal PET studies of aging, cognitive decline, and AD risk factors. They were volunteers responding to advertisement, subjects interested in research participation or family members of cognitively impaired patients. All signed IRB-approved consent forms and underwent medical, psychiatric, and neurological assessments, blood tests, ECG, MRI, and PET-PiB scans. PET examinations were performed between March 2009 and November 2013. Mild cognitive impairment and dementia were ruled out during a diagnostic interview. All subjects had ≥26 points on the mini mental state examination. Subjects scoring >17 on the 17-item Hamilton Depression Scale [19], subjects with brain tumor, neocortical infarction, and axis I disorders were excluded.

Laboratory tests (in a fasting state) included complete blood count, metabolic and lipid panel, liver function tests, and urinalysis. The clinical evaluation included an interview using the Brief Cognitive Rating Scale and rating on the Global Deterioration Scale (GDS) [20]. All subjects were diagnosed as cognitively healthy: with (GDS = 2) or without (GDS = 1) subjective memory complaints. From a larger pool of potential subjects, we report here on subjects ≥35 years, with technically good PET scans. Diagram in Fig. 1 describes an initial and final study sample.

2.1.1. Neuropsychological assessment

To fully characterize the cognitive status of our participants, we performed cognitive testing. It included the Uniform Data Set Neuropsychological Test Battery as chosen by National Alzheimer's Coordinating Center: Logical memory story A from Wechsler Memory Scale, (I: immediate and II: delayed recall), digits forward and backward, digit symbol substitution test (DSST), Trail Making Test parts A and B (TMT-A,B), Boston Naming Test (BNT), animal and vegetable categories [21]. Subjects also received tests from the Guild Memory Scale assessing immediate and delayed recall of orally presented paragraphs (initial: PARI, and delayed: PARD); and verbal paired associates (initial: PRDI and delayed: PRDD) [22]. Tests results of all tests were converted to age-adjusted, education-adjusted, and gender-adjusted standardized scores (z-scores) based on a normative population [23,24]. We subsequently grouped cognitive tests into memory (logic I and II, PARD, PARI, PRDD, and PRDI), executive function (TMT-B), attention (digits forward and backward), processing speed (DSST and TMT-A), and language (BNT, animals, and vegetables categories) domains. The score for each domain was an average of z scores of all tests combined.

2.1.2. Ascertainment of vascular risk factors

The presence of hypertension (HTN) was determined based on current antihypertensive treatment or blood pressure (BP) ≥140/90 mm Hg [25]. BP was taken in a sitting position, after 5 minutes of rest. Of 50 subjects classified as hypertensive 40 were taking medication, 10 were unmedicated with high blood pressure during in office visit. BMI was calculated as [weight (pounds) × 703]/height^2 (inches). All the subjects were classified as having a normal weight: BMI ≤24.99 or being overweight or obese: BMI ≥25. Subjects currently being treated with cholesterol-lowering medication (statins) or subjects with total cholesterol >200 were considered to have hypercholesterolemia [26].

2.1.2.1. Medication

We separately coded the following groups: angiotensin receptor blockers (ARBs) acting through blocking angiotensin receptor 1; angiotensin converting enzyme inhibitors (ACEi), preventing conversion of angiotensin I to angiotensin II; beta-blockers blocking β-adrenergic receptors in the heart and vascular smooth muscles; diuretics increasing water excretion from the body; statins and antidepressants. We did not analyze calcium channel blockers separately because these were taken only by five subjects.

2.1.2.2. Apolipoprotein E (APOE) genotyping

Genotyping was performed using polymerase chain reaction as previously described [27]. Study subjects were