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Impaired mental health and low-grade inflammation among fatigued bereaved individuals

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ABSTRACT

Background: Fatigue is a common symptom in stressed individuals. Bereavement is a major life event that has been associated with impaired mental health. Little research has investigated the prevalence of fatigue and its inflammatory correlates in bereaved individuals.

Objectives: To assess fatigue prevalence and its relationship with mental health outcomes and markers of inflammation, as indexed by C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) in bereaved individuals.

Methods: Seventy-eight-bereaved adults were examined for fatigue (SF-36 energy/vitality scale), perceived stress (PSS), depression (CES-D), sleep quality (PSQI), pain (SF-36 pain scale), and general health (SF-36 general), and their serum levels of CRP, IL-6 and TNF-α were measured. Group differences between fatigued versus non-fatigued individuals were estimated using analysis of covariance (ANCOVA), with adjustment for body mass index (BMI).

Results: Fatigued bereaved individuals (33%; SF-36 energy/vitality score 0–45) had significantly higher CRP levels ($p < .05$) as compared to non-fatigued bereaved individuals and reported higher levels of pain ($p < .001$), greater stress ($p < .001$), depression ($p < .001$), and sleeping problems ($p < .001$), as well as poorer social functioning ($p < .001$) and general health ($p < .001$) than those in the non-fatigued group. No group differences were found for IL-6 and TNF-α.

Conclusions: Fatigued bereaved individuals showed elevated systemic inflammation as measured by CRP in comparison to non-fatigued bereaved individuals. They were also more likely to report mental health problems that co-occur with fatigue in the context of immune activation. Continued research is needed to help clarify the involvement of inflammatory markers in the development of fatigue in a larger sample of bereaved adults.

1. Introduction

The loss of a spouse is considered one of the most stressful life events one may encounter [1]. Particularly in the immediate weeks and months after the loss, bereavement is associated with a significant increased risk of morbidity and mortality [2, 3]; cardiovascular diseases account for the largest proportion of theses deaths [4, 5].

Depression, anxiety and somatic complaints such as fatigue are hallmark characteristics of bereavement [6–9]. Although approximately half of the bereaved show resiliency against loss and adjust without professional psychological support [10], many others suffer from intense and prolonged grief reactions, which can result in comorbid conditions, such as depression, high blood pressure and/or cardiovascular disease [2, 5]. Furthermore, bereavement has been associated with increased inflammation [8, 11, 12]. It is important to be able to identify those bereaved individuals who are most at risk for adverse health outcomes.

Advances in our biobehavioral understanding of the time course and recovery from grief have pointed to notable parallels with recovery from extreme fatigue [12, 13]. This has led to some characterization of grief as a physiological manifestation of the sickness behavior of fatigue, including symptoms like exhaustion, sleep disturbances, cognitive impairment, attention, memory problems, and impaired immune response [12, 13]. Fatigue is characterized by a subjective, persistent

Abbreviations: BMI, Body Mass Index; CCI, Charlson Comorbidity Index; CES-D, Center for Epidemiologic Studies Depression Scale; CRF, Cancer-related fatigue; CRP, C-reactive protein; PSS, Perceived Stress Scale; PSQI, Pittsburgh Sleep Quality Index; SF-36, The RAND 36-Item Short Form Health Survey

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feeling of tiredness that is poorly relieved by rest; it can interfere with daily activities and quality of life, and is associated with considerable psychological and functional morbidity [14]. Indeed, when one is grieving, he or she loses strength and energy, feeling the constant need to sleep and withdrawals from social engagement, especially within the first three months after the loss [6, 7, 15].

Research in the field of psychoneuroimmunology has contributed considerably to our understanding of inflammatory pathways of fatigue [16–19]. Neuro-immune activation appears to underlie fatigue-like symptoms. Robust evidence in both animal and human studies suggests that c-reactive protein (CRP) and peripheral pro-inflammatory cytokines (e.g. interleukin-6, IL-6; interferon gamma, IFN-γ; tumor necrosis factor alpha, TNF-α) can lead to neuroinflammation, inducing sickness-behavior like fatigue, reduced appetite, sleep disorders, symptoms of depression and cognitive alterations [16, 17, 20–22].

Few empirical studies have comprehensively examined fatigue and its association with adverse health outcomes and inflammatory markers in recently bereaved individuals [23, 24].

We examined the prevalence of fatigue among bereaved individuals, and its relationship with CRP, IL-6 and TNF-α, important markers of inflammation to determine whether the inflammatory manifestation is similar to other clinical populations (e.g. cancer patients). We hypothesized that: (1) a minority of bereaved individuals will exhibit symptoms of fatigue using established cut-scores utilized in other clinical populations (e.g. breast cancer survivors); (2) fatigue would co-occur with physical and mental health problems (e.g. distress, depression, sleep disturbances, pain); and (3) fatigue would be associated with low-grade systemic inflammation, as measured by CRP.

