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Change in Inflammatory Markers and Cognitive Status among Oldest Old Women from the Study of Osteoporotic Fractures

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Abstract

OBJECTIVES—To determine the association between interleukin-6 (IL-6), IL-6 soluble receptor (sR) and tumor necrosis factor soluble receptor-1 (STNF-R1) and cognitive status among oldest old women.

DESIGN—20-year longitudinal cohort study.

SETTING—Four clinical sites in the United States.

PARTICIPANTS—905 women from the Study of Osteoporotic Fractures (mean age 88.3±2.8 years at cognitive status adjudication).

MEASUREMENTS—At Year 20, cognitive status was adjudicated as normal, mild cognitive impairment (MCI), or dementia. Inflammatory markers were measured from blood serum at Years 10 and 16 in a random sample of women.

RESULTS—Over 10 years, 199 (22.0%) developed MCI, and 145 (16.0%) dementia. There were no significant associations between IL-6 or STNF-R1 and cognitive status. High IL-6 sR

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Author Contributions: Dr. Metti contributed to study concept and design, data analysis, interpretation of data, and preparation of manuscript. Drs. Cauley, Yaffe and Stone all serve as SOF investigators, and thus were crucial in acquisition of data. Drs. Cauley and Yaffe contributed substantially to study concept and design, interpretation of data, and preparation of manuscript. Drs. Ganguli, Lopez, and Stone also contributed to interpretation of data and preparation of manuscript. Finally, Dr. Boudreau contributed to data analysis, interpretation of data, and preparation of manuscript.

(≥37401.36pg/ml, high tertile) at Year 16 was significantly associated with decreased risk for dementia (OR=0.54; 95% CI: 0.30, 0.97), compared to women with lower levels (<37401.36 pg/ml, lower two tertiles). Women with high IL-6 sR at both time points (OR=0.39; 95% CI: 0.17, 0.89) or who transitioned to a high level (OR=0.35; 95% CI: 0.14, 0.88) had reduced risk of dementia.

CONCLUSION—In this cohort of white, high functioning oldest old women, a consistently high or an increasing level of IL-6 sR is associated with reduced risk of dementia. Compared to other studies of younger old adults, this suggests the effect of inflammation on dementia may differ in younger old and oldest old. Understanding these differences will be crucial in interpreting results from ongoing clinical trials and in targeting therapeutic strategies to the oldest old.

Keywords

Dementia; mild cognitive impairment; inflammation; oldest old

INTRODUCTION

Although the prevalence of dementia continues to increase exponentially in the oldest old (≥85 years), little is known about risk factors for dementia in this group.[1] Both age and inflammation are associated with elevated risks of cognitive impairment, decline, and Alzheimer's disease (AD).[2–6] Intriguingly, the relationships between inflammatory markers and these disorders appear to weaken with advancing age, with studies showing inconsistent results among the oldest old.[7–11] This is critically important to understanding disease mechanisms and to designing appropriate intervention strategies. For example, clinical trials are currently investigating the potential role of anti-inflammatory drugs in AD patients,[12–14] and if there is a different association between inflammation and dementia among the oldest old, understanding these differences will be crucial in interpreting results from these trials and in targeting therapeutic strategies to the oldest old. Some limitations to the existing studies are cross-sectional study design, or measuring inflammatory markers at only one time point in longitudinal studies.[8, 10, 11] Thus, more studies are needed to determine the association between inflammation and cognitive status in the oldest old, and to investigate if change in inflammation over time is associated with cognitive function. Furthermore, very few studies have investigated the role of inflammatory marker soluble receptors. Thus, the objectives of this study were to determine the association between interleukin-6 (IL-6), the IL-6 soluble receptor (IL-6 sR) and tumor necrosis factor soluble receptor-1 (STNF-R1) measured at an initial and an interim visit and subsequent cognitive status among oldest old women. Because we had inflammation measured at more than one time point, a second objective was to determine the association between change in each inflammatory marker and cognitive status.

METHODS

Study Sample

The Study of Osteoporotic Fractures (SOF) is a prospective cohort study of community-dwelling women, with recruitment of 9,704 mostly Caucasian (99% non-Hispanic white)

women, aged 65 years or older occurring between 1986 and 1988 from four regions: Baltimore County, Maryland; Minneapolis, Minnesota; Portland, Oregon; and the Monongahela Valley near Pittsburgh, Pennsylvania. Originally designed to evaluate risk factors for falls and fractures, exclusion criteria included being unable to walk without assistance, and bilateral hip replacement. All women provided informed written consent, and SOF was approved by the Institutional Review Board (IRB) and each study site.

