Original Article

Phenotypic and Molecular Evidence Suggests That Decrements in Morning and Evening Energy Are Distinct but Related Symptoms

Bradley E. Aouizerat, PhD, MAS, Anand Dhruva, MD, Steven M. Paul, PhD, Bruce A. Cooper, PhD, Kord M. Kober, PhD, and Christine Miaskowski, RN, PhD

Schools of Nursing (B.E.A., S.M.P., B.A.C., K.M.K., C.M.) and Medicine (A.D.), and Institute for Human Genetics (B.E.A.), University of California, San Francisco, California, USA

Abstract

Context. Little is known about energy levels in oncology patients and their family caregivers.

Objectives. This study sought to identify latent classes of participants, based on self-reported energy levels and evaluate for differences in phenotypic and genotypic characteristics between these classes.

Methods. Energy subscale scores from the Lee Fatigue Scale were used to determine latent class membership. Morning and evening energy scores were obtained just before, during, and for four months after the completion of radiation therapy. Genetic associations were evaluated for 15 proinflammatory and anti-inflammatory cytokine genes.

Results. Two latent classes with distinct morning energy trajectories were identified. Participants who were younger, female, not married/partnered, black, and had more comorbidities, and a lower functional status were more likely to be in the low morning energy class. Two polymorphisms (*IL2* rs1479923 and *NFKB1* rs4648110) were associated with morning energy latent class membership. Two latent classes with distinct evening energy trajectories were identified. Participants who were younger and male and who had more comorbidities, decreased body weight, and a lower functional status were more likely to be in the moderate evening energy class. Five different polymorphisms (*IL1R2* rs4141134, *IL6* rs4719714, *IL17A* rs8193036, *NFKB2* rs1056890, and *TNFA* rs1800683) were associated with evening energy latent class membership.

Conclusion. This study provides preliminary evidence that decrements in morning and evening energy are associated with different phenotypic risk factors and cytokine gene variations. J Pain Symptom Manage 2015;50:599–614.

Key Words

Energy, fatigue, radiation therapy, growth mixture modeling, cytokines, single nucleotide polymorphisms, cancer, family caregivers

Introduction

Energy conservation is one of the earliest interventions that was recommended to reduce fatigue associated with cancer and its treatment.[1,2] In fact, this strategy is included in the latest Fatigue Guidelines published by the National Comprehensive Cancer Network.[3] Energy (also termed perceived energy, vigor, and vitality) and fatigue are often thought to be interchangeable symptoms.[4,5] For example, on the Memorial Symptom Assessment Scale,[6] fatigue is assessed using the phrase lack of energy.

However, increasing evidence suggests that fatigue and energy are distinct but related constructs.[7–9] For example, instruments like the Profile of Mood States (POMS)[10] have separate subscales for fatigue-inertia and energy-vigor. The energy subscale of the POMS evaluates the intensity of energy using a variety of descriptors (e.g., energetic, full of pep, vigorous, active, lively). Like the POMS, the Lee Fatigue Scale (LFS) has two subscales (i.e., a fatigue subscale with 13 items and an energy subscale with five items). The LFS asks participants to rate their level of energy using a 0–10

Address correspondence to: Christine Miaskowski, RN, PhD, Department of Physiological Nursing, University of California, 2 Koret Way – N631Y, San Francisco, CA 94143-0610, USA. E-mail: chris.miaskowski@ucsf.edu

Accepted for publication: May 19, 2015.

0885-3924/$ - see front matter
http://dx.doi.org/10.1016/j.jpainsymman.2015.05.008

Numeric Rating Scale (NRS) on five descriptors (i.e., energetic, active, vigorous, efficient, lively). The original psychometric evaluation of the LFS identified these two distinct subscales.[11] In addition, a recent Rasch analysis of the LFS found that fatigue and energy represented different symptoms.[12] Given these findings, additional research is warranted that provides a more detailed characterization (e.g., diurnal variations, changes in severity) of the symptom of energy.

