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Association between C-reactive Protein and Depressive Symptoms in Women with Rheumatoid Arthritis

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Abstract

Converging lines of evidence support an association between systemic inflammation and depressive symptoms. Neuroimmune pathways may account for the high prevalence of depression in individuals with inflammatory conditions such as rheumatoid arthritis (RA). However, this relationship is complicated by factors linked to both inflammatory disease activity and mood, such as pain and physical disability. The goal of this cross-sectional study was to examine the relationship between C-reactive protein (CRP) and depressive symptoms among 173 women with RA. Somatic symptoms of depression and circulating CRP were significantly associated in regression analyses adjusted for body mass index (β= .19, $p < 0.05$), but this relationship was attenuated when pain and disability were included as covariates (β= .09, $p = 0.24$). CRP was not significantly associated with negative mood symptoms of depression. Findings suggest that depression in the context of RA may result from the overlap of somatic depressive and RA symptoms rather than neuroimmune pathways.

Keywords

Rheumatoid arthritis; Autoimmune disorders; Inflammation; C-reactive protein; Depression

In response to infection, cytokines coordinate biological changes to clear the pathogen and promote tissue repair. Peripheral proinflammatory cytokines also act on neural substrates to produce psychiatric symptoms including fatigue, anorexia, impaired learning and memory, and reductions in exploratory, social, and sexual behavior (Dantzer et al., 2008; Maier and Watkins 1998). These “sickness behaviors” are hypothesized to serve evolutionary functions by prioritizing recuperation and allocating metabolic resources to fighting infection.

Striking overlap between sickness behaviors and symptoms of clinical depression has stimulated scientific interest in the role of inflammation in the pathophysiology of mood

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disorders (Maes et al., 1995; Raison, Capuron, & Miller, 2006). In healthy adults, experimental administration of inflammatory stimuli transiently increases both sickness behaviors and negative mood (Reichenberg et al., 2001; Wright et al., 2005). Community-based studies report a positive correlation between depressed mood and circulating markers of inflammation such as C-reactive protein (CRP; Bremmer et al., 2008; Ford & Erlinger, 2004; Suarez, 2004). These converging lines of evidence support a positive association between systemic inflammation and both somatic and affective depressive symptoms.

Neuroimmune pathways are postulated to explain the high prevalence of depression in inflammatory conditions such as rheumatoid arthritis (RA; Dantzer et al., 2008; Lorton, Lubahn, Zautra, & Bellinger, 2008). RA is a female-predominant autoimmune disease characterized by chronic inflammation of multiple joints and elevated levels of circulating inflammatory markers. Depression is a common comorbidity in RA patients, with a prevalence rate of 20% (Dickens et al., 2002; Katz & Yelin, 1993). Preliminary evidence supports an association between biomarkers of systemic inflammation (e.g., CRP and erythrocyte sedimentation rate) and depressive symptoms in RA patients (Dessein, Joffe, & Stanwix, 2004; Odegard et al., 2007). However, these biomarkers also reflect RA activity (Wolfe et al., 1997), and the association between inflammation and depression may be confounded by factors linked to both disease activity and mood such as pain, physical disability, and medications. Because symptoms of RA overlap considerably with somatic symptoms of depression (e.g., fatigue, sleep difficulties), the extent to which inflammatory processes are related to these sickness behavior-like symptoms versus negative mood in RA also warrants examination.

The goal of this study was to examine the relationship between CRP[1] and depressive symptoms among women with RA. We hypothesized that CRP would be positively associated with depressive symptoms, especially somatic symptoms, but that this relationship would be attenuated when pain and disability were statistically controlled.

Methods

Participants

Data for the present analyses were collected in a study of risk factors for cardiovascular disease in women with RA (Kao et al., 2008). Participants were recruited from the University of Pittsburgh Medical Center Arthritis Network outpatient practices between 2000 and 2004. Eligibility requirements included RA diagnosis at age ≥16 years and RA duration ≥ 2 years. The sample includes 173 women for whom self-report measures of depressive symptoms were collected.

Procedure

Participants visited the General Clinical Research Center after overnight fasting and provided blood samples before 11 a.m. for assessment of CRP. At this time, they also completed self-report measures, and a physician completed a physical examination and rating of disease activity and severity using 10 cm visual analog scale (VAS). Participants also completed electron beam computed tomography to assess coronary artery calcification; these data are reported elsewhere (Kao et al., 2008) and are not included in the current analyses.

