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Circulating inflammatory biomarkers in relation to brain structural measurements in a non-demented elderly population

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ABSTRACT

The aim of this investigation was to determine whether circulating inflammatory biomarkers c-reactive protein (CRP), interleukin-6 (IL6), and alpha 1-antichymotrypsin (ACT) were related to structural brain measures assessed by magnetic resonance imaging (MRI).

High-resolution structural MRI was collected on 680 non-demented elderly (mean age 80.1 years) participants of a community-based, multiethnic cohort. Approximately three quarters of these participants also had peripheral inflammatory biomarkers (CRP, IL6, and ACT) measured using ELISA. Structural measures including brain volumes and cortical thickness (with both global and regional measures) were derived from MRI scans, and repeated MRI measures were obtained after 4.5 years. Mean fractional anisotropy was used as the indicator of white matter integrity assessed with diffusion tensor imaging. We examined the association of inflammatory biomarkers with brain volume, cortical thickness, and white matter integrity using regression models adjusted for age, gender, ethnicity, education, *APOE* genotype, and intracranial volume.

A doubling in CRP ($b = -2.48$, $p = 0.002$) was associated with a smaller total gray matter volume, equivalent to approximately 1.5 years of aging. A doubling in IL6 was associated with smaller total brain volume ($b = -14.96$, $p < 0.0001$), equivalent to approximately 9 years of aging. Higher IL6 was also associated with smaller gray matter ($b = -6.52$, $p = 0.002$) and white matter volumes ($b = -7.47$, $p = 0.004$). The volumes of most cortical regions including frontal, occipital, parietal, temporal, as well as subcortical regions including pallidum and thalamus were associated with IL6. In a model additionally adjusted for depression, vascular factors, BMI, and smoking status, the association between IL6 and brain volumes remained, and a doubling in ACT was marginally associated with 0.054 ($p = 0.001$) millimeter thinner mean cortical thickness, equivalent to that of approximately 2.7 years of aging. None of the biomarkers was associated with mean fractional anisotropy or longitudinal change of brain volumes and thickness.

Among older adults, increased circulating inflammatory biomarkers were associated with smaller brain volume and cortical thickness but not the white matter tract integrity. Our preliminary findings suggest that peripheral inflammatory processes may be involved in the brain atrophy in the elderly.

1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia and the most common neurodegenerative disorder. As no effective cure is available for AD to date, there is a great need to understand its preclinical stage in order to prevent the disease from occurring, or at least prolong delay disease onset. Various pathological changes are believed to occur many years before the clinical

Abbreviations: ACT, alpha 1-antichymotrypsin; APOE, Apolipoprotein; CDR, Clinical Dementia Rating; CRP, C-reactive protein; CT, cortical thickness; DTI, diffusion tensor imaging; FA, fractional anisotropy; IL6, interleukin-6; ICV, intracranial volume; MRI, magnetic resonance imaging; ROI, region of interest; TBV, total brain volume; TGMV, total gray matter volume; TWMV, total white matter volume; WHICAP, Washington Heights/Hamilton Heights Inwood Columbia Aging Project.

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manifestation of AD (Raskin et al., 2015; Jack et al., 2010). Among healthy aging individuals, brain morphological changes, including both macro-(Resnick et al., 2003; Devanand et al., 2007; Driscoll et al., 2009; Querbes et al., 2009; Lerch et al., 2008) and micro-(Vernooij et al., 2009; Rosano et al., 2012) structural changes, are found to be important predictors of cognitive decline and development of AD.

Therefore, understanding factors that are related or contribute to the brain atrophy or disruption of white matter integrity may have important implications for prevention of the disease and intervention at the early stages. Systemic inflammation has been increasingly recognized to play a critical role in AD and other neurodegenerative diseases (Perry, 2010). Increased peripheral levels of C-reactive protein (CRP), interleukin-6 (IL6), and alpha 1-antichymotrypsin (ACT) have been associated with increased risk of dementia, AD, or cognitive decline (Noble et al., 2010; Gunstad et al., 2006; Tan et al., 2007; Dlugaj et al., 2012; Schmidt et al., 2002; Engelhart et al., 2004; Ravaglia et al., 2007; Eriksson et al., 2011; van Himbergen et al., 2012; Koyama et al., 2013; Singh-Manoux et al., 2014; Palta et al., 2015; Reale et al., 2009; Mooijaart et al., 2013; Economos et al., 2013; Yaffe et al., 2003; Dik et al., 2005; Weaver et al., 2002; Licastro et al., 1995; Matsubara et al., 1990).

