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Vascular Contributions to Alzheimer's Disease

Serum IL-8 is a marker of white-matter hyperintensities in patients with Alzheimer's disease

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Abstract

Introduction: Neuroinflammation and cerebrovascular disease (CeVD) have been implicated in cognitive impairment and Alzheimer's disease (AD). The present study aimed to examine serum inflammatory markers in preclinical stages of dementia and in AD, as well as to investigate their associations with concomitant CeVD.

Methods: We performed a cross-sectional case–control study including 96 AD, 140 cognitively impaired no dementia (CIND), and 79 noncognitively impaired participants. All subjects underwent neuropsychological and neuroimaging assessments, as well as collection of blood samples for measurements of serum samples interleukin (IL)-6, IL-8, and tumor necrosis factor α levels. Subjects were classified as CIND or dementia based on clinical criteria. Significant CeVD, including white-matter hyperintensities (WMHs), lacunes, and cortical infarcts, was assessed by magnetic resonance imaging.

Results: After controlling for covariates, higher concentrations of IL-8, but not the other measured cytokines, were associated with both CIND and AD only in the presence of significant CeVD (CIND with CeVD: odds ratios [ORs] 4.53; 95% confidence interval [CI] 1.5–13.4 and AD with CeVD: OR 7.26; 95% CI 1.2–43.3). Subsequent multivariate analyses showed that among the types of CeVD assessed, only WMH was associated with higher IL-8 levels in CIND and AD (WMH: OR 2.81; 95% CI 1.4–5.6).

Discussion: Serum IL-8 may have clinical utility as a biomarker for WMH in AD. Longitudinal follow-up studies would help validate these findings.

Keywords: Alzheimer's disease; Cognitive impairment; Dementia; Inflammation; Cerebrovascular disease; White-matter hyperintensities; IL-8

1. Introduction

Alzheimer's disease (AD), characterized by progressive loss of memory and cognitive function, is the most common form of dementia in the elderly [1], and a major

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source of health care burden worldwide. By 2050, the worldwide prevalence of AD will be quadruple that in 2006, which translates to 1 in every 85 people worldwide having AD [2].

Originally regarded as an "immune privileged" organ, the brain is now well known to exhibit key features of inflammation. Accumulating evidence suggests that neuroinflammation plays an essential role in AD pathogenesis [3], with alterations of brain cytokine levels reported [4,5]. Furthermore, activated microglia and astrocytes as well as increased concentrations of inflammatory mediators have been detected in the vicinity of amyloid plaques and neurofibrillary tangles in AD brain [3]. Indeed, meta-analyses of observational studies indicate a significant association between the long-term use of nonsteroidal anti-inflammatory drugs and lowered risk of AD [6].

Neuroinflammation, when occurring in the acute phase and resolved in a timely manner, is beneficial in combating pathogens and in tissue repair. But a chronic neuroinflammatory response may contribute to neurodegeneration [7]. Cytokines released from such neuroinflammatory processes are known to be mirrored in the periphery, thus allowing measurements of potential biomarkers [8,9], which at present include cerebrospinal fluid (CSF) markers (combined phosphotau and β-amyloid 38/42) and neuroimaging (hippocampal atrophy, amyloid positron emission tomography) [10–12]. However, the invasiveness and high costs associated with neuroimaging and CSF investigations have hindered their wide clinical application. In contrast, the minimal invasiveness and relative low cost of blood-based investigations have stimulated research into assessments of their feasibility as diagnostic and prognostic biomarkers. Indeed, several studies of circulating cytokines have been reported (albeit with inconsistent findings), with the majority of these studies focused on staging after a diagnosis of dementia has been made [4,5,13–16]. As neuroinflammation is thought to be involved in disease pathogenesis in early stages, it is important to also investigate inflammatory markers in predementia stages such as mild cognitive impairment or cognitive impairment no dementia (CIND), which are associated with increased risk of AD but may also represent better prospects for treatment and/or prevention [17,18].