Between 1997 and 1998, serum IL-6, IL-6 sR and STNF-R1were measured from blood drawn at the SOF Year 10 visit; thus SOF Year 10 will serve as the analytic baseline for this study. A random sample of 905 women also had cognitive status adjudicated 10 years later (SOF Year 20), and comprise our analytic cohort. These 905 women were free of cognitive impairment at Year 10; cognitive impairment was defined as a modified Mini-Mental State Examination (mMMSE) score ≤22 points, equivalent to ≥1.5 standard deviations below the mean.[15] Finally, a subset of these women (n=363 for IL-6, n=380 for IL-6 sR, n=393 for STNF-R1) had inflammatory markers measured at SOF Year 16, and were included in longitudinal analyses.

Primary Predictors

Inflammatory markers were measured from blood serum at Year 10 in a random sample of women using DuoSet enzyme-linked immunosorbent assays (ELISAs) from R&D systems. Year 16 inflammatory markers, also measured from blood serum, were assessed in a random sample of women from the Minnesota and Pennsylvania sites who participated in the SOF sleep study (were willing to wear an actigraphy watch) using the same assays. All assays were performed at the University of Maryland Cytokine Core Laboratory (Baltimore, MD). The coefficient of variation for STNF-R1 was 5%, and values ranged from 1250 to 80,000 pg/ml. For IL-6, the coefficient of variation was 8%, with a range of values from 2.3 to 150 pg/ml. The coefficient of variation for IL-6 sR was 4%, and values ranged from 1,500 to 100,000 pg/ml. To account for potentially non-linear relationships, and because some studies have shown that inflammation is only associated with cognitive function at the extreme ends,[5] we decided a priori to create tertile cutoffs for each inflammatory marker in order to compare those with the highest levels to those in the lower two tertiles.

Outcomes

The primary outcome of cognitively normal, dementia or MCI diagnosis was determined at SOF Year 20 (2006–2008), using a standard 2-step adjudication process, previously described in detail.[16] Study participants who had cognitive test data available from clinic or at home visits at Year 20 were eligible for screening and diagnosis of cognitive impairment. The first step in the adjudication process was identifying those “in need” of cognitive adjudication. Partcipants who met any of the following criteria at Year 20 were determined as being “in need”: Teng Modified Mini-Mental State Exam (3MS) Score of <88; California Verbal Learning Test (CVLT) Delayed (10 minute) Recall Score <4; Functional Assessment Questionnaire (IQCODE) Score ≥3.6; a self-reported history of dementia diagnosis; or living in a nursing home or personal care home. There were 760 participants who met one or more of these criteria, and had complete Year 20 data, as well as past visit data forwarded to the adjudication committee for cognitive status determination.

A panel of clinical experts, including one neurologist, two neuropsychologists, and one geropsychologist, adjudicated cognitive function of the 760 identified. Adjudication was performed using existing data on age, education, race, previously collected cognitive assessments (including 26 point modified Mini-Mental State Examination scores; MMSE scores; Trails B Test completion times; CVLT; verbal fluency test; and digit span test), geriatric depression scores, IQCODE functional assesments, instrumental activities of daily living and activities of daily living functional assessment, lifestyle (i.e. type of residence, living alone), medical history and medication use. A diagnosis of dementia was made based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, and included AD, vascular dementia, indeterminate and 'other'. MCI was diagnosed using the Petersen Criteria.[17] Those who did not meet criteria for MCI or dementia were classified as being cognitively normal. Those who did not meet any of the original five screening criteria were not adjudicated, and were considered cognitively normal.

Other Variables

Other variables were examined as potential covariates or confounders based on previously reported associations with inflammation or with cognitive function. Data on age, race and education were collected at the baseline visit. Weight and height were measured at Year 10 using a balance-beam scale and fixed stadiometer in light indoor clothing; body mass index (BMI) (kg/m^2) was calculated from direct height and weight measurements. Diabetes was defined as self-reported diabetes or taking medication for diabetes. Hypertension was defined as either systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or taking medications for high blood pressure. History of stroke and myocardial infarction were self-reported. The 15-item Geriatric Depression Scale (GDS) was used to assess depressive symptoms; a standard cutoff of ≥6 symptoms was used to define depression.[18] Apolipoprotein E (APOE) phenotype was determined by isoelectric focusing and immunoblotting[19] on most of the women from the Pittsburgh site; APOE was not included as a covariate in models due to the large amount of missing data (n=220, 24.31% of sample). Concentration of serum Cystatin-C was determined using a BN100 nephrolometer (Dade Behring Inc., Deerfield, IL). To determine medication use, participants were required to bring in all medications taken daily or almost daily in the 30 days prior to the study visit. Medications were classified according to a computerized coding dictionary, according to brand and generic names.[20]

