Neurobiology of Aging 36 (2015) 948–954

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Declines in inflammation predict greater white matter microstructure in older adults

Brianne Magouirk Bettcher [a,*], Kristine Yaffe [b,c,d,e], Robert M. Boudreau [f], John Neuhaus [a], Howard Aizenstein [g], Jingzhong Ding [h], Stephen B. Kritchevsky [h], Lenore J. Launer [i], Yongmei Liu [h], Suzanne Satterfield [j], Caterina Rosano [f], for the Health ABC study

[a] Neurology Department, Memory and Aging Center, University of California, San Francisco, San Francisco, CA, USA
[b] Department of Psychiatry, University of California, San Francisco, San Francisco, CA, USA
[c] Department of Neurology, University of California, San Francisco, San Francisco, CA, USA
[d] Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA
[e] San Francisco VA Medical Center, University of California, San Francisco, San Francisco, CA, USA
[f] Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA, USA
[g] Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA
[h] The Sticht Center on Aging, Wake Forest School of Medicine, Winston-Salem, NC, USA
[i] Laboratory of Epidemiology and Population Sciences, National Institute on Aging, Bethesda, MD, USA
[j] Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN, USA

ARTICLE INFO

Article history:
Received 22 April 2014
Received in revised form 29 August 2014
Accepted 5 November 2014
Available online 13 November 2014

Keywords:
CRP
Pro-inflammatory
Diffusion tensor imaging
Longitudinal

ABSTRACT

Protracted systemic inflammation has been associated with adverse effects on cognition and brain structure and may accelerate neurodegenerative disease processes; however, it is less clear whether changes in inflammation are associated with brain structure. We studied 276 black and white older adults (mean age = 83 years at time of imaging) enrolled in a prospective study of aging. Inflammation (measured with c-reactive protein, CRP) was assessed repeatedly over 6 years (i.e., year 2, 4, 6, and 8). Brain magnetic resonance imaging (MRIs) were obtained at years 10–11 with diffusion tensor imaging; regions of interest included late-myelinating areas vulnerable to aging, including frontal-parietal (superior longitudinal fasciculus [SLF]-dorsal) and temporal (SLF-temporal; uncinate) white matter tracts. Mean CRP values significantly declined ($t = -5.54$, $p < 0.0001$) over 6 years, and subject-specific slopes (best linear unbiased predictors of slopes) all showed a decline (mean = −0.57, standard deviation = 0.53) for our participant sample. More than 50% of study participants were still in the moderate to high cardiovascular risk range based on CRP values at year 8. After controlling for demographics, vascular risk factors and MRI white matter hyperintensities, larger decreases in CRP values over time were significantly associated with higher fractional anisotropy in the SLF-dorsal (beta = −0.0052, standard error [SE] = 0.003; 95% confidence interval [CI] = −0.0103 to −0.0025, $p = 0.04$), SLF-temporal (beta = −0.0109, SE = 0.004; 95% CI = −0.0189 to −0.0029, $p = 0.008$), and uncinate (beta = −0.0067, SE = 0.003; 95% CI = −0.0132 to −0.0001, $p = 0.05$) fasciculi. Results suggest that in a prospective cohort of older individuals, faster declines in inflammation over time are related to indicators of white matter health, even after accounting for vascular risk factors.

1. Introduction

Sustained proinflammatory processes have damaging effects on neurologic functioning that may hasten cognitive decline (Eikelenboom et al., 2012) and accelerate neurodegenerative disease course (Bermejo et al., 2008; Cunningham et al., 2009; Kravitz et al., 2009; McGeer and McGeer, 2001). Although inflammation was initially conceptualized as a downstream or "bystander" effect of neuronal death, it is now thought to be an early event that may precede the clinical manifestations of neurodegeneration (Bettcher and Kramer, 2013; Cagnin et al., 2001; Mancinella et al., 2009; Yaffe et al., 2004). Moreover, there is growing consensus that inflammatory processes play a contributory role in cognitive decline (Rosano et al., 2012; Tarkowski et al., 1999; Yaffe et al., 2003).

* Corresponding author at: Neurology Department, Memory and Aging Center, 675 Nelson Rising Ln, Suite 190, MC 1207, San Francisco, CA 94158, USA. Tel.: +1 415 476 1451; fax: +1 415 476 0213.
E-mail address: bbettcher@memory.ucsf.edu (B.M. Bettcher).

0197-4580/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2014.11.004

In particular, c-reactive protein (CRP) is an acute phase protein and marker of systemic low-grade inflammation that has received considerable research focus, as it has clear clinical utility in predicting vascular events (e.g., stroke and myocardial infarction), is amenable to risk stratification (Ridker, 2003a, 2003b), and also correlates with age-related cognitive impairment (Noble et al., 2010). Higher levels of CRP have been associated with future development of Alzheimer's disease (Engelhart et al., 2004), and elevations in inflammatory mediators may be present years before a dementia diagnosis (Koyama et al., 2013).

Despite the strong association between higher baseline inflammation and later dementia (Tan et al., 2007), little is known about longitudinal trajectories of inflammation in aging (Metti et al., in press) or how they relate to changes in brain structure. Specifically, although previous studies have suggested that increases in inflammatory markers over time are related to cognitive impairment, cardiovascular disease, and mortality (Danesh et al., 2008; Jenny et al., 2012), it is unclear how increases or decreases in inflammation may associate with neuroanatomy in older adults.