Besides β-amyloid mismetabolism and tau hyperphosphorylation, vascular disease has been suggested to play a role in AD [19]. Several neuroimaging markers of cerebrovascular disease (CeVD), such as white-matter hyperintensities (WMHs), cortical infarct, and lacunes, have been shown to be associated with AD [20], and may exacerbate the severity of dementia [21,22]. However, in previous inflammatory marker studies, the impact of CeVD was generally neglected. In this study, we aimed to measure serum proinflammatory cytokines, including interleukin 6 (IL-6), IL-8, and tumor necrosis factor α (TNFα), in a memory clinic cohort of CIND and AD who underwent neuroimaging assessments for CeVD.

2. Methods

2.1. Study cohort

A case–control design was used. Cases (CIND and dementia) with subjective complaints of memory loss and cognitive impairment on neuropsychological assessment were recruited from memory clinics from National University Hospital and Saint Luke's Hospital in Singapore. Controls were recruited from both memory clinics and the community and were defined as those with subjective memory impairment complaints but who were cognitively normal on objective neuropsychological assessment. All subjects underwent clinical, physical, and neuropsychological assessments and neuroimaging at the National University of Singapore from August 2010 till May 2014. Ethics approval for this study was obtained from the National Healthcare Group Domain-Specific Review Board (DSRB reference: 2010/00017; study protocol number: DEM4233), and written informed consent had been obtained from participants or their next-of-kin before study recruitment and procedures. The study was conducted in accordance with the Declaration of Helsinki.

2.2. Questionnaires

Relevant demographic and medical information was collected by administration of a detailed questionnaire. Data collected included age, gender, education, marital status, occupation, smoking, alcohol intake, ability to live independently, handedness, previous head trauma, and family history of dementia. Inquiries on medical history included stroke, cardiovascular diseases, hypertension, hyperlipidemia, diabetes mellitus, vitamin B12 deficiency, thyroid disease, urinary, and bowel incontinence, Parkinson disease, depressive symptoms, and psychiatric illnesses and were subsequently verified by review of the medical records. Barthel activities of daily living indices were assessed for functional status.

2.3. Neuroimaging

As previously described [23,24], a 3T Siemens Magnetom Trio Tim scanner with a 32-channel head coil was used for magnetic resonance imaging (MRI) at the Clinical Imaging Research Center of the National University of Singapore. CeVD was assessed using MRI markers for lacunes, cortical infarcts, and WMHs. Briefly, the presence and quantification of lacunes and cortical infarcts were defined on FLAIR and T2 sequences using the STRIVE criteria [25], whereas WMH grading was based on the Age-Related White Matter Changes (ARWMC) scale [26]. Significant CeVD was defined as the presence of cortical infarct and/or presence of two or more lacunes, and/or confluent WMH (ARWMC score $\geq$8) in two regions of the brain [23,24].

2.4. Assessments for cognitive impairment and AD

Diagnosis of cognitive impairment and dementia were made at weekly consensus meetings attended by clinicians and neuropsychologists, where clinical histories, psychometrics, and neuroimages were reviewed. CIND cases were diagnosed by clinical judgment and further confirmation by neuropsychological tests, namely, impairment in at least one domain of the neuropsychological test battery consisting of executive function, attention, language, visuomotor speed, visuoconstruction, verbal memory, and visual memory, in patients who did not meet the criteria for dementia [23,24]. AD cases were diagnosed using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association criteria. Noncognitively impaired (NCI) subjects were those assessed to be normal by neuropsychological tests.

2.5. Peripheral inflammatory markers

Nonfasting blood samples collected in serum-separating tubes were centrifuged at 2000 rcf for 10 minutes at 4°C, after which aliquots of serum were mixed well and stored at −80°C until use. All samples were subject to only one freeze-thaw cycle. Concentrations of interleukin 6 (IL-6), IL-8, and TNFα were measured in duplicate by multiplex xMAP®-based Luminex assays (Millipore Corp., Billerica, MA, USA) per manufacturer's instructions. The detectable concentration range of inflammatory markers is from 0.2 to 15,000 pg/mL (IL-6), 0.3 to 10,000 pg/mL (IL-8), and 0.3 to 10,000 pg/mL (TNFα).