Statistical Analyses

To examine the association between baseline characteristics, and adjudicated cognitive status, chi-square tests, analysis of variance tests (ANOVAs) and Wilcoxon rank sum tests were used, as appropriate. For all analyses, we first included all types of dementia, and then restricted analyses to individuals with adjudicated AD. The analyses were similar with respect to the strength and direction of associations for all-cause dementia and the AD subset, therefore all-cause dementia was used for analyses. Multinomial logistic regression was used to determine the association between each inflammatory marker at initial and interim visits and subsequent cognitive status (normal, MCI and dementia). Multinomial logistic regression was also used to determine the association between 6-year change in

inflammatory marker and subsequent cognitive status. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

The mean baseline age was 78.3±2.8 years and 88.3 years at the time of cognitive status determination. After 10 years, 199 (22.0%) women developed MCI and 145 (16.0%) dementia. Of the 145 women with dementia, 116 had AD (80.0%), 18 (12.4%) had vascular dementia, 2 were classified as “other” (1.4%) and 9 (6.2%) were indeterminate. At baseline, compared to those who were cognitively normal, those with dementia or MCI were significantly older ($p<0.001$) and had less education ($p=0.005$) (Table 1). There was also a non-significant associations suggesting those with MCI or dementia were slightly more likely to be depressed ($p=0.09$) and to have poorer kidney function (higher Cystatin-C, $p=0.06$) (Table 1). All of these variables were included as covariates in models. Furthermore, although they did not differ by cognitive status, non-steroidal anti-inflammatory drug (NSAID) use and statin use were included in models because of their effects on inflammation. When comparing women who were lost to follow-up or died, to those in our analytic cohort, those lost to follow-up were more likely to have a history diabetes ($p=0.002$) and a previous MI ($p<0.0001$); however there was no difference on history of stroke ($p=0.33$), and the women in our cohort were more likely to have hypertension ($p=0.0002$).

There were no significant associations between initial or interim level of IL-6 or STNF-R1 and risk of MCI (IL-6 OR=1.19; 95% CI: 0.83, 1.69 and STNF-R1 OR=1.16; 95% CI: 0.78, 1.70) or dementia (IL-6 OR=1.32; 95% CI: 0.88, 1.97 and STNF-R1 OR=1.12; 95% CI: 0.73, 1.73) in either unadjusted or adjusted models (Table 2). While there was no significant association between the initial level of IL-6 sR and subsequent cognitive status (Table 2), those with a high level of IL-6 sR at Year 16 were significantly less likely to be subsequently diagnosed with dementia in unadjusted (OR=0.54; 95% CI: 0.30, 0.97), and adjusted models (Table 2). When looking at change in inflammatory marker from Year 10 to Year 16, and subsequent cognitive status, there were no significant associations between IL-6 or STNF-R1 and MCI or dementia. However, a high IL-6 sR level at both time points was associated with a reduced risk of a dementia diagnosis in unadjusted (OR=0.39; 95% CI: 0.17, 0.89) and adjusted models (Table 3); this was similar among those who did not have a high IL-6 sR level at the initial, but transitioned to a high level at the interim visit (unadjusted OR=0.35; 95% CI: 0.14, 0.88) (Table 3). There was a borderline significant protective association for those who had an initial high level and transitioned to a low level (adjusted OR=0.40; 95% CI: 0.15, 1.04).

DISCUSSION

In this study of oldest old women, we found that those with a high level of IL-6 sR were significantly less likely to be diagnosed with dementia. This was true for women with a high level of IL-6 sR at both time points, and for those who began at a low level, but increased to a high level over time. The association among women who had a high level and transitioned to a low level approached significance, suggesting that having a high level at any time point

may be associated with decreased risk for dementia. Our results are supported by at least one previous study which found that in cerebrospinal fluid (CSF) of AD patients, there were significantly decreased levels of IL-6 sR, when compared to cognitively normal controls.[21] There have been other conflicting results on the association between IL-6 sR and AD and cognitive function. For example, several early studies reported an association between lower CSF and serum IL-6 sR level and increased risk for AD[22, 23], and others have reported no significant differences.[24]