Recent evidence suggests that higher inflammation induces changes in vascular permeability (Cuff et al., 1996), endothelial function (Csiszar et al., 2004), and microvascular structure (Sprague and Khalil, 2009; Zhang et al., 2009), all of which may contribute to the pathogenesis of cerebrovascular disease and alterations in white matter microstructure. Consistent with these potential mechanisms, higher levels of inflammation have recently been associated with lower white matter microstructure in older adults using diffusion tensor imaging (Bettcher et al., 2013; Wersching et al., 2010). However, it is unclear whether the association between inflammation and white matter structure is driven by vascular risk factors or if it is an independent contributor to myelin and axonal integrity. Furthermore, lower white matter microstructure has to date only been related to cross-sectional levels of inflammation, which may obscure the impact of longitudinal change in peripheral proinflammatory markers.

The goal of this study is to assess whether changes in the proinflammatory marker, CRP, are associated with white matter microstructure in a prospective cohort of community-dwelling black and white older adults. We hypothesized that change in CRP levels would predict white matter microstructure in late-myelinating temporal and frontal-parietal tracts, and this association would remain even after controlling for vascular risk and health history factors.

2. Methods

2.1. Study participants

We studied a subset of participants enrolled in the Health, Aging, and Body Composition Study (Health ABC). The Health ABC began in 1997–1998 as a longitudinal observational cohort study of 3075 well-functioning older white and black men and women, 70–79 years old, from Pittsburgh, PA and Memphis, TN (Simonsick et al., 2001) who reported no difficulty walking a quarter of a mile (400 m), climbing 10 steps, or performing activities of daily living. Participants were enrolled if they were free of life-threatening cancers with no active treatment within the prior 3 years and had planned to remain within the study area for at least 3 years. Between 2006 and 2007 (i.e., study years 10 and 11), 315 Health ABC participants from the Pittsburgh site who were interested and eligible for a brain 3T magnetic resonance imaging (MRI) (e.g., no metal implants, pacemaker, and so forth) participated in the ancillary study called the Healthy Brain Project. Medical histories were reviewed to rule out endocrinal, neurologic, and psychological illnesses. Participants received a brain MRI in addition to Health ABC assessments. Among the 315 participants, 310 individuals had at least 2 measurements of blood between baseline and the time of MRI and 276 had complete diffusion tensor imaging data available (see Fig. 1). A global cognitive function measure (Modified Mini Mental Status Exam [3 MS]) and test of executive functions (Digit Symbol Substitution Test [DSST]) were also available for all participants.

This study was approved by the institutional review boards of the clinical site (University of Pittsburgh) and the coordinating center (University of California, San Francisco).

2.2. Inflammatory marker assessment

Blood measures were obtained after an overnight fast, frozen at −70 °C, and shipped to the Health ABC Core Laboratory at the University of Vermont. Serum and plasma levels of CRP were measured in duplicate by enzyme-linked immunosorbent essay based on purified protein and polyclonal anti-CRP antibodies (Calbiochem, San Diego, CA). The CRP assay was standardized according to the World Health Organization's First International Reference Standard, with a sensitivity of 0.08 μg/mL (for clinical risk comparisons, 1 μg/mL = 1 mg/L) (Ridker, 2003a, 2003b). Blind duplicate analyses for CRP showed an average interassay coefficient of variation of 8.0%. CRP measures were available at study years: 2, 4, 6, and 8. Years 2, 4, and 6 utilized serum samples, whereas year 8 employed citrated plasma samples. Year 8 CRP levels were recalibrated for longitudinal comparison with the 3 prior time points (Kalogeropoulos et al., 2010). Across all time points, 14 CRP measurements were considered outliers (i.e., >30 μg/mL) and were removed from further analyses because of concerns that the individuals may have had an acute inflammatory event or an underlying chronic illness. According to standard guidelines for cardiovascular disease risk, CRP levels less than 1.0 μg/mL are considered low, 1.0–2.9 μg/mL intermediate, and greater than 3.0 μg/mL high risk (Ridker, 2003a, 2003b).

2.3. Neuroimaging evaluation

2.3.1. Magnetic resonance imaging acquisition

MRI scanning used a Siemens 12-channel head coil and was performed on a 3 T Siemens Tim TrioMR scanner at the MR Research Center of the University of Pittsburgh in year 10 of the study. Magnetization-prepared rapid gradient echo T1-weighted images were acquired in the axial plane: TR = 2300 ms; TE = 3.43 ms; TI = 900 ms; flip angle = 9; slice thickness = 1 mm; FOV = 256 × 224 mm; voxel size = 1 mm × 1 mm; matrix size = 256 × 224; and number of slices = 176. Diffusion-weighted images were acquired using single-short spin-echo sequence with the following parameters: TR = 5300 ms; TE = 88 ms; TI = 2500 ms; flip angle = 90; FOV = 256 × 256 mm; 2 diffusion values of b = 0 and 1000 s/mm; 12 diffusion directions; 4 repeats; 40 slices; matrix size = 128 × 128; voxel size = 2 mm × 2 mm; slice thickness = 3 mm; and Generalized Autocalibrating Partially Parallel Acquisition (GRAPPA) = 2. A radiologist verified that the T1 MR images for this study did not have abnormalities with potential clinical relevance. No images were excluded because of unexpected findings.

2.3.2. Image processing and analysis

Full imaging protocol details are reported in prior publications (Rosano et al., 2012); in brief, white matter hyperintensity volumes were obtained from T2-weighted fluid-attenuated inversion recovery images using an automated method for quantification and localization of white matter hyperintensity (WMH). The WMH quantification was done using a fuzzy connected algorithm with automated seed selection (Wu et al., 2006). Total WMH volume was