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Psychoneuroimmunological Relationships in Women with Fibromyalgia

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Abstract

Introduction—The purpose of this pilot study was to characterize the relationships among perceived stress, pain, fatigue, depression, anxiety, biomarkers and functional status in women with fibromyalgia syndrome (FMS) using a psychoneuroimmunological (PNI) framework.

Materials and Methods—Using a cross-sectional, correlational design, we asked 50 women diagnosed with FMS to complete the Perceived Stress Scale, Brief Pain Inventory, Brief Fatigue Inventory, Center for Epidemiological Studies-Depression scale, State-Trait Anxiety Inventory and Functional Impact Questionnaire. We analyzed plasma levels of 17 cytokines using a BioPlex® assay and levels of C-reactive protein (CRP) using a high-sensitivity ELISA assay.

Results—Compared to published guidelines (> 3 mg/L reflects high inflammation), CRP levels were elevated in participating women. Perceived stress demonstrated positive correlations with pain, fatigue, depression, anxiety and functional status and negative correlations with monocyte chemotactic protein-1 ($r = -0.30$) and interleukin-1 β ($r = -0.29$). Pain severity correlated with macrophage inflammatory protein-1 β ($r = 0.29$), and pain interference negatively correlated with interleukin-1 β ($r = -0.30$). Fatigue negatively correlated with interleukin-1 β ($r = -0.32$), interleukin-10 ($r = -0.31$) and granulocyte colony stimulating factor ($r = -0.31$). Depressive symptoms correlated with CRP ($r = 0.31$).

Discussion—Relationships among perceived stress and symptoms supported the PNI framework. Study findings are similar to previous studies showing that cytokines in persons with FMS do not show a consistent pattern. The elevated CRP levels suggest higher levels of generalized inflammation in the sample and provide evidence for continued development of biobehavioral interventions to address both symptoms and their biological markers over time.

Keywords

fibromyalgia; psychoneuroimmunology; cytokine; C-reactive protein; stress

Fibromyalgia (FMS) is a chronic pain syndrome in which pathogenesis is complex and cure is not known. It affects approximately 5 million adults in the United States, with 80–90% of diagnoses being reported in women (National Institute of Arthritis and Musculoskeletal and Skin Diseases, 2009). The symptom profile of FMS includes pain, fatigue and distressed mood. Sequelae of FMS include physical and psychological distress, loss of work productivity, reduced quality of life, and increased use of health resources. Although the incidence of FMS is rising, the etiology remains unclear. A major theory is that inflammatory mediators lead to complex neuroendocrine aberrations of the hypothalamic-pituitary-adrenal (HPA) axis (Mease et al., 2007). Increased levels of cytokines, key inflammatory mediators such as C-reactive protein (CRP), have been associated with symptoms of pain, fatigue, and distressed mood in multiple conditions (Wallace, 2006). This symptom profile mimics the representative symptoms of FMS. Thus, it is theoretically plausible that these nonspecific inflammatory mediators may also contribute to the symptoms of pain, fatigue, and distressed mood in FMS. However, results to date examining the association of cytokine alterations with FMS and its symptoms have been mixed (Menzies & Lyon, 2010).

Psychoneuroimmunology (PNI) is concerned with mechanisms of multidimensional psychobehavioral-neuroendocrine-immune system interactions. Within the PNI framework, modulating perceived stress is thought to reduce the secretions of stress hormones, while increasing perceived stress is thought to contribute to immunosuppression (McCain, Gray, Walter, & Robins, 2005). Investigators have reported levels of perceived stress to be the predictor variable accounting for the greatest amount of variance associated with FMS symptoms. Although the potential relationships among the neuroimmune, neuroendocrine and autonomic nervous systems are recognized, researchers to date have not used a PNI framework to examine the relationships among perceived stress; symptoms of pain, fatigue, distressed mood such as depression or anxiety; alterations in cytokines or CRP; and functional status in women with FMS. Because the symptoms of FMS may be worsened by perceived stress or influenced by an interaction of physiological and psychosocial processes (Wallace, 2006), further understanding of the relationships among stress, functional status, FMS symptoms and PNI-based biomarkers is needed to better explain potential mechanisms of this syndrome. Therefore, the purpose of this biobehavioral pilot study was to characterize the relationships among perceived stress, pain, fatigue, depression, anxiety, biomarkers and functional status in women diagnosed with FMS using a PNI framework (Figure 1).