Measures

Depressive symptoms—The Center for Epidemiological Studies – Depression Scale (CES-D; Radloff, 1977) is a 20-item scale assessing the frequency of depressive symptoms in

[1]Relationships between erythrocyte sedimentation rate and depressive symptoms were also examined. No significant associations were observed in unadjusted or adjusted models, and these data are not shown.

the past week. Total scores range from 0 to 60 with higher scores indicating more depressive symptomatology. The CES-D contains four subscales (negative affect, lack of positive affect, somatic complaints, and interpersonal symptoms), and the 5-item negative affect and somatic symptom subscales were examined in addition to the total score. The CES-D has been used in a variety of clinical populations, including individuals with RA, and has demonstrates excellent psychometric properties (Blalock, DeVellis, Brown, & Wallston, 1989).

CRP—CRP was measured using latex immunonephelometry at the Laboratory of Clinical Biochemistry Research (University of Vermont, Burlington, VT, USA). Samples were assayed in a single batch and blinded to clinical data. This assay has inter-assay coefficient of variation < 5%. Because of skewed distribution, CRP values were log-transformed prior to analyses.

RA-related disability and pain—Participants completed the modified Health Assessment Questionnaire (mHAQ), a well-validated instrument used to calculate arthritis-related disability (Pincus et al., 1983). The 15 cm VAS component of the mHAQ was used to determine pain. Participants also reported on current medications, including use of corticosteroids and anti-cytokine agents.

Covariates—General health and demographic covariates examined for inclusion in the multivariate models included participant age, ethnicity, education, marital status, body mass index (BMI; calculated from measurements of weight and height), menopausal status, and current smoking. Pearson correlations were examined to identify which demographic and general health covariates should be included in models.

Statistical Analyses

Statistical analyses were conducted using SPSS for Windows (version 15.0). Primary analyses were hierarchical linear regression analyses to determine the variance in depressive symptomatology (total, depressed mood, and somatic) accounted for by CRP and RA-related factors. First, general health and demographic covariates that were significantly correlated with depressive symptoms ($p < .05$, two-tailed) were entered in the first step of the model, followed by log-transformed CRP. The second set of models included RA-related variables associated with CES-D scores ($p < .05$, two-tailed). In these fully adjusted models, demographic and general health covariates were entered in the first step, RA-related variables in the second step, and CRP in the third step.

Results

Characteristics of the sample are presented in Table 1, along with bivariate correlations between demographic and general health factors, CRP, and depressive symptoms. Mean CES-D scores were 15.1, comparable to previous RA samples (Covic, Tyson, Spencer, & Howe, 2006), and 40% of respondents had scores that exceeded the cutoff of 16 suggestive of clinical depression (Radloff, 1977). Higher education was associated with higher CRP, married women reported less negative mood, and BMI was positively correlated with somatic depressive symptoms. Thus, marital status was included as a covariate in regression models predicting negative mood, and BMI was a covariate in regression models predicting somatic symptoms. Self-reported pain was associated with higher circulating CRP and more depressive symptoms, including both more somatic complaints and greater negative mood. Consistent with more severe or active RA, CRP was associated with higher physician-rated RA activity and severity, greater physical disability, and current corticosteroid use. Current use of TNF inhibitors was associated with lower levels of circulating CRP.

Associations between CRP and depressive symptoms

As noted in the bivariate correlations displayed in Table 1, CRP was marginally associated with total CES-D scores (β= .13, ΔR^2 = .02, p = 0.08). Negative mood was not associated with CRP in bivariate correlations or in regression analyses controlling for marital status (β= .09, p = .27). After controlling for BMI, the bivariate relationship between somatic complaints and CRP persisted and was statistically significant (see Table 2).

The role of RA-related factors

In adjusted regression models predicting total CES-D scores, pain was marginally associated with depressive symptoms (β= .15, p = .07) and the previously marginal effect of CRP became nonsignificant (β= .16, p = .37). Neither pain (β= .13, p = .12) nor CRP (β= .01, p = .95) predicted negative affective symptoms of depression. When BMI, pain, and disability were entered as predictors of somatic symptoms, pain emerged as a significant predictor while the previously significant effect of CRP was reduced to nonsignificance (see Table 2).

Discussion

Results suggest that somatic depressive symptoms and CRP, a marker of systemic inflammation, are significantly and positively associated in women with RA and that this relationship is partially accounted for by disease-related factors, such as greater pain among women with higher levels of inflammation. Thus, rather than mediated by immune-brain pathways (Dantzer et al., 2008), the prevalence of depression among RA patients may be better explained by the overlap of RA symptoms with somatic symptoms of depression. In the current sample, CRP was not significantly associated with negative affective symptoms of depression.