2.6. Covariates

Demographic information and information about risk factors such as hypertension, hyperlipidemia, diabetes, smoking, and cardiovascular diseases were collected from physical and clinical interview and medical records and classified as absent or present. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or use of antihypertensive medications. Cardiovascular diseases were classified as a previous history of atrial fibrillation, congestive heart failure, and/or myocardial infarction. Apolipoprotein E (*APOE*) genotyping using DNA extracted from the buffy coat of blood samples were as previously described [27] for the determination of *APOE* ε4 carrier status (presence of at least one *APOE* ε4 allele).

2.7. Statistical analyses

Statistical analysis was performed using SPSS software (version 21, IBM Inc., Armonk, NY, USA). For group comparisons, one-way analyses of variance (ANOVAs) were used for normally distributed continuous variables (age); chi-square tests for categorical variables (gender, education, *APOE* ε4, hypertension, hyperlipidemia, smoking, diabetes, cardiovascular disease); nonparametric Kruskal–Wallis ANOVA with Dunn's post hoc were used for skewed distributed continuous variables (inflammatory markers). Binary logistic regression was used to assess the association between inflammatory markers and primary diagnosis (NCI, CIND, or AD). The levels of inflammatory markers were included as determinants in the logistic models and were categorized into tertiles, whereas CIND and AD were listed as outcomes. Odds ratios and 95% confidence intervals were reported for both CIND and AD. All the models were adjusted for age, gender, education, *APOE* ε4 carrier status, diabetes mellitus, hypertension, and cardiovascular diseases. A *P*-value of <.05 was considered statistically significant for all analyses.

3. Results

A total of 383 elderly subjects (95 NCI, 164 CIND, 124 AD) were recruited, of whom 315 (79 NCI, 140 CIND, and 96 AD) had available blood samples and MRI data. Of

Table 1
Demographic characteristics and inflammatory markers stratified by baseline diagnosis

Characteristics	NCI, $n = 79$	CIND, $n = 140$	AD, $n = 96$	*P*-value
Age, year, mean (SD)	68.27 (6.0)	71.23 (8.1)	77.25 (7.3)	**<.001***
Female, *n* (%)	41 (51.9)	67 (47.9)	60 (62.5)	.08
Low education, *n* (%)	24 (30.4)	67 (47.9)	73 (76)	**<.001**†
APOE genotype‡				
APOE ε2 carrier, *n* (%)	8 (10.1)	16 (11.4)	16 (16.7)	.36
APOE ε3 carrier, *n* (%)	76 (96.2)	134 (95.7)	88 (91.7)	.31
APOE ε4 carrier, *n* (%)	14 (17.7)	42 (30.0)	32 (33.3)	.06
Diabetes mellitus, *n* (%)	17 (21.5)	53 (37.9)	44 (45.8)	**.003**†
Hypertension, *n* (%)	43 (45.4)	96 (68.6)	81 (84.4)	**<.001**†
Hyperlipidemia, *n* (%)	53 (67.1)	106 (75.7)	70 (72.9)	.39
Smoking, *n* (%)	18 (22.8)	42 (30.0)	27 (28.1)	.51
Cardiovascular disease, *n* (%)	4 (5.1)	23 (16.4)	18 (18.8)	**.02**†
Inflammatory markers				
IL-6, pg/mL, median (range)	0.78 (11.9)	1.03 (45.3)	1.59 (59.8)	**.046**§
IL-8, pg/mL, median (range)	4.53 (12.2)	5.42 (20.2)	5.90 (44.8)	**<.001**‖
TNFα, pg/mL, median (range)	4.05 (12.9)	4.51 (15.2)	5.28 (16.6)	**.001**¶

Abbreviations: NCI, noncognitively impaired; CIND, cognitive impairment no dementia; AD, Alzheimer's disease; SD, standard deviation; IL, interleukin; TNFα, tumor necrosis factor α; ANOVA, analysis of variance.

NOTE. Bold text indicates *P* values <.05.

*Significant one-way ANOVA with post hoc Bonferroni tests: NCI versus CIND, $P = .01$; NCI versus AD, $P < .001$; CIND versus AD, $P < .001$.

†Significant chi-square tests.

‡*APOE* genotype: *APOE* ε2, *APOE* ε3, *APOE* ε4 carrier denotes presence of at least one *APOE* ε2, *APOE* ε3, or *APOE* ε4 alleles, respectively.