Materials and Methods

Study Design

We used a cross-sectional, correlational design for this study. The sample comprised 50 women diagnosed with FMS. We recruited participants using brochures and flyers placed in physicians' offices and ambulatory care clinics affiliated with the Virginia Commonwealth University Health System (VCUHS). The Institutional Review Board of Virginia Commonwealth University approved the protocol. Volunteers who agreed to participate signed an informed consent form before we screened them for eligibility. Inclusion criteria included age ≥ 18, female, diagnosis of FMS; impaired functional status as indicated by an FMS Impact Questionnaire (FIQ) score ≥ 25 (Burckhardt, Clark, & Bennett, 1991); no known major psychiatric or neurological conditions that would interfere with study

participation; and an ability to understand and sign the consent form and complete the study questionnaires. We based our criteria for diagnosis of FMS on the 1990 American College of Rheumatology criteria (Wolfe et al., 1990). Exclusion criteria included presence of other systemic rheumatologic conditions, being immunocompromised (e.g., HIV/AIDS); receiving corticosteroid treatments; or being pregnant. We confirmed self-reported diagnosis of FMS, where possible, with the participant's primary physician or rheumatologist.

We assessed 103 potential participants for eligibility. Of those, 77 met inclusion criteria, but 23 chose not to participate. Initial enrollment thus totaled 54 women. However, we did not include data from 4 women in the final analysis because of their inability to complete the study protocol, resulting in a sample size of 50 women. With sample size set at $N=50$, we had a power of 91% to be able to detect correlations as small as 0.45 using two-sided Fisher's z -test at $\alpha = .05$.

Setting and Procedure

Volunteers who were interested in participating in the study met with the investigator in the Center for Biobehavioral Clinical Research (CBCR). If enrolled, screened and eligible, study participants were administered a set of questionnaires followed by venipuncture and collection of a 3 cc blood sample for biomarker analysis (cytokine and CRP levels). The investigator placed blood samples in an appropriate biohazard container and transported them to the CBCR laboratory. Each participant received \$25 as compensation for her time and effort.

Measures

Questionnaires—We used a self-report form to obtain information regarding age, race/ethnicity, marital status, length of time since diagnosis of FMS, socioeconomic status and psychiatric, medical and medication history. We measured stress using the Perceived Stress Scale (PSS). The 10-item PSS measures the degree to which the individual perceived events in her life over the previous month to be stressful. The scale has an internal reliability of 0.78 and demonstrated construct validity (Cohen & Williamson, 1988). We measured pain using the Brief Pain Inventory (BPI) Short Form (Cleeland, 1989). The BPI assesses pain severity (BPI-S) and pain interference (BPI-I) using 0–10 numeric scales for item rating; higher scores indicate increased pain/interference. Pain severity indicates the intensity of the pain experienced, while pain interference measures the degree to which pain interferes with activities of daily living (Cleeland, 1989). In widespread testing, the Cronbach's alpha reliability ranges from 0.71 to 0.91 (M.D. Anderson Cancer Center Pain Research Group, n.d.b). We measured fatigue using the Brief Fatigue Inventory (BFI), a simple, 9-item scale that taps into a single dimension of fatigue severity and the interference fatigue creates in daily life. A score of 7 or higher indicates severe fatigue (Mendoza et al., 1999). The BFI has demonstrated excellent reliability in clinical trials, ranging from 0.82 to 0.97 (M.D. Anderson Cancer Center Pain Research Group, n.d.a). We measured depression using the Center for Epidemiological Studies Depression Scale (CES-D). The CES-D is a 20-item self-report instrument comprised of four factors assessing cognitive and affective components of depression. This instrument has very good construct validity, internal consistency, and test–retest reliability (Radloff, 1977). We measured anxiety using the State-Trait Anxiety Inventory (STAI). The STAI, developed to measure state and trait anxiety in both research and clinical settings, has excellent construct validity, internal consistency and test–retest reliability (Spielberger, 1983). We measured functional status using the Fibromyalgia Impact Questionnaire (FIQ), a self-administered instrument composed of 10 items that ask respondents to rate their status within the last week. Higher scores indicate a more negative impact on activities of daily living. Validity and reliability of the FIQ were

documented in a study of 64 patients. Test–retest reliability coefficients for each item on the FIQ ranged from 0.56 for pain to 0.95 for physical function (Burckhardt et al., 1991),

