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Cardiovascular risk factors, cortisol, and amyloid-β deposition in Alzheimer's Disease Neuroimaging Initiative

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Abstract

Background: There is epidemiological evidence that cardiovascular risk factors (CVRF) also are risk factors for Alzheimer's disease, but there is limited information on this from neuropathological studies, and even less from in vivo studies. Therefore, we examined the relationship between CVRF and amyloid-β (Aβ) brain burden measured by Pittsburgh Compound B-positron emission tomography (PiB-PET) studies in the Alzheimer's Disease Neuroimaging Initiative.

Methods: Ninety-nine subjects from the Alzheimer's Disease Neuroimaging Initiative cohort who had a PiB-PET study measure, apolipoprotein E genotyping data, and information available on CVRF (body mass index [BMI], systolic blood pressure, diastolic blood pressure [DBP], and cholesterol and fasting glucose test results) were included. Eighty-one subjects also had plasma cortisol, C-reactive protein, and superoxide dismutase 1 measurements. Stepwise regression models were used to assess the relation between the CVRF and the composite PiB-PET score.

Results: The first model included the following as baseline variables: age, clinical diagnosis, number of apolipoprotein ε4 alleles, BMI ($P = .023$), and DBP ($P = .012$). BMI showed an inverse relation with PiB-PET score, and DBP had a positive relation with PiB-PET score. In the second adjusted model, cortisol plasma levels were also associated with PiB-PET score ($P = .004$). Systolic blood pressure, cholesterol, or impaired fasting glucose were not found to be associated with PiB-PET values.

Conclusion: In this cross-sectional study, we found an association between Aβ brain burden measured in vivo and DBP and cortisol, indicating a possible link between these CVRF and Aβ burden measured by PiB-PET. These findings highlight the utility of biomarkers to explore potential pathways linking diverse Alzheimer's disease risk factors.

Keywords: Alzheimer disease; Vascular risk factors; PiB; Amyloid-β; Cortisol; Blood pressure; Body mass index

1. Introduction

Dementia is the fourth highest cause of loss of disability-adjusted life years in high-income countries [1], with a projected 300% prevalence increase over

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the first half of this century [2]. Alzheimer's disease (AD) is the most common cause of dementia, but it is frequently accompanied by vascular pathology, especially with increasing age, as shown by postmortem studies [3]. No preventive or disease-modifying treatment for AD is available presently, but if measures are undertaken to reduce the exposure to modifiable risk factors (RF), the incidence and prevalence of AD could, in theory, be reduced [2].

We now know that pathological hallmarks of AD begin to appear decades before symptom onset [4], and long before the dementia stage is reached, there is a preclinical phase of many years' duration, during which the two signature lesions of AD—amyloid-β (Aβ) deposits and fibrillar tau lesions—progressively accumulate in the brain [5,6]. Therefore, many RF could exert their effects at stages in the life span when AD pathology progressively accumulates, but well before symptom onset. Many of these RF were previously acknowledged as cardiovascular risk factors (CVRF), but there is also evidence that hypertension [7,8], obesity [9], and diabetes [8,10,11] increase the risk of AD. Many conflicting reports of AD RF have been published, and the discrepancies may be a result of many methodological issues [12], including the fact that the effects of RF might differ based on the age of individuals [13]. For example, in the case of diastolic blood pressure (DBP), high levels at midlife [7] and low levels at advanced age both act as RF for dementia [14,15]. High cholesterol levels in midlife have also been associated with increased risk for AD, and a decrease in cholesterol levels after midlife has been described as a risk marker for dementia [16]. Further, it is important to consider that part of this effect could be attributed to genetic and early-life environmental factors that contribute to the linkage between RF and AD [17]. As CVRF can be treated with drugs that are already available, the incidence of AD could be reduced if treatments and adequate lifestyle changes are implemented and started at midlife [18], as pointed out by some observational studies [8,19]. These epidemiological findings have not been accompanied by studies of the association between CVRF and biomarker measurements that ascertain the burden of Aβ deposits or Aβ load. Further, cortisol levels have been related to worse cognitive scores and clinical outcomes [20,21], and they show an inverse correlation with hippocampal volume [21]. This has led to the hypothesis that increased glucocorticoid exposure promotes hippocampal damage and even AD neuropathology [22]. Therefore, we studied the relationship between body mass index (BMI), systolic blood pressure (SBP), DBP, altered fasting glucose, plasma levels of cortisol and acute-phase proteins, and Aβ burden, as measured by Pittsburgh Compound B-positron emission tomography (PiB-PET) studies, in subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI).

2. Methods

2.1. Subjects

The ADNI is a large, multicenter, longitudinal neuroimaging study that was launched in 2004 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations. ADNI 1 consists of 819 adult subjects—229 cognitively normal (CN), 398 with mild cognitive impairment (MCI), and 192 with AD. Of these subjects, we included 22 CN, 51 MCI, and 26 AD subjects who had at least one PiB-PET measure. Participants in ADNI undergo baseline and periodic physical and neurologic examinations and standardized neuropsychological assessments, and they provide biological samples (blood, urine, and, in a subset, cerebrospinal fluid) throughout the study. Physical examination includes measurements of height, weight, SBP, and DBP. BMI was calculated as weight (kg) divided by the square of height (m). Imaging (magnetic resonance imaging and, for a subset, fluorodeoxyglucose PET and PiB-PET) is performed at baseline and at regular intervals thereafter, as reviewed previously [23,24] (http://www.adni-info.org/index). All AD subjects met National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD, with a Mini-Mental State Examination score between 20 and 26, a global clinical dementia rating of 0.5 or 1, and a sum of boxes clinical dementia rating of 1.0 to 9.0, and were therefore mildly impaired. Inclusion criteria for amnestic MCI subjects include a Mini-Mental State Examination score of 24 to 30 and a Memory Box score of at least 0.5. Further details on the ADNI cohort can be found at http://www.adni-info.org/index. Exclusion criteria include any serious neurological disease other than possible AD, history of brain lesions or head trauma, or psychoactive medication use (including antidepressants, neuroleptics, chronic anxiolytics, or sedative hypnotics). Subjects had to have a Hachinski Ischemic Score of $\leq$4 and good general health with no diseases precluding enrollment in ADNI. The selection criteria and methodology have been extensively described by Petersen et al [25] and are available at http://www.adni-info.org/index.

Subjects were classified based on fasting glucose levels as not altered ($<$100 mg/dL) or impaired ($\geq$100 mg/dL) according to criteria of the American Diabetes Association [26]. Fasting glucose measures were available for only 66.7% of the sample.

2.2. Apolipoprotein E genotyping

Apolipoprotein E (*APOE*) genotyping was performed using TaqMan polymerase chain reaction assays, as described previously [27].