§Significant Kruskal–Wallis ANOVA with post hoc Dunn's tests: NCI versus AD, $P = .02$.

‖Significant Kruskal–Wallis ANOVA with post hoc Dunn's tests: NCI versus CIND, $P < .01$; NCI versus AD, $P < .001$.

¶Significant Kruskal–Wallis ANOVA with post hoc Dunn's tests: NCI versus AD, $P = .001$.

these, 17 NCI (21.5%), 68 CIND (48.6%), and 53 AD (55.2%) subjects had significant CeVD on MRI. Table 1 shows the demographic variables of the study cohort. In comparison to NCI, CIND and AD were older, had lower education levels, higher prevalence of diabetes, hypertension, and cardiovascular disease. The concentration values of inflammatory markers in the samples ranged from 0.3 to 60.0 pg/mL for IL-6, 1.3 to 47.0 pg/mL for IL-8, and 0.9 to 17.5 pg/mL for TNFα. The lowest detectable values were used in statistical analyses for cases whose concentrations fell below detectable range (0.2 pg/mL was used for IL-6 for 28 cases in NCI group, 50 cases in CIND group, and 20 cases in AD group; 0.3 pg/mL was used for TNFα for two cases in NCI group and 1 case in CIND group). As shown in Table 1, levels of IL-6, IL-8, and TNFα were highest in AD and lowest in NCI, with intermediate levels in CIND. The differences were statistically significant for IL-8 in both CIND and AD, whereas IL-6 and TNFα were significantly raised only in AD.

Table 2 shows the multivariate analyses of associations between serum inflammatory markers and clinical diagnoses. There was no association between IL-6 and CIND or AD after adjustment for covariates of age, gender, education, *APOE* ε4 carrier, diabetes mellitus, hypertension, and cardiovascular diseases, whereas the highest tertile of IL-8 was associated with CIND and AD. In contrast, the highest tertile of TNFα was associated with AD but not CIND when unadjusted (data not shown), but the association did not remain after adjusting for covariates. Interestingly, when stratified by the presence or absence of significant CeVD (Table 3), the highest tertile of IL-8 was associated with both CIND and AD only in the presence of CeVD, whereas no associations were found for IL-6 and TNFα in the presence or absence of CeVD. Finally, to uncover whether IL-8 was associated with a specific type of CeVD, we performed separate logistic regression analyses for WMH, presence of cortical infarcts and lacunes with adjustment for unmatched demographic and risk factors, as well as the corresponding nontested MRI markers. Table 4 shows the association between the highest tertile of IL-8 and MRI markers was with WMH (ARWMC total score ≥ 8), but not with presence of cortical infarct nor lacunes (two or more).

Table 2
Association of inflammatory markers (in tertiles) with CIND and AD, expressed as odds ratios with 95% confidence intervals

Inflammatory markers	CIND odds ratio (95% CI)*	AD odds ratio (95% CI)*
IL-6		
1st tertile	1	1
2nd tertile	0.72 (0.4–1.5)	1.29 (0.5–3.6)
3rd tertile	0.95 (0.5–2.0)	1.15 (0.4–3.4)
IL-8		
1st tertile	1	1
2nd tertile	0.81 (0.4–1.6)	0.57 (0.2–1.6)
3rd tertile	**2.80 (1.2–6.7)**	2.41 (0.7–8.9)
TNFα		
1st tertile	1	1
2nd tertile	1.27 (0.6–2.7)	1.00 (0.3–2.9)
3rd tertile	1.17 (0.5–2.5)	1.23 (0.4–3.6)

Abbreviations: CIND, cognitive impairment no dementia; AD, Alzheimer's disease; CI, confidence interval; IL, interleukin; TNFα, tumor necrosis factor α.

NOTE. *N* values for CIND = 140; AD = 96. Bold text indicates *P* values <.05.

*Adjusted for age, gender, education, *APOE* ε4 carrier, diabetes mellitus, hypertension, and cardiovascular diseases.

