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Trajectories of inflammatory markers and cognitive decline over 10 years

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ABSTRACT

We aimed to examine trajectories of inflammatory markers and cognitive decline over 10 years. Cox proportional hazards models were used to examine the association between interleukin-6 and C-reactive protein (CRP) trajectory components (slope, variability, and baseline level) and cognitive decline among 1323 adults, aged 70–79 years in the Health, Aging, and Body Composition Study. We tested for interactions by sex and apolipoprotein E (APOE) genotype. In models adjusted for multiple covariates and comorbidities, extreme CRP variability was significantly associated with cognitive decline (hazard ratio [HR] 1.6, 95% confidence interval [CI]: 1.1–2.3). This association was modified by sex and APOE e4 ($p <$ 0.001 for both), such that the association remained among women (HR = 1.8; 95% CI: 1.1, 3.0) and among those with no APOE e4 allele (HR = 1.6; 95% CI: 1.1, 2.5). There were no significant associations between slope or baseline level of CRP and cognitive decline nor between interleukin-6 and cognitive decline. We believe CRP variability likely reflects poor control of or greater changes in vascular or metabolic disease over time, which in turn is associated with cognitive decline.

1. Introduction

The relationship between inflammation and dementia or Alzheimer's disease (AD) has been widely investigated for several reasons. First, inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP) have been found in the amyloid plaques and neurofibrillary tangles that develop in AD (Neuroinflammation Working Group et al., 2000). It has also been proposed that inflammatory markers contribute to the etiologic progression of dementia via several pathways, including vascular disease and overall neurodegeneration (Brunello et al., 2000; Eagan et al., 2012; Ridker et al., 2002). Although many studies have found a significant association between elevated CRP and IL-6 measured from one time point, and risk of AD or cognitive decline (Kravitz et al., 2009; Schmidt et al., 2002; Yaffe et al., 2003), several studies have not supported such associations (Gallacher et al., 2010; Sundelof et al., 2009; Tan et al., 2007; van Oijen et al., 2005). Although inflammatory markers are variable in nature, it has recently been suggested that levels of inflammation over time have considerable intra-individual variability, and that this fluctuation in levels of inflammatory markers over time is greater than originally expected (deGoma et al., 2012). Specifically, CRP has been shown to have considerable intra-individual variability over time, with a minimum of 3 CRP measurements suggested to accurately determine the association with cardiovascular outcomes (Koenig et al., 2003). Thus, previous studies are greatly limited by having inflammation measured at only one point in time, often many years before the measurement of the outcome. By trying to characterize highly variable inflammatory markers with only one measurement,

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valuable information about how these markers change over time is missing, and such information may provide further insight as to how inflammatory markers are contributing to the process of cognitive decline. More studies are needed to investigate the association between inflammatory markers measured at multiple time points and cognitive function.

The objectives of this study were to examine the association between IL-6 and CRP trajectory patterns and incident cognitive decline and impairment over 10 years. We hypothesized that the slope and variability of IL-6 and CRP trajectories over time would be stronger predictors of cognitive function than individual levels of either marker, because of intra-individual variability over time. A second objective was to determine if these associations were modified by sex or apolipoprotein E (APOE) genotype. As previous studies have found stronger associations among non-APOE e4 carriers and women, we hypothesized that our results would be similar (Eriksson et al., 2011; Kravitz et al., 2009).

2. Methods

2.1. Study population

Community-dwelling white and black older adults were enrolled in the ongoing Health Aging and Body Composition (Health ABC) study. This prospective cohort study began in 1997 and included adults ranging in age from 70 to 79 years at enrollment who lived in Memphis, TN or Pittsburgh, PA. Participants were recruited from a random sample of Medicare eligible adults living within designated zip codes and were eligible if they reported no difficulties performing activities of daily living, walking a quarter mile, or climbing 10 steps without resting. They also had to be free of life-threatening cancers and plan to remain within the study area for at least 3 years. Our analytic cohort consisted of 1323 participants who had CRP and IL-6 measured at a minimum of 3 time points (baseline, plus at least 2 other time points). All participants included in this analytic cohort were also free of cognitive impairment at baseline; consistent with previous literature, cognitive impairment was defined as a Modified Mini-Mental Status Exam (3MS) score <80 (Slinin et al., 2010). This study was approved by the institutional review boards of the University of Pittsburgh and the University of Tennessee, Memphis, and that of the Coordinating Center, the University of California San Francisco. All participants signed a written informed consent.

