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The association of mid-to late-life systemic inflammation with white matter structure in older adults: The Atherosclerosis Risk in Communities Study

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ABSTRACT

We examined whether the pattern of middle- to late-life systemic inflammation was associated with white matter (WM) structural abnormalities in older adults. A total of 1532 participants (age = 76.5; standard deviations = 5.4) underwent 3T brain magnetic resonance imaging to quantify white matter hyperintensity volume and whole-brain WM microstructural integrity (fractional anisotropy, mean diffusivity). High-sensitivity C-reactive protein (CRP), a marker of systemic inflammation, was measured at 3 visits (21 and 14 years before, and concurrent with, neuroimaging). Participants were categorized into 1 of 6 groups based on their 21-year pattern of low (<3 mg/L) versus elevated (≥3 mg/L) CRP. Compared to the group with low CRP at all 3 visits, the group that transitioned from low to elevated CRP during midlife demonstrated greatest white matter hyperintensity volume and poorest WM microstructural integrity, after adjusting for demographic variables and cardiovascular risk factors. Participants with high CRP at all visits also demonstrated greater WM structural abnormalities, but only after accounting for differential attrition. These results suggest that increasing and persistent inflammation in the decades spanning middle-to late-life may promote WM disease in older adults.

1. Introduction

Cerebral white matter (WM) abnormalities are common among older adults and are independently associated with cognitive decline and dementia (Hahn et al., 2013; Knopman et al., 2015). Understanding the biological antecedents of these WM changes in older adults has become a priority in recent years. Although systemic inflammation has been associated with WM abnormalities in older adults, it remains unclear whether systemic inflammation is a potential driver of late-life WM changes or merely an associated feature (Wersching et al., 2010; Zhu et al., 2017). With few exceptions (i.e., Bettcher et al., 2015; Metti et al., 2014a, b), previous studies have been limited by the cross-sectional assessment of inflammatory biomarkers, capturing only a snapshot of what is likely a dynamic inflammatory process. Accordingly, it remains unknown how the trajectory and chronicity of systemic inflammation in the decades leading up to older adulthood relates to magnetic resonance imaging (MRI)-defined markers of WM structure in older adults.

Given current theories that implicate aberrant immune functioning and chronic inflammation as potential drivers of neurodegenerative disease, it is essential to develop an understanding of how the long-term trajectory of systemic inflammation influences

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structural brain abnormalities in older adults (Carret-Rebillat et al., 2015; Cunningham and Hennessy, 2015). Using a large community sample of white and African-American adults, the objective of the present study was to examine how the 21-year longitudinal pattern of high-sensitivity C-reactive protein (CRP), a widely used marker of systemic inflammation, relates to the development of white matter hyperintensities (WMH) and diffusion tensor imaging- (DTI) defined WM microstructural abnormalities in nondemented older adults. Specifically, we evaluated the relationship between discrete dynamic patterns of ascending, descending, and persistent mid-to late-life systemic inflammation and measures of WM structure in older adults. We tested the hypothesis that individuals with chronically elevated CRP and a higher average CRP level would have greater WM structural abnormalities as older adults. In light of evidence for sex-and race-based differences in peripheral immune function (Kim et al., 2010; Oertelt-Prigione, 2012), effect modification by these demographic factors, as well as apolipoprotein E (*APO*) ε4 status, was also examined.

2. Methods

2.1. Study population

We conducted an analysis of data from the atherosclerosis risk in communities (ARIC) study, an ongoing community-based, prospective study, which initially enrolled 15,792 adults between ages 45 and 65 from 4 communities within the U.S.: Washington County, MD; Forsyth County, NC; northwestern suburbs of Minneapolis, MN; and Jackson, MS (all African-American) (The ARIC Investigators, 1989). Following a baseline visit (1987–1989), participants were invited back for 3 additional in-person visits occurring approximately 3 years apart until visit 4 (1996–1998) and a fifth visit (visit 5, 2011–2013) approximately 14 years later. The ARIC study protocols were approved by the institutional review boards at each site. All participants gave written informed consent.

Brain MRIs were conducted on a subset of 1,978 participants at visit 5. Selection of participants was based on safety inclusion criteria, previous participation in ARIC brain MRI study (2004–2006), and evidence of cognitive impairment. An age-stratified random sample of participants without cognitive impairment was also included (Knopman et al., 2015). Participant inclusion and exclusion criteria are described in detail in Fig. 1.