Our results differ from several previous studies which have reported associations between a high level of inflammation and increased risk for cognitive decline or dementia.[2, 3, 5, 6, 10] There are several potential explanations for this finding. First, it could be that what we are seeing is a healthy participant bias. A relationship between a high level of inflammation and mortality has been previously documented,[25] and in our sample, women who had diabetes or a MI were more likely to be lost to follow-up before Year 20 when cognitive status was adjudicated. Another potential explanation is that we are seeing the pleiotropic nature of inflammation in oldest old adults; while a high level is harmful at some time points, in this age group, it is beneficial. It has been proposed that high inflammation is perhaps an indicator of a well-functioning immune system in the oldest old, demonstrating the ability for the body to successfully fight off illness, infection, and injury.[26] Our results may also be highlighting the complexity of immune system abnormalities we see in both normal and pathological aging. Another explanation could be that a high level of IL-6 sR mediates or modifies the effects of IL-6 in the brain. For example, a high level of IL-6 sR may mediate trans-signaling of IL-6, expanding IL-6 upregulation to different areas of the brain where it less likely to have effects specific to dementia, such as executive function or memory.[27] Finally, some studies may use different assay techniques, and have examined different cutoffs for categorical, or continuous measures of inflammatory markers. However, in sensitivity analyses to examine this possibility, we looked at the log-transformed, continuous measures of IL-6 sR, and found results consistent with those previously reported.

There are several strengths and weaknesses that should be considered when interpreting the results of this study. One strength is having inflammatory markers measured at multiple time points. Furthermore, we collected data on a large number of potential confounders and covariates, so all analyses could be adjusted for these factors. A weakness of this study was having a relatively small sample size, especially in follow-up years. We were also unable to see if these results were modified by APOE e4 genotype due to a small sample size with APOE assessed. The markers chosen in this study were originally selected due to their involvement in bone remodeling. In spite of this weakness, peripheral IL-6 and TNF levels have been shown to be related to cognitive decline and dementia.[2–4, 7] Finally, this study was originally designed to investigate osteoporosis, rather than dementia, so initial cognitive assessments were not as extensive as the adjudication at Year 20.

In conclusion, findings suggest a consistently high or an increasing level of IL-6 sR is associated with a subsequent reduced risk of dementia. This could be due to a healthy survivor effect. Our results may also be highlighting the pleiotropic nature of inflammation, and the complexity of the immune system in older adults. Understanding these differences

will be crucial in interpreting results from ongoing clinical trials and in targeting therapeutic strategies to oldest old.

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Conflict of Interest Checklist: Below is the completed conflicts of interest checklist for all co-authors.

Elements of Financial/Personal Conflicts	ALM		KY		RMB		MG		OLL		KLS		JAC	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Employmentor Affiliation		X		X		X		X		X		X		X
Grants/Funds	X		X			X	X			X		X		X
Honoraria		X		X		X		X		X		X		X
Speaker Forum		X		X		X		X		X		X		X
Consultant		X	X			X		X	X			X		X
Stocks		X		X		X		X		X		X		X
Royalties		X		X		X		X		X		X		X
Expert Testimony		X		X		X		X		X		X		X
Board Member		X	X			X		X		X		X		X
Patents		X		X		X		X		X		X		X
Personal Relationship		X		X		X		X		X		X		X

***Authors can be listed by abbreviations of their names**

For "yes", provide a brief explanation: ALM is funded by a NIH training grant 2T32AG000181. KY has served as a consultant for Eli Lilly and Novartis, and has served on data safety monitoring boards for Pfizer, Inc., Medivation, Inc., Takeda Pharmaceuticals, Inc., and the NIH (NIMH and NIA trials). KY has also received research support from the NIH (NIA, NIDDK, and NIMH), the Department of Defense, American Health Assistance Foundation, Anonymous Foundation, and the Alzheimer Association. MG is funded by NIA grant K24AG022035. OLL is a consultant for Baxter, Eli Lilly, and Grifols.