Immune assays—We collected blood samples into heparinized vacutainer tubes for measuring biomarkers. Plasma samples were cryopreserved and batch processed to reduce interassay variability. We analyzed plasma levels of interferon-gamma (IFN- γ), tumor necrosis factor-alpha (TNF- α), interleukin (IL)-1 β , IL-2, granulocyte macrophage colony-stimulating factor (GM-CSF), IL-12, IL-17, IL-8, monocyte chemotactic protein (MCP-1), macrophage inflammatory protein-1 beta (MIP-1 β), IL-6, IL-7, IL-4, IL-5, IL-10, IL-13, and granulocyte colony stimulating factor (G-CSF) using the 17-plex kit with the BioPlex Pro® (Bio-Rad; Hercules, CA). We determined CRP levels in plasma using a high-sensitivity ELISA assay (ALPCO).

Data Analysis

We analyzed data using SPSS software version 16.0 and JMP software version 8.0. For each study variable, we examined distributional properties to assess normality. The cytokine data were non-normal (skewed positively), thus we used a log transformation on these variables. We examined the internal consistency reliability of the scales and subscales using Cronbach's alpha and calculated correlations using Pearson's correlation coefficient. We set the level of significance at $\alpha = .05$.

Results

The mean age of participants was 48 years ($SD = 11.8$). Of the 50 participants who completed the study, 26 (52%) were Caucasian, 18 (36%) were Black or African American, 1 was American Indian/Alaskan Native, 1 was native Hawaiian or other Pacific Islander, and 4 did not report race. More than half (58%) of the participants reported being married or living as married, 42% were employed full time, and 36% had an education level >16 years. Income levels ranged from less than \$14,000 to more than \$50,000, with 42% reporting an income above \$50,000. We calculated means and standard deviations for perceived stress, pain, fatigue, depression, anxiety and functional status scores (Table 1).

The interassay variability of the cytokines was 6.5% for high values and 9.6% for low values; intra-assay variability was 5.6% for high values and 8.8% for low values. The interassay variability for the CRP ELISA, run in duplicate, was 11.2% for high values and 13.2% for low values; intra-assay variability was 5.6% for high values and 6.3% for low values.

There were significant correlations among perceived stress, pain severity, pain interference, fatigue and depression and select biomarkers (see Tables 2 and 3). Neither anxiety nor functional status correlated with any of the biomarkers. Levels of perceived stress demonstrated positive correlations with pain severity, pain interference, fatigue, depression, anxiety and functional status (Table 2). Levels of perceived stress negatively correlated with the pro-inflammatory biomarkers MCP-1 and IL-1 β (Table 3). Levels of pain severity were positively related to the pro-inflammatory biomarker MIP-1 β , while the level of pain interference was negatively correlated with the pro-inflammatory biomarker IL-1 β (Table 3). Levels of fatigue were negatively correlated with the pro-inflammatory biomarker IL-1 β and the anti-inflammatory cytokines IL-10 and G-CSF (Table 3). Levels of depressive symptoms were positively correlated with the generalized immune activation marker CRP (Table 3). Table 3 also includes means and standard deviations for biomarkers found to be significantly correlated with stress, pain, fatigue and depression.

Discussion

The purpose of this biobehavioral pilot study was to characterize the relationships among perceived stress, pain, fatigue, mood (depression, anxiety), biomarkers (cytokines and CRP) and functional status in women diagnosed with FMS, using a PNI framework. Findings demonstrated several statistically significant correlations between biomarkers and levels of perceived stress, pain severity, pain interference, fatigue and depression.