The hypothesis that inflammatory mechanisms lead to depression for some RA patients warrants more careful consideration in longitudinal studies. Given the potential of inflammatory processes to elicit hyperalgesia (Watkins & Maier, 2000), repeated assessments of mood, pain, and inflammatory biomarkers will be essential in delineating the temporal relationships between RA-related inflammation and sickness behaviors. The current study suggests that the predictive utility of RA-related factors differs between somatic and affective depressive symptoms. To better predict which individuals with RA are vulnerable to the affective symptoms of depression, it will be important to assess additional psychological factors such as illness perceptions or coping (Groarke, Curtis, Coughlan, & Gsel, 2004).

Several important limitations of the current study must be noted. First, the cross-sectional nature of the analyses precludes causal analyses and elucidation of temporal relationships. Second, corrections were not made for multiple comparisons. Third, the sample included only women with RA and cannot be generalized to men, as the relationship between inflammatory markers and depressive symptoms may be stronger in men (Ford & Erlinger, 2004). Fourth, although we examined use of steroid and anti-cytokine medications as potential covariates due to their anti-inflammatory properties and possible neuropsychiatric side effects, we did not have a sufficiently large sample to evaluate the effects of other classes of medications commonly used by RA patients (e.g., antidepressants or non-steroidal anti-inflammatory drugs), making it difficult to make full sense of the current findings. We also did not systematically evaluate the effect of comorbid medical conditions or all relevant health behaviors (e.g., diet, exercise) in the current analyses. Finally, the current study included a limited number of biomarkers and notably, did not assess proinflammatory cytokines which have been demonstrated to mediate sickness behavior (e.g., interleukin (IL)-1beta, tumor necrosis factor (TNF)-alpha). Although CRP represents an end product of the inflammatory cascade and tends to be significantly correlated with these cytokines (Cesari et al., 2003),

relationships with psychological factors may be stronger for more proximal inflammatory mediators.

In summary, CRP was significantly associated with depressive symptoms among women with RA, particularly somatic symptoms such as sleep disturbances and low energy. This relationship was attenuated when pain and physical disability were included as covariates. Our date provide limited support for a relationship between systemic inflammation associated with RA and negative mood, independent of the RA-related symptoms.

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Table 1

Descriptive statistics and bivariate correlations (n = 173)

	M (SD) or %	Correlation coefficients			
Demographic/general health		**CRP**	**CES-D Total**	**CES-D Neg Mood**	**CES-D Somatic**
Age (years)	58.9 (10.4)	.08	−.13	−.06	−.05
Body mass index (kg/m^2)	28.0 (6.1)	.13	.12	.06	.18*
Ethnicity (Caucasian)[a]	95%	.04	.03	.07	.08
College/graduate degree[a]	56%	.15*	−.03	−.04	.04
Married[a]	66%	.14	−.10	−.18*	−.07
Postmenopausal[a]	80%	.11	−.08	−.05	.02
Current smoker[a]	8%	−.05	.00	.10	.10
Rheumatoid arthritis variables					
RA duration (years)	16.3 (10.8)	.03	−.02	−.04	−.05
Current corticosteroid use[a]	44%	.16*	.12	.06	.13
Current use of TNF inhibitors[a]	31%	−.19*	.03	.01	.07
Pain in past week (15 cm VAS)	4.7 (3.4)	.29***	.17*	.16*	.30***
mHAQ Disability Index (0–3)	0.7 (0.6)	.29***	.10	.12	.20**
Physician-rated RA Activity (VAS)	2.5 (2.5)	.33***	.00	−.02	.07
Physician-rated RA Severity (VAS)	4.9 (3.3)	.21**	−.03	−.05	.08
Inflammatory markers					
C-reactive protein (mg/L)[b]	12.5 (18.1)	-	.13	.06	.20**

[a] Point-biserial.

[b] Correlation computed using log-transformed values.

* $p < .05$

** $p < .01$

*** $p < .001$.

Table 2

Contributions of demographic and general health covariates, RA-related factors, and inflammatory markers to prediction of somatic depressive symptoms in hierarchical linear regression models

		ΔR^2	*B*	*B (se)*	*p*
Step 1: F(1,167) = 5.65, p = .02		.03			
	BMI		.18	.08 (.03)	.02
Step 2: F(2,166) = 6.10, p = .003		.03			
	CRP		.19	1.07 (.44)	.02
Step 1: F(1,164) = 5.32, p = .02		.03			
	BMI		.17	.07 (.03)	.03
Step 2: F(3,162) = 7.61, p < .001		.09			
	Pain		.24	.19 (.07)	.01
	Disability		.06	.27 (.36)	.45
Step 3: F(4,161) = 6.07, p < .001		.01			
	CRP		.09	.54 (.46)	.24