2. Methods

2.1. Study design and procedures

The present study is a secondary analysis of a larger prospective observational study, examining the relationship between bereavement and cardiovascular risk. Between October 2015 and May 2017, study participants were recruited from the Baylor College of Medicine and the general community of Houston. Individuals who recently experienced the loss of their spouse were contacted and recruited from obituaries, support groups, flyer distribution, online posting, and community events. Initially, 369 bereaved individuals were contacted. Of those, 109 individuals agreed to be screened. A total of 84 individuals were eligible to participate. Of those, 78 bereaved participated in the baseline visit, and had “both fatigue and antibody titer data available at the time of data analysis”.

Research assistants administered assessments at the participants' home or in the Bioscience Research Collaborative Community Research Center in the Texas Medical Center. During these visits, participants completed a questionnaire packet, which included self-report demographic questionnaires and clinical questionnaires. Anthropometric measurements including weight, height, and waist circumference and non-fasting blood samples were collected during the early hours of the morning. All samples were collected between 7:30 and 11:00 AM to control for diurnal variation. All study procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study and its recruitment strategy were reviewed and approved by the Institutional Review Board at Rice University. All subjects provided written informed consent prior to their participation.

2.2. Participants

All individuals who had lost a spouse within the past three months were considered eligible for inclusion unless they: (1) were unable to read and write in English; (2) had significant visual or auditory impairment; (3) were pregnant or nursing; (4) had autoimmune and/or inflammatory disease (including rheumatoid arthritis and ulcerative colitis); (5) experienced the loss of a loved one in addition to their spouse (e.g., mother, child, etc.); (6) had divorced within the past year; or (7) were currently undergoing surgery, chemotherapy, and/or radiation to treat cancer.

2.3. Immune assays

Blood samples were drawn between 7:30 AM and 11:00 AM. Serum and plasma samples were frozen and remained at −80 °C until assayed. Standardized enzyme-linked immunosorbent assay (ELISA) methods were utilized to measure serum C-reactive protein (CRP), interleukin-6 (IL-6) and TNF-receptor alpha (TNF-α). Particle enhanced immunoturbidimetric assay (Cobas5S Roche) was utilized for the in vitro quantitative determination of high sensitive CRP. Subjects with CRP levels > 10 mg/L were excluded.

2.4. Questionnaires

2.4.1. The RAND 36-Item Short Form Health Survey

The RAND 36-Item Short Form Health Survey (SF-36) is a 36-item measure that contains eight multi-item subscales: physical functioning; role limitations due to physical health; role limitations due to emotional problems; energy/fatigue; pain; general well-being; social functioning; and general health. The SF-36 is a widely-utilized measure with well-documented robust psychometric properties [25]. For this study, four SF-36 questionnaire subscales were utilized. Fatigue was measured with the *SF-36 energy/vitality subscale*, assessing general level of fatigue over the past four weeks using four items (‘Did you feel full of life?’; ‘Did you have a lot of energy?’; ‘Did you feel worn out?’; ‘Did you feel tired?’). The final score ranges from 0 to 100, with lower scores indicating more fatigue. Cronbach's alpha was 0.89. A “case categorical” variable of the *SF-36 energy/vitality scale* has been commonly used in a series of studies assessing the biological mechanisms underlying cancer-related fatigue [26–29]. In accord with this prior work, those who scored 50 or below were considered fatigued, while those who scored above 50 were considered non-fatigued.

The SF-36 bodily pain subscale was used to assess pain severity and impact over the last four weeks via two items (‘How much bodily pain have you had?’; ‘How much did pain interfere with your normal work?’). Once again, the scale ranges from 0 to 100, with higher scores indicating less-severe, lower-impact pain. The SF36 bodily pain subscale exhibited good internal consistency (Cronbach's alpha of 0.76).

The *social role functioning subscale* includes two items (‘To what extent has your physical health or emotional problems interfered with your normal social activities?’; ‘How much of the time has your physical health or emotional problems interfered with your social activities?’). The final score ranges between 0 and100, with higher scores indicating better social role functioning. Cronbach's alpha for the social role functional subscale was 0.81.

The *general health subscale* (SF-36 General) includes five items (‘In general, how would you estimate your health?’; ‘I seem to get sick a little easier than other people’; ‘I'm as healthy as anybody I know’; ‘I expect my health to get worse’; ‘My health is excellent’). The final score ranges from 0 to 100, with higher scores representing better general health. Internal consistency for this subscale was acceptable, with a Cronbach's alpha of 0.78.

2.4.2. Depression

The Center for Epidemiological Studies Depression Scale (CES-D) was used to assess depressive symptomatology [30]. The CES-D is a widely-used and well-validated 20-item measure with possible scores ranging from 0 to 60. A total score is computed by summating the individual item scores. In accordance with a recent meta-analysis, a cut-off point of 20 and above was used in the present study to indicate clinically-