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Inflammatory pathway genes associated with inter-individual variability in the trajectories of morning and evening fatigue in patients receiving chemotherapy

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ABSTRACT

Fatigue, a highly prevalent and distressing symptom during chemotherapy (CTX), demonstrates diurnal and interindividual variability in severity. Little is known about the associations between variations in genes involved in inflammatory processes and morning and evening fatigue severity during CTX. The purposes of this study, in a sample of oncology patients (N = 543) with breast, gastrointestinal (GI), gynecological (GYN), or lung cancer who received two cycles of CTX, were to determine whether variations in genes involved in inflammatory processes were associated with inter-individual variability in initial levels as well as in the trajectories of morning and evening fatigue. Patients completed the Lee Fatigue Scale to determine morning and evening fatigue severity a total of six times over two cycles of CTX. Using a whole exome array, 309 single nucleotide polymorphisms SNPs among the 64 candidate genes that passed all quality control filters were evaluated using hierarchical linear modeling (HLM). Based on the results of the HLM analyses, the final SNPs were evaluated for their potential impact on protein function using two bioinformational tools. The following inflammatory pathways were represented: chemokines (3 genes); cytokines (12 genes); inflammasome (11 genes); Janus kinase/signal transducers and activators of transcription (JAK/STAT, 10 genes); mitogen-activated protein kinase/jun amino-terminal kinases (MAPK/JNK, 3 genes); nuclear factor-kappa beta (NFkB, 18 genes); and NFkB and MAP/JNK (7 genes). After controlling for self-reported and genomic estimates of race and ethnicity, polymorphisms in six genes from the cytokine (2 genes); inflammasome (2 genes); and NFkB (2 genes) pathways were associated with both morning and evening fatigue. Polymorphisms in six genes from the inflammasome (1 gene); JAK/STAT (1 gene); and NFkB (4 genes) pathways were associated with only morning fatigue. Polymorphisms in three genes from the inflammasome (2 genes) and the NFkB (1 gene) pathways were associated with only evening fatigue. Taken together, these findings add to the growing body of evidence that suggests that morning and evening fatigue are distinct symptoms.

1. Introduction

During chemotherapy (CTX), over 45% of patients experience clinically meaningful levels of fatigue that decrease their ability to tolerate treatments, engage in social relationships, and maintain regular work activities [1]. However, a growing body of evidence demonstrates that inter-individual variability exists in fatigue severity across cancer diagnosis [2–4] and treatments [5,6]. In addition, recent work from our group [7–11] and others [4,12] demonstrates that morning and evening fatigue are distinct yet related symptoms. Some of this inter-individual variability is explained by different phenotypic characteristics that distinguish

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between higher levels of morning (e.g., higher body mass index (BMI), lack of regular exercise, higher state anxiety) and evening (e.g., being white, higher years of education, child care responsibilities) fatigue [9,10]. In addition to phenotypic differences, preliminary evidence suggests that variations in cytokine genes are associated with inter-individual differences in morning (e.g., tumor necrosis factor alpha (*TNFA*) [13] and evening (e.g., interleukin (*IL*)*4* [14] and *IL6* [15]) fatigue severity.

While considered to be multi-factorial, a growing body of evidence suggests that cytokine dysregulation, as well as many other neuroinflammatory processes may modulate fatigue severity in a number of chronic conditions [16–19]. Increased knowledge of the mechanisms that underlie fatigue is essential for the development of effective treatments for this devastating symptom. However, no definitive conclusions can be drawn from studies that evaluated associations between fatigue severity and various biomarkers of cytokine dysregulation (for reviews see [18,19]).

1.1. Associations between fatigue and serum markers of inflammation

To examine this cytokine dysregulation hypothesis, several studies evaluated the associations between fatigue severity and serum cytokine levels. To date, results are inconclusive, with some studies finding positive associations between fatigue severity and circulating levels of TNF-α [20,21] and IL-6 [18,20,22–29] and others finding no associations with TNF-α [18,22,30–33], IL-6 [30,34–38], and IL-4 [25,36,38]. These inconsistent results may be related to the challenges associated with the measurement of serum cytokines, as well as circadian variations in cytokine levels [39].