4. Discussion

Although all three inflammatory markers (IL-6, IL-8, and TNFα) were found to be significantly different among NCI, CIND, and AD patients, only elevated IL-8 was associated with CIND and AD after adjustment for age, gender, education, *APOE* ε4 carrier, diabetes mellitus, hypertension, and cardiovascular diseases. Furthermore, the associations with IL-8 were significant only in the presence of CeVD, and more specifically, with the presence of WMH when adjusted for covariates.

IL-8 (also known as CXCL8) is a chemokine which induces chemotaxis in target cells, migrating neutrophils, basophils, and T cells to the site of infection [28]. In this study, we found that high-serum IL-8 was associated with both CIND and AD only in the presence of CeVD, specifically with significant WMH, independent of age, gender, education, *APOE* ε4 carrier status, diabetes mellitus, hypertension, cardiovascular diseases, as well as cortical infarct and lacunes. This finding corroborates previous work showing high IL-8 in cognitively impaired patients associated with vascular cognitive impairment [29]. IL-8 has been known to initiate acute inflammation, and our data support the involvement of elevated IL-8 in the chronic neuroinflammation of AD which may be related to cerebrovascular damage [30]. Actually, significant elevations in plasma IL-8 levels in cognitive impairment have also been reported by others [5,13], although there are also conflicting data showing lower IL-8 level in mild cognitive impairment and AD [31]. The mechanism underlying associations of IL-8 with WMH is at present unclear. The disease processes may be related to microglial activation-associated upregulation of cytokines besides inducible nitric oxide synthase [32], which in turn trigger increases in proinflammatory and pro-oxidant nitric oxide, affect brain microvessel endothelia, and result in white-matter lesions detectable as WMH by MRI [33,34]. Although these lesions have been shown to be associated with, and predict for, cognitive impairment [35–37], whether such processes actually link IL-8 with white-matter lesions will require follow-up studies.

IL-6 can be produced by a variety of immune cells as well as endothelial cells and fibroblasts and is a primary inducer of acute proteins and hormones which mediate fever and immune cell expansion in response to infection or injury [28]. Interestingly, IL-6 also has anti-inflammatory

Table 3
Associations of inflammatory markers with CIND and AD stratified by the presence of CeVD, expressed as odds ratios with 95% confidence intervals

	With CeVD*		Without CeVD*	
Inflammatory markers	CIND odds ratio (95% CI)	AD odds ratio (95% CI)	CIND odds ratio (95% CI)	AD odds ratio (95% CI)
IL-6				
1st tertile	1	1	1	1
2nd tertile	0.73 (0.3–1.8)	0.84 (0.2–3.4)	0.65 (0.3–1.6)	2.12 (0.6–7.7)
3rd tertile	0.89 (0.4–2.1)	0.96 (0.3–3.6)	0.86 (0.4–2.1)	1.14 (0.3–4.6)
IL-8				
1st tertile	1	1	1	1
2nd tertile	1.00 (0.4–2.4)	0.31 (0.1–1.5)	0.58 (0.3–1.3)	0.74 (0.2–2.6)
3rd tertile	**4.53 (1.5–13.4)**	**7.26 (1.2–43.3)**	1.99 (0.7–5.4)	1.09 (0.2–5.7)
TNFα				
1st tertile	1	1	1	1
2nd tertile	1.17 (0.5–2.9)	0.86 (0.2–3.6)	1.31 (0.6–3.0)	0.99 (0.3–3.7)
3rd tertile	1.42 (0.6–3.5)	1.32 (0.3–5.6)	1.00 (0.4–2.5)	1.12 (0.3–4.3)

Abbreviations: CIND, cognitive impairment no dementia; AD, Alzheimer's disease; CeVD, cerebrovascular disease; CI, confidence interval; IL, interleukin; TNFα, tumor necrosis factor α.

NOTE. N values for CIND with CeVD = 68; AD with CeVD = 53. Bold text indicates P values <.05.

*Adjusted for age, gender, education, *APOE* ε4 carrier, diabetes mellitus, hypertension, and cardiovascular diseases.

effects [38]. This functional dichotomy may underlie conflicting results where a few studies have shown increased levels of serum or plasma IL-6 levels in AD [4,15], whereas other studies reported unchanged peripheral levels of IL-6 between control, mild cognitive impairment, and AD [14,39–41]. In the present study, although higher IL-6 was found in AD, subsequent multivariate analyses did not support associations of serum IL-6 with AD or concomitant CeVD.