2.2. Inflammatory markers

High-sensitivity CRP was measured at visits 2, 4, and 5 from blood stored at −70 °C. Visit 2 CRP (mg/L) was measured from serum using an immunoturbidimetric assay on the Roche Modular P chemistry analyzer (Roche Diagnostics, Indianapolis, IN). Visit 4 CRP was measured from plasma using the nephelometric method on the Siemens Dade Behring BN II analyzer (Siemens Healthcare Diagnostics, Deerfield IL). Visit 5 CRP levels were measured from plasma using an immunoturbidimetric assay on the Beckman Coulter Olympus AU400^e analyzer (Beckman Coulter Inc, Brea, CA). Laboratory calibration studies conducted to evaluate potential CRP measurement differences between laboratories, assay method, instrument, specimen type, and time of measurement found differences that were not large enough to warrant calibration (bias <10%) (Parrinello et al., 2015).

Each participant was categorized as having "low" or "elevated" CRP levels at each visit using a cutoff of 3 mg/L. A CRP level at or above 3 mg/L is suggestive of ongoing systemic inflammation (Castoldi et al., 2007; Nyström, 2007). Using this "low" versus "elevated" CRP dichotomization, participants were categorized into 1 of 6 groups (see Fig. 1), each with a distinct trajectory of mid- to late-life CRP levels.

- Stable low: low CRP levels (<3 mg/L) at all 3 visits
- Early ascending: low CRP at visit 2, and elevated CRP (≥3 mg/L) at visits 4 and 5
- Late ascending: low CRP at visits 2 and 4, and elevated CRP at visit 5
- Early descending: elevated CRP at visit 2, and low CRP at visits 4 and 5
- Late descending: elevated CRP at visits 2 and 4, and low CRP at visit 5
- Stable elevated: elevated CRP at visits 2, 4, and 5.

Each of the 6 prespecified patterns represents an aging/inflammation phenotype that has been described previously in the aging literature (e.g., Franceschi et al., 2007). For example, it has been shown that systemic inflammation increases with age in a subset of individuals (Jenny et al., 2012). Such a transition to a state of elevated systemic inflammation may occur during midlife in some individuals or later in life in others (Cohen-Manheim et al., 2015; Metti et al., 2014a, b). Conversely, there is evidence for aging/inflammation phenotypes characterized by reduced inflammation

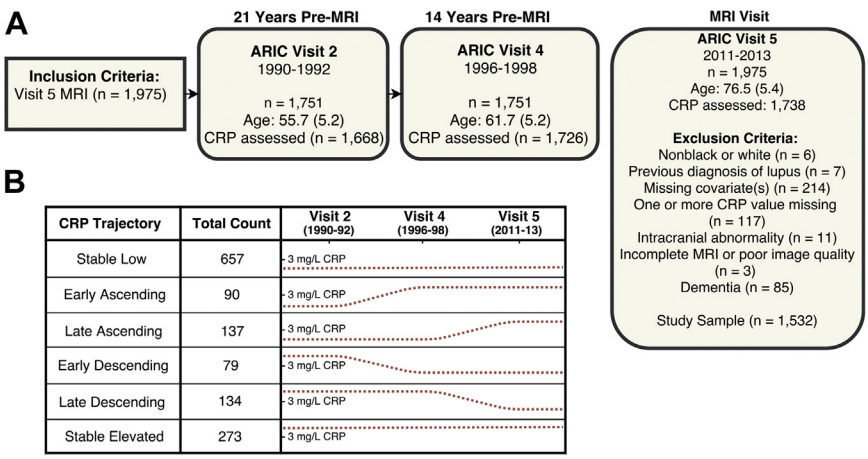

Fig. 1. Study flowchart and CRP trajectory grouping. (A) Study design and primary inclusion and exclusion criteria. (B) Participants were assigned to 1 of 6 CRP trajectory groups based on CRP levels at visits 2, 4, and 5. The dotted line denotes CRP levels at each time point. A line above the tic mark indicates a CRP level ≥3 mg/L. Abbreviation: CRP, C-reactive protein.