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Peripheral inflammatory markers indicate microstructural damage within periventricular white matter hyperintensities in Alzheimer's disease: A preliminary report

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Abstract

Introduction: White matter hyperintensities (WMH) presumed to reflect cerebral small vessel disease and increased peripheral inflammatory markers are found commonly in Alzheimer's disease (AD), but their interrelationships remain unclear.

Methods: Inflammatory markers were assayed in 54 elderly participants ($n = 16$ with AD). Periventricular WMH were delineated from T1, T2/proton density, and fluid-attenuated magnetic resonance imaging using semiautomated fuzzy lesion extraction and coregistered with maps of fractional anisotropy (FA), a measure of microstructural integrity assessed using diffusion tensor imaging.

Results: Mean FA within periventricular WMH was associated with an inflammatory factor consisting of interleukin (IL)-1β, tumor necrosis factor, IL-10, IL-21, and IL-23 in patients with AD ($\rho = -0.703$, $P = .002$) but not in healthy elderly ($\rho = 0.217$, $P = .190$). Inflammation was associated with greater FA in deep WMH in healthy elderly ($\rho = 0.425$, $P = .008$) but not in patients with AD ($\rho = 0.174$, $P = .520$).

Discussion: Peripheral inflammatory markers may be differentially related to microstructural characteristics within the white matter affected by cerebral small vessel disease in elders with and without AD.

Keywords: Small vessel disease; Cerebrovascular disease; Diffusion tensor imaging; Cytokine; Inflammation; Microstructure; White matter disease; Alzheimer's disease; Confirmatory factor analysis

1. Introduction

Many inflammatory markers are increased in peripheral blood in people with Alzheimer's disease (AD), although most findings have been inconsistent, showing high

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heterogeneity between studies [1]. Several studies have suggested longitudinal relationships between peripheral inflammatory markers and cognitive decline in AD [2], but how these observations relate precisely to changes in brain tissue is not well understood.

Lesions to the white matter because of disease of the small cerebral blood vessels may contribute to the onset and progression of AD [3]. Observed clinically as white matter hyperintensities (WMHs) on T2-weighted magnetic resonance imaging (MRI), these lesions may result from hypoperfusion secondary to arteriosclerosis, cerebral amyloid angiopathy, or venous disease with collagenosis or tortuosity [4]. Pathology studies reveal loss of the ventricular ependyma in the vicinity of periventricular WMH and arteriolar sclerosis within deep WMH [4,5]. Immunohistochemistry reveals markers of hypoxia and endothelial activation in WMH, in concert with microglial and astrocyte activation [4], suggesting a link between WMH and inflammatory activation.

The purpose of this study was to determine how peripheral blood cytokines related to AD or implicated in hypoxic responses are related to deep and periventricular WMH, both in people with and without AD. Recently reduced microstructural integrity was found in WMH, with lower fractional anisotropy (FA) particularly in cases of more severe WMH [6]. Appreciating that WMHs are associated with inflammatory mechanisms that may threaten white matter microstructural integrity, here we examine the relationship between peripheral inflammatory markers and FA within white matter lesions.

2. Methods

To represent strata of high WMH and low WMH burden, patients from transient ischemic attack (non-AD with extensive WMH) and memory clinics (AD with and without extensive WMH) and healthy control subjects of similar age (minimal WMH) were recruited. Patients with cortical infarcts were excluded.

MRI (T1, proton density/T2, and fluid-attenuated inversion recovery [FLAIR]) was performed at 3.0 T and intensity inhomogeneity corrected using N3. Deep and periventricular WMH were delineated using Lesion Explorer, an in-house semiautomatic segmentation (www.sabre.brainlab.ca) with a three-dimensional connectivity algorithm [7].

Diffusion tensor imaging (DTI) was obtained, and WMH masks were transformed to DTI space using parameters obtained from the T2 and the DTI B0 images. Values of FA were derived after eddy-current and motion-correction using the FMRIB Diffusion Toolbox; means, medians, and standard deviations were calculated for deep and periventricular WMH regions separately.

Certain inflammatory markers with suspected roles in AD [1] or cerebral hypoxic responses [8–10] were assayed by multiplex magnetic bead immunoassay (EMD Millipore) from serum samples obtained at the time of MRI (stored at −80°C). It was considered that hypoxia might contribute to the production of interleukin (IL)-23, IL-21, and IL-17 cytokines [9]; tumor necrosis factor (TNF), IL-1β, and IL-6 are also involved in hypoxic responses [10] and AD [1]; and these can induce IL-10 release [10] as part of the immune response. Confirmatory factor analysis (CFA) was used to identify a single factor accounting for variation (and covariation) in cytokine data (Mplus, version 7.4, Muthén & Muthén, Los Angeles, CA, USA). To evaluate the proposed model we considered a nonsignificant χ^2, comparative fit index >0.90, Tucker-Lewis Index >0.95, root mean square error of approximation <0.06, and weighted root mean square residual near or <0.08 to indicate adequate fit [11]. Inflammatory factor scores were compared with mean FA values in deep and periventricular WMH using Spearman's rho in AD and non-AD participants separately, and Bonferroni corrected ($\alpha = 0.05/4$).

3. Results

Concentrations of IL-1β, TNF, IL-10, IL-21, and IL-23 informed an inflammatory factor (Fig. 1) with excellent fit indices ($\chi^2_{(5)} = 6.8774$, $P = .230$; root mean square error of approximation = 0.070, comparative fit index = 0.972, Tucker-Lewis Index = 0.945, and weighted root mean square residual = 0.049), although IL-6, IL-17A, and IL-17F were excluded from the model because of poor factor loadings, resulting in poor fit indices.

MRI volumetrics and FA maps were obtained for 54 participants including 16 AD (76.4 ± 7.7 years, 51.2% male) and 38 non-AD subjects (71.4 ± 9.5 years, 44.8% male) similar in age and gender proportion ($P > .05$). Volumes of deep (2136 ± 2550 vs. 1627 ± 2049 mm^3, $P = .331$) and periventricular (19,274 ± 21,947 vs. 15,812 ± 19,279 mm^3, $P = .464$) WMH did not differ between AD and non-AD participants. Mean FA in deep

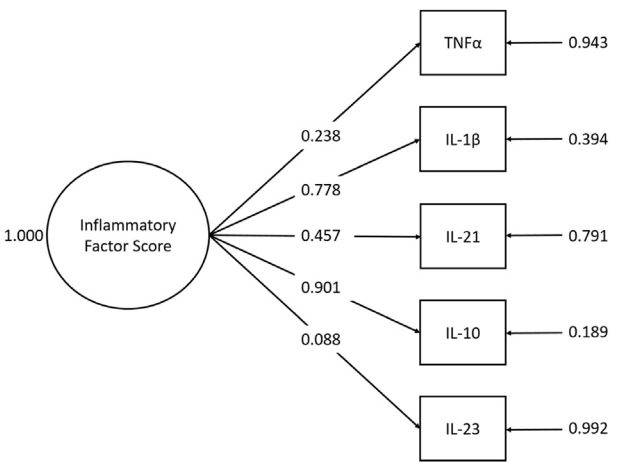

Fig. 1. Structure of an inflammatory factor informed by five cytokines. Factor loadings onto the inflammatory factor for each cytokine shown in column at right and residual variances shown in column at left. Abbreviations: IL, interleukin; TNF, tumor necrosis factor.