Higher levels of the systemic inflammation marker CRP were associated with higher levels of depression in this study. This finding is consistent with those of several other studies that have found a relationship between CRP levels and depression (Bazzichi et al., 2007; Kadetoff & Kosek, 2010; Ortega, Bote, Giraldo, & Garcia, 2010). Published guidelines have established categories of inflammation based on peripheral blood concentrations of CRP with recommendations that values > 3 mg/L reflect high levels of inflammation (Ridker, 2007). In the current study, CRP levels were 9.2 mg/L, a finding that suggests that an inflammatory process was occurring and that it was related to symptoms of depression in women with FMS.

Study results demonstrated that lower levels of the anti-inflammatory cytokines IL-10 and G-CSF correlated with higher levels of fatigue. While prior researchers have not reported G-CSF as a biomarker in FMS patient populations, prior studies exploring the levels of IL-10 in FMS have been inconsistent. For example, following the administration of intravenous immunoglobulin, Üçeyler et al. (2006) reported a significant reduction of IL-10 ($p = .03$) in FMS patients compared with healthy controls. However, they reported no significant correlations among FMS symptoms of fatigue and cytokine levels. Two studies reported higher levels of IL-10 in persons with FMS as compared to healthy controls (Bazzichi et al., 2007; Ortega et al., 2010). Ortega et al. (2010) reported increased IL-10 ($p < .001$) over time in FMS patients who completed an aquatic exercise intervention as compared to healthy controls, suggesting an enhanced immune response postintervention. Given the high levels of systemic inflammation present in FMS, as measured by CRP, the association between the lower levels of IL-10 and G-CSF and fatigue may be related to an imbalanced inflammatory network. Additionally, in a study of IL-10-deficient (IL-10 $-/-$) and -positive (IL-10 $+/+$) mice exposed to a bacterial challenge, IL-10-deficient mice had increased levels of fatigue (Krzyszton et al., 2008), demonstrating a direct link between IL-10 and fatigue symptoms and supporting the findings of the present pilot study.

There were several other significant relationships among biomarkers and study variables. Lower levels of IL-1 β were associated with higher levels of perceived stress, pain interference and fatigue. This is consistent with the findings of Wallace et al. (2001), who examined the production of cytokines in a sample of 56 adults diagnosed with FMS compared to 39 healthy controls and found no increased serum levels of IL-1 β . However, the authors also reported a 55% increase in IL-1 receptor antagonist (IL-1Ra), which blocks the uptake of IL-1 β into the cell. Alternatively, Ortega et al. (2010) found that FMS patients produced more IL-1 β ($p < .001$) over time (pre-post intervention), indicating that an exercise program may have mediated a return to physiological homeostasis. When considering the disparate findings in the current study, we also observed variations in IL-1 β values. A scan of the data revealed two outliers, that is, two subjects demonstrated much higher levels of IL-1 β levels than the others. This finding may be related to a missense mutation in the MEFV gene that has been linked to high IL-1 β values in a subset of FMS patients (Feng et al., 2009). When we removed these outliers from the data analysis, the mean level of IL-1 β decreased from 4.08 to 0.85 pg/mL.

Lower levels of MCP-1 correlated with higher levels of perceived stress, while higher levels of MIP-1 β were related to higher levels of pain severity. This finding is the first report of an association between MIP-1 β and stress and pain severity in FMS. Although we can hypothesize that higher levels of circulating MIP-1 β might be associated with higher levels of pain due to the perpetuation of inflammatory processes via inflammatory cell recruitment by MIP-1 β (Murdoch & Finn, 2000), we do not have a rationale for the relationship of lower levels of MCP-1 with higher perceived stress. Within the context of elevated CRP levels, these inconsistencies among cytokines and FMS symptoms may indicate a disruption of the HPA axis as there are potential etiological links among the HPA axis, alterations in the stress response system, and FMS such that HPA-axis dysfunction has the capacity to induce hypocortisolism in persons with FMS (Tak et al., 2011).