Inflammation may also be a key contributor to AD-related brain changes. However, only a few studies explored the relationship between peripheral inflammatory biomarkers in relation to brain measures among older adults without dementia, and the results remain inconclusive (Frodl and Amico, 2014). Only three studies (Wersching et al., 2010; Miralbell et al., 2012; Arfanakis et al., 2013) investigated white matter microstructure and showed that systemic inflammation was associated with reduced fractional anisotropy (FA), an indicator of white matter integrity. CRP or IL6 was associated with reduced total brain volume (TBV) Jefferson et al., 2007, total gray matter volume (TGMV) Satizabal et al., 2012; Marsland et al., 2015; Taki et al., 2013, total white matter volume (TWMV) Marsland et al., 2015, and hippocampal volume (Satizabal et al., 2012; Marsland et al., 2015, 2008). However, CRP and IL6 were not associated with brain volumes in other studies (Wersching et al., 2010; Miralbell et al., 2012; Baune et al., 2009; Zhang et al., 2016; Schmidt et al., 2016). Only two studies examined whether inflammatory biomarkers were associated with cortical thickness (CT) and they found inconsistent results (Marsland et al., 2015; McCarrey et al., 2014). In one study of elderly adults, higher IL-6 was associated with accelerated annual rates of cortical thinning in the inferior temporal poles bilaterally (McCarrey et al., 2014), while another study found no cross-sectional associations of IL6 or CRP with CT in adults aged 30–54 years (Marsland et al., 2015). Thus, inconsistency remains regarding the relationship between peripheral inflammatory biomarkers and brain volume; some brain measures such as microstructural white matter integrity (Wersching et al., 2010; Miralbell et al., 2012; Arfanakis et al., 2013), CT (Marsland et al., 2015; McCarrey et al., 2014), as well as regional brain volumes (Marsland et al., 2015) were rarely examined. The role of ACT in brain structure is largely unknown despite its involvement in the Aβ-related pathogenesis in AD (Abraham et al., 1990; Porcellini et al., 2008). Longitudinal data are scarce. Additional studies are needed for older populations who are thought to manifest a systemic, progressive inflammatory state (Franceschi et al., 2000).

We examined whether circulating levels of inflammatory markers most likely to be important for neurodegeneration (i.e., CRP, IL6, and ACT)(Koyama et al., 2013) were associated with macrostructural brain measures (i.e. TBV, TGMV, TWMV, mean CT, and regional brain volumes and CT) and microstructural white matter integrity (using mean FA as the indicator) among elderly participants of a community-based, multiethnic cohort, the Washington Heights/Hamilton Heights Inwood Columbia Aging Project (WHICAP).

2. Materials and methods

2.1. Study participants

The current study included participants from an ongoing prospective study of aging and dementia (WHICAP) who were identified from a probability sample of Medicare beneficiaries elderlies (≥65 years) residing in northern Manhattan (Tang et al., 2001). The original sample for this study included 2776 participants. At baseline, a physician obtained each participant's medical and neurological history, and conducted a standardized physical and neurological examination. Participants also received assessments of health and function, and were assessed using a neuropsychological battery (Stern et al., 1992). Participants were followed every 18 months, repeating the baseline examinations. The diagnosis of dementia or its absence was based on standard research criteria Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R)American Psychiatric Association, 1987, using all available information at a consensus conference. The type of dementia was subsequently determined using the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association for the diagnosis of probable or possible AD (McKhann et al., 1984), and mild cognitive impairment (MCI) was diagnosed using Petersen (Petersen, 2004) criteria as previously described (Manly et al., 2005).

The imaging sub-study was started in 2004 among ongoing dementia-free WHICAP participants (Brickman et al., 2008). In total, 769 WHICAP participants received MRI scans, and they were slightly younger, and were more likely to be African Americans or male compared to those who were eligible but did not undergo MRI (Brickman et al., 2008). Among them, a total of 508 subjects had CRP and 435 had IL6/ACT measured among those with baseline structural MRI scans, 228 had CRP and 195 had IL6/ACT among those received second structural MRI scans 4.5 (SD = 0.8) years later, and 183 had CRP and 154 had IL6/ACT among those who received DTI scan (Fig. 1). A total of 357 subjects were included in the baseline cross-sectional analysis after excluding 78 subjects whose IL6 level were out of the measurement range.

2.2. Standard protocol approvals, registrations, and patient consents

The Columbia University Institutional Review Board has reviewed and approved this project. All individuals provided written informed consent.

2.3. MRI protocol

Scans were acquired on a 1.5T Philips Intera scanner at Columbia University. T1-weighted images were acquired with the following parameters: repetition time, 20 ms; echo time, 2.1 ms; field of view, 240 cm; 256 × 160–pixel matrix with 1.3-mm section thickness, and voxel size 1 × 1 × 1.3 mm. All the T1 images were analyzed using Freesurfer (V.5.1) (http://surfer.nmr.mgh.harvard.edu/). Freesurfer output underwent visual quality control and manual correction whenever necessary, and then Freesurfer steps were repeated. Regional cortical thicknesses and volumetric measures were obtained in 34 regions of interest (ROI) in each hemisphere through a series of steps including removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne et al., 2004), followed by automated Talairach transformation, segmentation of the subcortical white matter (WM) and