Original Article

The Role of Central and Peripheral Muscle Fatigue in Postcancer Fatigue: A Randomized Controlled Trial

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Abstract

Context. Postcancer fatigue is a frequently occurring problem, impairing quality of life. Little is known about (neuro) physiological factors determining postcancer fatigue. It may be hypothesized that postcancer fatigue is characterized by low peripheral muscle fatigue and high central muscle fatigue.

Objectives. The aims of this study were to examine whether central and peripheral muscle fatigue differ between fatigued and non-fatigued cancer survivors and to examine the effect of cognitive behavioral therapy (CBT) on peripheral and central muscle fatigue of fatigued cancer survivors in a randomized controlled trial.

Methods. Sixteen fatigued patients in the intervention group (CBT) and eight fatigued patients in the waiting list group were successfully assessed at baseline and six months later. Baseline measurements of 20 fatigued patients were compared with 20 non-fatigued patients. A twitch interpolation technique and surface electromyography were applied, respectively, during sustained contraction of the biceps brachii muscle.

Results. Muscle fiber conduction velocity (MFCV) and central activation failure (CAF) were not significantly different between fatigued and non-fatigued patients. Change scores of MFCV and CAF were not significantly different between patients in the CBT and waiting list groups. Patients in the CBT group reported a significantly larger decrease in fatigue scores than patients in the waiting list group.

Conclusion. Postcancer fatigue is neither characterized by abnormally high central muscle fatigue nor by low peripheral muscle fatigue. These findings suggest a difference in the underlying physiological mechanism of postcancer fatigue vs. other fatigue syndromes. J Pain Symptom Manage 2015;49:173–182.

Key Words

Postcancer fatigue, cognitive behavioral therapy, central muscle fatigue, peripheral muscle fatigue, central activation failure, muscle fiber conduction velocity, twitch interpolation technique, surface electromyography

Introduction

An estimated 19% to 39% of the cancer survivors suffer from persistent fatigue, long after finishing treatment.[1–3] Postcancer fatigue is a debilitating problem, with profound effects on quality of life.[4,5] Previous studies have shown that cognitive behavioral therapy (CBT), specifically designed for postcancer fatigue, is an effective treatment for severely fatigued cancer survivors.[6] However, although it is now possible to effectively treat postcancer fatigue, the etiology remains unknown.

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In the medical literature, the term fatigue usually refers to fatigue experienced by the patient, but it also can refer to physiological fatigue. In physiology, fatigue is generally defined as the loss of voluntary force-producing capacity during exercise.[7] Loss of force-producing capacity can have a peripheral and a central origin because muscles do not function autonomically but are activated by the nervous system.[8]

During peripheral muscle fatigue, a decrease in pH, accumulation of lactate, and changes in intra- and extracellular ion concentrations influence membrane excitability of the muscle tissue.[9] Multichannel surface electromyography (sEMG) can reveal the propagation velocity of an action potential over the muscle fiber, denoted as muscle fiber conduction velocity (MFCV). Under isometric conditions, MFCV is an indicator of peripheral fatigue.[8] Another measure of peripheral fatigue is the decrease in muscular force response to artificial electrical stimulation from pre- to postexercise.

Besides peripheral factors, a failure of drive from the central nervous system may also contribute to the loss of voluntary force-producing capacity during exercise.[10] Submaximal central activation during exercise, or central activation failure (CAF), is an indicator of central muscle fatigue[8] and can be determined with a twitch interpolation technique.[11]

Low peripheral muscle fatigue and high central muscle fatigue appear to be a shared neurophysiological feature of fatigue in patients with chronic fatigue syndrome (CFS)[12] and neuromuscular diseases.[13] It may be hypothesized that postcancer fatigue is also characterized by low peripheral muscle fatigue and high central muscle fatigue. The aims of this study were to examine whether peripheral and central muscle fatigue differ between severely fatigued and non-fatigued cancer survivors and to examine the effect of CBT on peripheral and central muscle fatigue of severely fatigued cancer survivors in a randomized controlled trial.

Methods

Trial Registration

The study is registered at ClinicalTrials.gov (NCT01096641).

Data Collection

The local ethics committee of the Radboud University Medical Center (RUMC, Nijmegen, The Netherlands) approved the study, and all participants provided written informed consent. In Part A of the study, severely fatigued and non-fatigued cancer survivors were compared (Fig. 1). In Part B of the study, severely fatigued cancer survivors were randomly assigned to either the intervention group (CBT) or the waiting list group (Fig. 1). Fatigue severity was measured by the fatigue severity subscale of the Checklist Individual Strength (CIS-fatigue)[14,15] during screening and right before the start of the study. Patients who appeared to be not severely fatigued during the second assessment were not included in the study. Severe fatigue was defined by a cutoff score of $\geq$35 points.[6,16–18] CAF, an indicator of central muscle fatigue, was measured using a twitch interpolation technique. MFCV, an indicator of peripheral muscle fatigue, was measured using sEMG. Both the twitch interpolation technique and sEMG were applied during a sustained contraction of the biceps brachii muscle.

Participants

All participants had completed curative treatment of a malignant solid tumor at least one year earlier and had no evidence of disease recurrence. Patients with a comorbidity that could explain fatigue, patients suffering from severe lymphedema and patients who could not use their left arm extensively were excluded. General health status was checked using the Research and Development 36-Item Health Survey,[19] and patients were screened for depression with the Beck Depression Inventory for Primary Care.[20] The minimum age at disease onset was 18 years, and patients were no older than 65 years when entering the study.

Severely fatigued cancer survivors ($n = 66$), who were referred for CBT to the Expert Center for Chronic Fatigue of the RUMC, were asked to participate in the parallel-group randomized controlled trial (Part B). Baseline measurements of 20 of the 66 fatigued cancer survivors were compared with 20 age- and sex-matched non-fatigued cancer survivors, recruited from the outpatient clinics of Medical Oncology and Radiation Oncology of the RUMC (Part A). Non-fatigued patients were assessed only once at the RUMC. Fatigued patients ($n = 64$; two patients refused participation) were randomly (3:1) assigned to either the intervention group ($n = 50$) or the waiting list group ($n = 14$). Random assignment was done by means of a sequence of labeled cards contained in sealed numbered envelopes prepared by a statistical adviser. The envelopes were opened by the psychologists in the presence of the patient. Patients randomized to the intervention group were immediately treated with CBT as described previously.[10] In six modules, CBT focused on six perpetuating factors of postcancer fatigue, including insufficient coping with the experience of cancer, fear of disease recurrence, dysfunctional cognitions concerning fatigue, dysregulation of sleep, dysregulation of activity, and low social support and negative social interactions. The therapy was tailored to the individual patient, and the number of one-hour sessions with the psychologist was determined by the number of modules used