One limitation to cytokine analysis in clinical research is the inherent biological variability in human subjects, which manifests in wide ranges and large standard deviations for cytokine values. Though this phenomenon is often unexplainable, investigators have observed it in many other chronic disease processes as well, including Alzheimer's (Swardfager et al., 2010) and periodontal disease (Gorska et al., 2003). Additionally, in many animal studies where homogeneity is a strength of the model, researchers have difficulty establishing baseline cytokine levels (Tarrant, 2010). Many factors such as stress, diurnal variation, physical activity, dietary changes and medications affect cytokine levels within subjects; therefore, large between-subject variations are often expected (Zhou, Fragala, McElhaney, & Kuchel, 2010).

In addition to a dysregulated HPA axis or disturbances in cytokine networks, another reason for inconsistencies among our study findings may be due to the presence of nonsteroidal anti-inflammatory medications (NSAIDs). Although the study was not powered for subcategories, we explored the potential for the effects of medications to obscure study findings. Using a two-sided *t*-test, we found that the group who reported taking analgesics ($n = 27$; NSAIDs and/or narcotics) had a significantly lower log IL-1 β level ($p = .04$) than the group who reported not taking analgesics ($n = 23$). Of the 27 participants taking analgesics, 18 reported taking NSAIDs. In a study exploring the long-term effect of NSAIDs on the production of a series of inflammatory mediators by blood cells from 30 patients with severe knee osteoarthritis, researchers found that IL-1 β production decreased significantly at 3 months (González, de la Cruz, de Nicolás, Egido, & Herrero-Beaumont, 1994). There were no other findings related to the effect of medication treatment as potential confounders of cytokine expression in the current study population. Time since diagnosis is another potential cofactor related to inconsistent findings among cytokines and FMS symptoms, meaning that in some individuals there may be accommodation, that is, the immune system accommodates to the increased levels of CRP, thus contributing to an altered pro- and anti-inflammatory cytokine response.

To date, results of prior studies examining the associations of cytokine levels with FMS and its symptoms have reported disparate findings, with cytokine levels in persons with FMS not showing a consistent pattern (Menzies & Lyon, 2010). Overall, findings of the current study demonstrate this same inconsistency. One explanation for such findings may be that cytokines have a short half-life in cytokine-bound receptors and go undetected in blood work (Wallace, 2006; Tarrant, 2010). Other explanations may be that medications, dietary intake, stress level, time of day, exercise and other participant behaviors prior to sampling, as well as the participant's health status, can impact reported levels of cytokines (Zhou et al., 2010). FMS is a complex disorder with wide variation in phenotypic presentation, which might also explain wide variations in cytokines. Additionally, in this study we evaluated circulating levels of cytokines without taking into consideration cellular receptor levels or cytokine receptor antagonists that would also impact the amount of circulating cytokines.

Cellular cytokine receptor expression is beyond the scope of this study and warrants further investigation.

This was a cross-sectional study conducted in a relatively small sample of study participants, all of whom were women. For diagnosis of FMS, we relied on physicians to use the ACR criteria and confirm FMS diagnosis by return letter. Further, this study was not powered for multiple comparisons specifically because it was exploratory in nature and was not testing a priori hypothesis. Unlike a confirmatory trial in which the number of statistical tests are controlled via an alpha level adjustment, the pilot nature of the current study allowed the researchers to conduct many tests without consideration to the multiplicity. For the former (confirmatory trial), the investigator must control the number of tests in order to prevent the inflation of the type I error, while the testing in the latter (pilot study) serves only to indicate potential relationships to be tested and confirmed in a later trial. To better explicate the relationships among stress, biomarkers and symptoms of FMS, future studies should be powered for multiple comparisons.

Investigators involved in the search for biomarkers that can be used to objectively measure disease activity or to identify and diagnose FMS in individuals face the challenge of disparate measurement and research design methodologies among the research community. The Bio-Plex and other multiplex technologies have more precise measurement capability with broader ranges and expanded numbers of measures per sample than methods used in the past. Thus, it may be that investigators will discover or define new patterns and relationships as research on biobehavioral mechanisms expand in this patient population. Such understanding may inform future PNI-based nursing intervention strategies as well as help identify biomarkers that have reproducibility and practical, predictive value in FMS (Mease et al., 2007).