TNFα is a proinflammatory cytokine, produced primarily by activated macrophages, T cells, and NK cells. It is a mediator of both acute and chronic inflammation and can activate vascular endothelium and increase vascular permeability [28]. Similar to the other markers, there are inconsistent results on the status of peripheral TNFα in AD with reports of significantly lower [14,42], unchanged [43,44], or increased [45,46] TNFα in mild cognitive impairment and/or AD. The present study showed that, like the other two markers, serum TNFα was increased in AD, although the association was not statistically significant when adjusted for covariates. This suggests confounding by concomitant risk factors. Indeed, there is evidence of TNFα involvement in cardiovascular disease [47–49] which was included as a covariate in our study.

The strengths of this study include the following: (1) a relatively large cohort; (2) inclusion of covariates such as age, gender, education, *APOE* ε4 carrier status, diabetes mellitus, hypertension, and cardiovascular diseases in analyses; and (3) use of neuroimaging to classify cases with CeVD and hence allowing the assessment of CeVD impact. However, our study has several limitations as well. First, because of the case–control design of the study, it is not possible to establish the temporal association between these markers and the development of cognitive impairment. Further follow-up prospective validation studies will address these limitations. Furthermore, the cases and controls, though representative of the elderly population in Singapore, were derived from two settings, that is, memory clinic and community. Finally, the control group was relatively younger and had lower CeVD burden compared to cases which could have resulted in selection bias and residual confounding.

In conclusion, the present study suggests that IL-8 has potential clinical utility as a biomarker of small vessel CeVD

Table 4
Associations of IL-8 (in tertiles) with MRI markers of CeVD, expressed as odds ratios with 95% confidence intervals

Inflammatory marker	WMH (ARWMC ≥ 8), odds ratio (95% CI)*	Cortical infarct, odds ratio (95% CI)†	≥2 lacunes, odds ratio (95% CI)‡
IL-8			
1st tertile	1	1	1
2nd tertile	1.28 (0.7–2.5)	2.10 (0.6–7.6)	0.94 (0.3–3.2)
3rd tertile	**2.81 (1.4–5.6)**	3.50 (0.9–13.1)	2.70 (0.9–8.4)

Abbreviations: IL, interleukin; MRI, magnetic resonance imaging; CeVD, cerebrovascular disease; WMH, white-matter hyperintensity; ARWMC, age-related white-matter changes; CI, confidence interval; CIND, cognitive impairment no dementia.

NOTE. N values for CIND with CeVD = 68; AD with CeVD = 53. N values for significant WMH (ARWMC ≥ 8) = 118, cortical infarcts = 28, lacunes (≥2) = 37. Bold text indicates P values <.05.

*Adjusted for age, gender, education, *APOE* ε4 carrier, hypertension, diabetes mellitus, cardiovascular diseases, presence of cortical infarct, and lacunes.

†Adjusted for age, gender, education, *APOE* ε4 carrier, hypertension, diabetes mellitus, cardiovascular diseases, WMH, and presence of lacunes.

‡Adjusted for age, gender, education, *APOE* ε4 carrier, hypertension, diabetes mellitus, cardiovascular diseases, WMH, and presence of cortical infarct.

such as WMH in cognitive impairment and AD. However, follow-up longitudinal studies are needed for validation.

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RESEARCH IN CONTEXT

1. Systematic review: Although neuroinflammation is widely considered to play a pathogenic role in Alzheimer's disease (AD), the extent to which changes in peripheral inflammatory markers may reflect concomitant cerebrovascular disease (CeVD) has not been studied in either cognitive impairments no dementia (CIND), a predementia stage, or in AD, despite evidence in the literature indicating the exacerbating effects of concomitant CeVD on dementia severity.
2. Interpretation: Of the three acute inflammatory markers investigated, only elevated IL-8 was associated with white-matter hyperintensities in CIND and AD, suggesting that interleukin-8 is a potential biomarker for small vessel CeVD in cognitive impairment and AD.
3. Future directions: A case–control design was used for our study. Follow-up longitudinal studies are needed for validation.

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