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Brief Report

Pro-inflammatory cytokines and depression in a familial cancer registry

Mary-Frances O'Connor*, Michael R. Irwin, Joyce Seldon, Lorna Kwan and Patricia A. Ganz
Cousins Center for Psychoneuroimmunology, UCLA Semel Institute for Neuroscience and Human Behavior, Los Angeles, CA, USA

Correspondence to: Cousins Center for Psychoneuroimmunology, UCLA Semel Institute for Neuroscience and Human Behavior, 300 Medical Plaza, Room 3156, Los Angeles, CA 90095-7076, USA E-mail: mfoconnor@mednet.ucla.edu

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Abstract

Patients undergoing cancer treatment (e.g., interferon or IL-2 treatment) develop depression, and there is a positive relationship between their depression and circulating levels of proinflammatory cytokines. Depressed patients who are medically healthy also show increases in circulating markers of inflammation. The present study characterized baseline levels of inflammatory cytokine activity in 18 pairs of depressed and non-depressed persons at high risk for cancer and matched for age, ethnicity and all unaffected by a personal history of cancer. Circulating levels of interleukin-6 (IL-6), soluble IL-6 receptor (sIL-6R), tumor necrosis factor-α-receptor (TNF-RII), and soluble intercellular adhesion molecule (sICAM) did not differ between those with and without depression. The present data are important for characterizing persons at high risk for cancer who may later acquire knowledge of further increased risk through genetic testing.

Keywords: cancer; oncology; depression; cytokines; interleukin-6; high risk

Introduction

Inflammation may contribute in part to the pathophysiology of depression. Medically ill patients, who exhibit evidence of immune activation and/or inflammation, exhibit high rates of depression [1]. Those patients undergoing cancer treatment (e.g. interferon or IL-2 treatment) develop depression, and there is a positive relationship between their depression and proinflammatory cytokine levels [2,3]. Second, depressed patients who are medically healthy show increases in circulating markers of inflammation including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and soluble intercellular adhesion molecule (sICAM) [4–7]. Third, experimentally induced immune activation with the release of proinflammatory cytokines (e.g. IL-6, TNF-α) and their receptors (e.g., soluble IL-6 receptor, sIL-6R; tumor necrosis factor-α-receptor II, TNF-RII) leads to increases in depressive symptoms [8–10]. Co-expression of the IL-6 soluble receptor (sIL-6R) combines with IL-6 to serve as an agonist signal in mediating the action of this proinflammatory cytokine.

Examination of the inter-relationships between proinflammatory cytokine activity and depression in cancer populations is limited. One study found that cancer patients with depression have significantly higher levels of IL-6 as compared to cancer patients without depression and healthy comparison subjects [11]. Correlations have been found between cancer patient's serum levels of TNF-α and IL-6 and poor quality of life [12]. However, levels of proinflammatory cytokines in depressed and non-depressed persons at high risk for cancer have not been examined.

Being at risk for cancer poses a significant psychosocial stress [13] which can lead to the onset of depression. However, there is striking variability in the occurrence of depression even among persons at risk for cancer [14]. Among those at risk for cancer, pro-inflammatory cytokines may be a biomarker for depression. In this cross-sectional study, we tested whether serum levels of proinflammatory cytokine activity (e.g. IL-6, sIL-6R, sTNF-RII, sICAM), would be higher in participants with depressive symptoms as compared to participants without depressive symptoms.

Methods

Biological specimens came from a repository linked to research participants in the UCLA Familial Cancer Registry and Genetic Evaluation Program at the Jonsson Comprehensive Cancer Center. The Registry is a shared resource designed to facilitate genetic, behavioral, psychosocial and biological research. Participants must be at very high risk for the development of a familial or hereditary cancer and/or be affected themselves and a member of

such a family. Participants agree to complete questionnaires assessing health status, psychological well-being, life style and health behaviors, as well as donate blood and tissue specimens (when appropriate), all before any genetic testing may occur. These materials are then available for subsequent research. Among the questionnaire instruments used are the Center for Epidemiologic Studies Depression Scale (CES-D), a measure of depressive symptomatology [15] and the Medical Outcomes Short Form 36 item Scale (SF-36) [16], a measure of health functioning. All participants gave signed, informed consent to participate in the research protocol, approved by the Institutional Review Board of UCLA, before undergoing sampling. This consent included the use of their specimens and data in subsequent research by other researchers using IRB exemption procedures.

From the larger Registry, 36 participants' serum samples were analyzed. Eighteen participants were chosen because they had CES-D scores greater than 16 (depressed group) and 18 participants were selected with CES-D scores below 5 (non-depressed group). These samples were all taken from women who had been unaffected by a personal history of cancer. Smokers were excluded due to the effect of smoking on pro-inflammatory cytokine levels. The two groups were matched on age and non-white ethnicity.