Our research team has used growth mixture modeling (GMM) to identify subgroups (i.e., latent classes) of oncology patients and their family caregivers (FCs) who differed in their experiences with depression,[13] sleep disturbance,[14] fatigue,[15] and attentional fatigue.[16] In all these GMM analyses, the phenotypic and molecular data from patients and their FCs were combined for a number of reasons. First, both patients and their FCs experience the stress associated with a cancer diagnosis. For the FC, numerous physical, psychological, social, and economic stressors impact their mental and physical health.[17–23] In addition, both groups of individuals have other chronic medical conditions and demands on their time that could result in decreased energy. Finally, both patients and FCs experience significant and comparable levels of sleep disturbance,[24,25] which contribute to decreases in both morning and evening energy levels.

Inflammation may influence energy levels through a variety of mechanisms, including activation of immunomodulators,[26] alterations in mitochondrial function,[27] and/or changes in the activity of the hypothalamic-pituitary-adrenal axis.[28] Inflammation is mediated in part by changes in proinflammatory and anti-inflammatory proteins, their receptors, and a number of transcriptional regulators that affect both the peripheral and the central nervous systems. Therefore, it is reasonable to hypothesize that variations in cytokine genes may contribute to interindividual variability in morning and evening energy levels.

Given the paucity of research on variations in energy levels in oncology patients and their FCs, the purposes of this study were to identify subgroups of individuals (i.e., latent classes derived using GMM) based on their subjective reports of morning and evening energy levels from before the initiation to four months after the completion of the patients' radiation therapy (RT) and to evaluate for differences in demographic, clinical, and symptom characteristics between these latent classes. In addition, based on the results of the GMM analyses for morning and evening energy, variations in a number of genes that encode for cytokines, their receptors, and related transcription factors were evaluated between the latent classes. Separate analyses were done for morning and evening energy.

Methods

Participants and Settings

This descriptive study is part of a larger longitudinal study that evaluated multiple symptoms in both patients who underwent primary or adjuvant RT and their FCs. The methods for this study are described in detail elsewhere.[13] In brief, patients and their FCs were recruited from two RT departments located in a Comprehensive Cancer Center and a community-based oncology program at the time of the patient's simulation visit.

Patients were eligible to participate if they were 18 years or older; were scheduled to receive primary or adjuvant RT for breast, prostate, lung, or brain cancer; were able to read, write, and understand English; gave written informed consent; and had a Karnofsky Performance Status (KPS) score of ≥60. Patients were excluded if they had metastatic disease, more than one cancer diagnosis, or a diagnosed sleep disorder. FCs were eligible to participate if they were 18 years or older; were able to read, write, and understand English; gave written informed consent; had a KPS score of ≥60; were living with the patient; and did not have a diagnosed sleep disorder.

Instruments

The demographic questionnaire obtained information on age, gender, marital status, education, ethnicity, employment status, and the presence of a number of comorbid conditions.

Lee Fatigue Scale. The LFS comprises 18 items designed to assess *physical* fatigue and energy.[11] Each item was rated on a 0–10 NRS. The energy subscale score was calculated as the mean of the five energy items, with higher scores indicating higher levels of energy. Participants were asked to rate each item based on how they felt right now, within 30 minutes of awakening (i.e., morning energy), and before going to bed (i.e., evening energy). Cutoff scores of ≤6.0 and ≤3.5 indicate low levels of morning and evening energy, respectively.[29] The LFS was chosen for this study because it is relatively short, easy to administer, and has well-established validity and reliability.[30,31] In this study, Cronbach's alphas for evening and morning energy were 0.95 and 0.96 for patients and 0.95 and 0.96 for FCs, respectively.

Spielberger State-Trait Anxiety Inventories. These inventories consist of 20 items each that are rated from one to four. The scores for each scale are summed and can range from 20 to 80. Cutoff scores of ≥31.8 and ≥32.2 indicate high levels of trait and state anxiety, respectively. The Spielberger State-Trait Anxiety Inventory-State subscale and Spielberger State-Trait