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Figure 1.

Psychoneuroimmunological (PNI) Relationships in Women with Fibromyalgia. The purpose of this biobehavioral pilot study was to characterize the relationships among perceived stress, pain, fatigue, depression, anxiety, biomarkers and functional status in women diagnosed with fibromyalgia using a PNI framework.

Table 1

Means and Standard Deviations of Perceived Stress, Pain, Fatigue, Depression, Anxiety and Functional Status in Women with Fibromyalgia.

Measure	<i>M</i>	<i>SD</i>
PSS	23.5	7.2
BPI-Severity	6.0	1.7
BPI-Interference	6.0	2.3
BFI	6.4	2.3
CES-D	23.2	12.0
STAI-State	44.1	13.5
STAI-Trait	48.9	12.8
FIQ	63.3	16.8

Note. PSS = Perceived Stress Scale; BPI = Brief Pain Inventory; BFI = Brief Fatigue Inventory; CES-D = Center for Epidemiologic Studies—Depression Scale; STAI-S and STAI-T = State Trait Anxiety Inventory—State and Trait; FIQ = Fibromyalgia Impact Questionnaire.

Table 2
Significant Correlations Among Stress, Pain, Fatigue, Depression, Anxiety and Functional Status in Women with Fibromyalgia

Measure	Stress			Pain		Fatigue		Depression		Anxiety		Functional Status	
	PSS	BPI-S	BPI-I	BPI-S	BPI-I	BFI	CES-D	STAI-S	STAI-T	FIQ			
PSS	-	0.34*	0.68**	0.72**	0.80**	0.68**	0.74**	0.71**					
BPI-S	-	-	0.70**	0.55**	0.43**	0.32*	-	0.70**					
BPI-I	-	-	-	0.83**	0.66**	0.45**	0.44**	0.69**					
BFI	-	-	-	-	0.65**	0.44**	0.49**	0.74**					
CES-D	-	-	-	-	-	0.72**	0.83**	0.64**					
STAI-S	-	-	-	-	-	-	-	0.46**					
STAI-T	-	-	-	-	-	-	-	-	0.49**				

Note: PSS = Perceived Stress Scale; BPI-S = Brief Pain Inventory—Severity; BPI-I = Brief Pain Inventory—Interference; BFI = Brief Fatigue Inventory; CES-D = Center for Epidemiological Studies—Depression Scale; STAI-S and STAI-T = State Trait Anxiety Inventory—State and Trait; FIQ = Fibromyalgia Impact Questionnaire.

* $p < .05$;
** $p < .01$.

Table 3

Significant Correlations Among Symptom Variables and Biomarkers

Symptom Variable & Measure	Cytokine/CRP			
	Pro-Inflammatory		Anti-Inflammatory	
	Immune Marker	Mean(SD) ^a	r	Immune Marker Mean(SD) [†]
Perceived stress (PSS)	IL-1β	4.1(19.5)	-0.29 *	-
	MCP-1	40.9(30.9)	-0.30 *	-
Pain severity (BPI-S)	MIP-1β	91.6(78.1)	0.29 *	-
Pain interference (BPI-I)	IL-1β	4.1(19.5)	-0.30 *	-
Fatigue (BFI)	IL-1β	4.1(19.5)	-0.32 *	IL-10 1.1(2.7) -0.31 *
	CRP	9.2(1.31)	0.31 *	G-CSF 87.9(42.5) -0.31 *
Depression (CES-D)				

Note: CRP = C-reactive protein; PSS = Perceived Stress Scale; BPI-S = Brief Pain Inventory—Severity; BPI-I = Brief Pain Inventory—Interference; BFI = Brief Fatigue Inventory; CES-D = Center for Epidemiological Studies – Depression; IL = interleukin; MCP = monocyte chemotactic protein; MIP-1β = macrophage inflammatory protein—1 beta; G-CSF = granulocyte colony stimulating factor.

^a Cytokines measured in pg/mL; CRP measured in mg/L.

* $p < .05$