An alternative approach is to measure circulating levels of biomarkers of immune activation (e.g., cellular receptors) [40]. Again, these results are inconclusive. Some studies found positive associations between fatigue and changes in serum levels of IL-1 receptor antagonist (IL-1ra) [24,35,41,42], soluble TNF receptor II (sTNF-RII) [41,43,44], sTNF-RI [45], and sIL-6R [37,46,47]. However, other studies found no associations between fatigue severity and changes in serum levels of IL-1ra [27,34,36], sTNF-RII [36,42], and sIL-6R [46]. Of note, none of these studies evaluated for associations between diurnal variations in fatigue severity and changes in these serum markers.

1.2. Changes in gene expression and fatigue

Another approach to examine the role of inflammation in fatigue is to evaluate for changes in the expression of inflammatory genes. To date, seven studies have evaluated for changes in gene expression associated with fatigue severity in oncology patients [34,48–53]. Five of these studies [34,48,50,52,53] examined changes in gene expression related to inflammation/immune function. In four of these studies higher levels of fatigue were associated with upregulation of genes that regulate cytokine production (i.e., interferon alpha-inducible protein 27 (*IFI27*) [48], α-synuclein (*SNCA*) [52], *IL1* [34], *IL6* [34], *IL4* [50]). In another study [53], differentially perturbed cytokine pathways were associated with higher levels of evening fatigue. However, across these studies only mean or evening fatigue scores were evaluated. In addition, the sample sizes for these studies were relatively small (i.e., 15 [49] to 137 [50] patients).

1.3. Associations between fatigue and variations in cytokine genes

A third approach that can be used to examine the role of inflammation in fatigue is to evaluate for associations between fatigue severity and variations in cytokine genes. Single nucleotide polymorphisms (SNP) in *TNFA* [54,55], *IL6* [37,56,57], and *IL1RA* [58] were associated with increased levels of fatigue. To date, only three studies evaluated for associations between variations in cytokine genes and diurnal variations in fatigue severity [13–15]. In a study of oncology patients (n = 185) and their family caregivers (n = 103), SNPs in *TNFA* (i.e., rs1800629, rs3093662) and *IL6* (i.e., rs4719714) were associated with higher levels of morning and evening fatigue [13–15]. Additionally, a polymorphism in *IL4* rs2243248 was associated with lower levels of evening fatigue [14]. While the studies cited above provide preliminary evidence that variations in cytokine genes are associated with diurnal variations in fatigue severity, two of the studies evaluated only one polymorphism [13–15] and none of them evaluated oncology patients undergoing CTX.

While evidence exists for the role of cytokine dysregulation as a modulator of neuroinflammation, recent studies found other pathways and processes that contribute to the development of inflammation (e.g., the mitogen-activated protein kinase (MAPK) pathway [59], and inflammasomes [19,60]). However, the contribution of these pathways to fatigue severity in oncology patients undergoing CTX has not been evaluated. Increased knowledge of whether additional inflammatory pathways are associated with diurnal variations in fatigue severity would enhance our understanding of the various mechanisms that contribute to this devastating symptom.

Recently, we identified common and distinct phenotypic characteristics for morning [9] and evening [10] fatigue severity in oncology patients undergoing CTX. This study extends these findings to identify associations between variations in genes associated with a variety of inflammatory processes and the severity of morning and evening fatigue. Since genes interact with one another [61], the polymorphisms that were evaluated were grouped into common inflammatory pathways to provide insights into the role of related genes and the severity of morning and evening fatigue. The purposes of this study, in a sample of oncology patients with breast, gastrointestinal (GI), gynecological (GYN), or lung cancer who received two cycles of CTX, were to determine whether variations in genes involved in inflammatory processes were associated with inter-individual variability in initial levels as well as in the trajectories of morning and evening fatigue.

2. Methods

2.1. Patients and settings

Some of the details of the phenotypic [9–11,62] and genotypic [63,64] methods used in this study are published elsewhere. In brief, patients were recruited from two comprehensive cancer centers, one Veteran's Affairs hospital, and four community-based oncology programs. Patients with a diagnosis of breast, GI, GYN, or lung cancer were eligible to participate if they were ⩾18 years of age; had received CTX within the previous four weeks; were scheduled to receive at least two additional cycles of CTX; were able to read, write, and understand English; and gave written informed consent.

2.2. Instruments

Patients completed a demographic questionnaire, the Karnofsky Performance Status (KPS) scale [65], and the Self-Administered Comorbidity Questionnaire (SCQ) [66]. In addition, patients completed a number of questionnaires to evaluate anxiety [67], depression [68], and sleep disturbance [69].

Fatigue was evaluated using the 18 item Lee Fatigue Scale (LFS) that assesses physical fatigue and energy [70]. Each item was rated