Serum samples had been separated previously according to standard procedures and stored at -70°C for subsequent study. Serum concentrations of IL-6, sIL-6R, sTNF-RII and sICAM were measured using commercially available enzyme-linked immunosorbent assays (ELISAs). IL-6 was measured using Quantikine High Sensitivity Immunoassay kits (R&D Systems, Minneapolis, MN). sIL-6R, sICAM, sTNF-RII were measured with Quantikine Immunoassay kits (R&D Systems). The measurement of cytokine and activation marker levels was performed according to the manufacturer's instructions. Quality control procedures for our laboratory were conducted in the usual manner [17]. The intra-assay precision of all tests was less than or equal to 14% for in-house quality-control samples. All samples were assayed by personnel who were blind to the diagnostic identity of the study subjects. Differences between groups for continuous variables were tested by *t*-tests; differences in categorical variables (e.g. ethnicity, menopausal status) were tested using chi-square.

Results

Consistent with subject matching procedures, the two groups did not significantly differ in age, race, education, or menopausal status (Table 1). As compared to the non-depressed group, the depressed group showed impairments in health functioning with lower SF-36 scores for domains of general health, vitality, social functioning, role-emotional, and mental health; no group differences were found for physical functioning, role-physical, or bodily pain. The depressed- and non-depressed

Table 1. Demographic characteristics, SF-36 scores, and circulating levels of inflammatory markers among depressed and non-depressed female participants at high risk for cancer, but without a personal history of cancer

	Depressed CES-D >16	Non-depressed CES-D <5	Difference score	*p*-value
Age	41.7 (10.5)	41.6 (10.2)	−0.02	0.98
% White*	83.3	94.4	1.13	0.60
% College (vs <college)	22.2	44.4	2.00	0.16
% $100K income	33.3	55.6	1.80	0.18
% Menopausal	16.7	38.9	2.22	0.14
% Employed FT/PT	66.7	77.8	0.55	0.46
% Committed relationship	66.7	94.4	4.43	0.08
SF-36 domains				
Physical functioning	84.7 (19.1)	93.9 (10.2)	1.80	0.08
Role physical	83.3 (28.4)	95.8 (17.7)	1.58	0.12
Bodily pain	74.7 (27.8)	81 (21.5)	0.75	0.46
General health	57.5 (24.1)	82.8 (11.1)	4.03	<0.001
Vitality	49.7 (23.5)	76.7 (8.6)	4.56	<0.001
Social functioning	70.1 (26.5)	95.8 (7.4)	3.96	<0.001
Role emotional	48.1 (40.0)	98.1 (7.9)	5.21	<0.0001
Mental health	60.2 (17.8)	88.7 (6.9)	6.33	<0.0001
Inflammatory Marker				
IL-6	1.8 (1.35)	1.50 (.90)	0.01	0.99
sIL-6r	30759.8 (10636.13)	34877.98 (8308.26)	0.89	0.38
sTNF-R2	2044.72 (533.11)	2133.67 (406.54)	0.70	0.50
sICAM	236.34 (43.32)	253.43 (30.8)	1.48	0.15

Means were tested with *t*-test; frequencies were tested with chi-square, unless denoted with a * in which case Fisher's exact test was used. FT/PT = full/part time.

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groups showed similar levels of IL-6, sIL-6r, TNF-RII, and sICAM (Table 1).

Discussion

The present study characterized baseline inflammation levels in persons at high risk for cancer, including IL-6, sIL-6r, TNF-RII and sICAM. Whereas higher levels of IL-6 and sICAM have been associated with depression [4–7,11], differences in IL-6 and other circulating markers of inflammation were not found between those with and without depression in this sample.

Chronic psychosocial stress has been associated with higher IL-6 levels compared to controls [18], and it is possible that the non-depressed group had elevated levels of inflammation due to the stress of being at high risk for cancer. However, in the present study, levels of pro-inflammatory cytokine are within the range for women of this age who do not have such stress (i.e., Nurses Health Study) [19,20].

Limitations of the present study include the cross-sectional nature of the study; hence, we do not know how long these individuals had depressive symptoms. In addition, it is not possible to control for prior levels of the participants' inflammatory markers and future research should utilize a prospective design to allow participants to serve as their own controls. The sample size in the present study is moderate; however, previous studies have detected differences in inflammatory markers in studies of this size [7,11].

The present data are important for characterizing high-risk patients who may later acquire knowledge of increased cancer risk through genetic testing. The present study provides a baseline with which to compare other studies, in particular, studies investigating the effects of stress that come from the acquisition of knowledge of genetic status.

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