2.2. Cognitive function

Cognitive function was assessed with the 3MS at baseline (year 1), and study years 3, 5, 8, and 10. The 3MS is an assessment of global cognitive function with components for orientation, concentration, language, praxis, and immediate and delayed memory with scores ranging from 0 to 100 (higher scores indicating higher function) (Teng and Chui, 1987). Consistent with previous studies, we examined 2 potential outcomes: (1)incident cognitive decline defined as the first decline of 5 points or more from baseline, which is equivalent to 1 SD of baseline 3MS scores; and (2) incident cognitive impairment defined as the first occurrence of a score ≤ 80 on the 3MS (Lin et al., 2013; Stweart et al., 2013). We chose to examine both incident cognitive decline and incident cognitive impairment a priori because we believe both outcomes represent clinically important entities; cognitive decline showing a gradual worsening of cognitive function perhaps similar to a diagnosis of mild cognitive impairment, and cognitive impairment indicating a more significant loss in cognitive abilities, perhaps similar to a more severe clinical diagnosis.

2.3. Inflammatory markers

Measures of high sensitivity CRP and IL-6 were obtained from frozen serum collected 5 times throughout the study, at baseline (year 1), and years 2, 4, 6, and 8, between 7 AM and 9 AM, after an overnight fast. Samples were frozen at -70 °C and were shipped to the Core Laboratory at the University of Vermont (Yaffe et al., 2003). At baseline, serum CRP was measured by enzyme-linked immunosorbent assay on the basis of purified protein and polyclonal anti-CRP antibodies, and assays were standardized according to the World Health Organization First International Reference Standard with a sensitivity of 0.08 μg/mL (Kalogeropoulos et al., 2010). In years 2, 4, and 6, serum CRP was measured using an automated chemoluminescent immunoassay system from Diagnostics Products Corporation (Los Angeles, CA, USA) at Wake Forest University. The inter-assay coefficients of variation for this assay were 12%, 10%, and 15% for low, medium, and high ranges, respectively. In year 8, plasma CRP was measured at Wake Forest University from citrated plasma using commercially available high sensitivity assays from R&D Systems (Minneapolis, MN, USA). Because of the different measurement techniques over the years, a calibration based on pilot studies was conducted at Wake Forest University to convert the baseline values and the year 8 values to values comparable with those measured in the other 3 years, and allow for longitudinal analyses. Baseline serum IL-6 was measured by ELISA kits from the R&D Systems (Yaffe et al., 2003). In years 2, 4, and 6, serum IL-6 was measured at Wake Forest University using the high sensitivity Quantikine calorimetric immunoassay kit from R&D Systems. The inter-assay coefficients of variation for this assay were 14%, 11%, and 13% for low, medium, and high ranges, respectively. In year 8, IL-6 was measured at Wake Forest University from citrated plasma using the same kit from R&D Systems as in previous years. Similar to the method used for CRP and because of the different measurement techniques over the years, a calibration based on pilot studies was conducted at Wake Forest University to convert the baseline values and the year 8 values to values comparable with those measured in the other 3 years and allow for longitudinal analyses.

2.4. Covariates

At baseline, demographic data including self-reported participant age, race, sex, and education were recorded. Prevalent disease algorithms based on both self-report and physician diagnoses, recorded medications, and laboratory data were used to create comorbidity variables indicating the presence of diabetes mellitus, hypertension, stroke or transient ischemic attack, and myocardial infarction. Body mass index (BMI) (kg/m^2) was calculated from direct height and weight measurements at baseline. The Center for Epidemiologic Studies Depression Scale was used to assess depressive symptoms with a score ≥ 16 consistent with possible depression (Radloff, 1977). APOE genotype was determined using standard single-nucleotide polymorphism genotyping techniques and dichotomized into having one or more APOE e4 alleles versus no allele (Hixson and Vernier, 1990). Creatinine and cystatin-C were obtained from frozen serum collected at baseline after an overnight fast. Samples were frozen at -70 °C and were shipped to the Core Laboratory at the University of Vermont. An inventory of prescription and over-the-counter medications was recorded at baseline by examining the participants' medication bottle(s). Consistent with a previous study using anti-inflammatory medication use as a covariate, we coded medications according to the Iowa Drug Information System (IDIS) code (Pahor et al., 1994; Yaffe et al., 2003). With use