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Table 1

Year 10 characteristics of the 905 oldest old women by cognitive status

Characteristic Mean (±SD), Median, or N (%)	Cognitively Normal (n=561)	Mild Cognitive Impairment (n=199)	Dementia (n=145)	p-value
Age	77.8 (2.6)	78.6 (2.8)	79.4 (3.6)	<0.001
Black Race	2 (0.4%)	2 (1.0%)	0 (0%)	0.34
Education, ≤High School	309 (55.1%)	136 (68.3%)	88 (60.7%)	0.005
Diabetes	19 (3.4%)	5 (2.5%)	7 (4.8%)	0.51
Hypertension	170 (30.3%)	67 (33.7%)	56 (38.6%)	0.15
Stroke	17 (3.0%)	4 (2.0%)	1 (0.7%)	0.24
Myocardial Infarction	8 (1.4%)	1 (0.5%)	1 (0.7%)	0.49
Depression	22 (3.9%)	11 (5.5%)	12 (8.3%)	0.09
Body Mass Index	27.2 (4.3)	27.2 (4.6)	26.9 (5.1)	0.79
APOE e4 carriers *	10 (1.8%)	3 (1.5%)	7 (4.8%)	0.03
Cystatin-C (mg/L) **	0.95	0.98	0.95	0.06
Interleukin-6 (pg/ml) **	2.48	2.68	2.98	0.19
Interleukin-6 Soluble Receptor (pg/ml) **	45304.16	45630.41	45140.51	0.79
Tumor Necrosis Factor Soluble Receptor 1 (pg/ml) **	3299.42	3393.24	3280.31	0.32
NSAID use	156 (27.8%)	55 (27.6%)	31 (21.4)%	0.28
Statin use	55 (9.8%)	15 (7.5%)	12 (8.3%)	0.59

* N= 220;

** Wilcoxon Rank Sum tests used to compare medians rather than means because of skewed distributions.

Table 2

Adjusted association of inflammation markers at Year 10 or Year 16 and subsequent cognitive status

Inflammation Marker	Odds Ratio (95%CI)	
	Mild Cognitive Impairment	Dementia
	Interleukin-6 (IL-6) Year 10* (n=905)	
Low	Reference	Reference
High	1.19 (0.83, 1.69)	1.32 (0.88, 1.97)
	IL-6 Year 16* (n=360)	
Low	Reference	Reference
High	1.26 (0.72, 2.21)	1.08 (0.56, 2.09)
	IL-6 Soluble Receptor (IL-6 sR)Year 10* (n=905)	
Low	Reference	Reference
High	1.06 (0.75, 1.52)	0.85 (0.57, 1.26)
	IL-6 sRYear 16* (n=377)	
Low	Reference	Reference
High	0.79 (0.46, 1.36)	0.48 (0.25, 0.91)
	Tumor Necrosis Factor Soluble Receptor 1 (STNF-R1) Year 10* (n=905)	
Low	Reference	Reference
High	1.16 (0.78, 1.70)	1.12 (0.73, 1.73)
	STNF-R1Year 16* (n=390)	
Low	Reference	Reference
High	0.79 (0.46, 1.38)	1.06 (0.54, 2.06)

* Models are adjusted for age, education, depression, cystatin-C, statin use and NSAID use.

** Low IL-6 ≤1.87 pg/ml and high IL-6 >1.87 pg/ml; low IL-6 sR≤37401.36 pg/ml and high IL-6 sR>37401.36; low STNF-R1 <11.98 pg/ml and high STNF-R1 >11.98 pg/ml.

Table 3

Adjusted* associations of change in inflammation markers over time and Year 20 cognitive status

Inflammation Marker	Odds Ratio (95%CI)	
	Mild Cognitive Impairment	Dementia
	Interleukin-6 (IL-6)	
Low, Low	Reference	Reference
High, Low	1.59 (0.61, 4.16)	3.09 (0.89, 10.66)
Low, High	1.99 (0.80, 4.98)	2.42 (0.69, 8.44)
High, High	1.50 (0.64, 3.47)	2.15 (0.68, 6.79)
	IL-6 Soluble Receptor (IL-6 sR)	
Low, Low	Reference	Reference
High, Low	0.67 (0.28, 1.65)	0.40 (0.15, 1.04)
Low, High	0.50 (0.21, 1.23)	0.23 (0.09, 0.64)
High, High	0.70 (0.31, 1.57)	0.30 (0.13, 0.75)
	Tumor Necrosis Factor Soluble Receptor 1 (STNF-R1)	
Low, Low	Reference	Reference
High, Low	1.02 (0.43, 2.44)	1.32 (0.44, 4.00)
Low, High	0.75 (0.30, 1.89)	1.30 (0.43, 3.93)
High, High	0.82 (0.39, 1.73)	1.20 (0.46, 3.19)

*Models are adjusted for age, education, depression, cystatin-C, statin use and NSAID use.

**Low IL-6 ≤1.87 pg/ml and high IL-6 >1.87 pg/ml; low IL-6 sR≤37401.36 pg/ml and high IL-6 sR>37401.36; low STNF-R1 <11.98 pg/ml and high STNF-R1 >11.98 pg/ml.