

Childhood Cancer Survivor Study Analysis Concept Proposal

Title: Prevalence of Fatigue and Sleep Disturbance in Survivors of Childhood Cancer

Working Group: Psychosocial Working Group

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Background and Rationale:

Complaints of fatigue and sleep disturbance have become more common in the general population. While the exact prevalence of fatigue is unclear, estimates range between 7-45% depending upon methods of measurement and over what time period. The impact of sleep disorders on individual and public health has become gradually more recognized and understood over the last 20 years. An estimated 20-30 million Americans, of all ages, experience intermittent sleep-related problems, and up to 40 million are chronically ill due to a sleep disorder. The impact of sleep deprivation upon quality of life is significant and is often responsible for impaired cognition, reduced productivity, and fatigue-related accidents.

Fatigue has also become more recognized as a side effect of cancer therapy that significantly impacts quality of life. Most studies have concentrated on issues of fatigue during active therapy, while few have investigated its prevalence following treatment. These studies, most involving survivors of Hodgkin's disease and breast cancer, have reported a prevalence of moderate to severe fatigue as high as 17-30% up to 12 years following therapy. None, however, have assessed fatigue or possible sleep disorders in survivors of pediatric malignancies.

The etiology of persistent fatigue following cancer therapy is unclear and likely multifactorial. It is possibly related to sleep disturbances, depression, prior treatment, medical conditions and/or treatment-related sequelae. Age of diagnosis and treatment may also play a role by affecting the developing brain and disrupting sleep cycles. This may have an impact upon the occurrence of fatigue and/or sleep disturbances later in life.

There are limited data reported in the medical literature concerning fatigue and sleep disorders as a late effect of cancer therapy. Moreover, there is no information regarding its presence in survivors of pediatric cancers.

Specific Aims/Objectives/Research Hypotheses:

This study will use existing data from the Childhood Cancer Survivor Study (CCSS) to determine the prevalence of fatigue among this cohort and assess its relationship to sleep disturbance, diagnoses, age, age at diagnosis, treatment, indicators of depression and other late medical complications.

Additionally, this study will survey selected CCSS participants to assess current levels of fatigue and possible sleep disturbance. The study sample will include all HD survivors (1700), and random samples of ALL (400), CNS tumor (400), bone tumor (200) and soft tissue sarcoma (200) survivors. A random sample of 400 siblings of these participants will be used as a control.

These diagnoses were selected for study based on existing data in survivors of HD (Green, DM et al., 2002 ASCO abstract 1580), possible effects of cranial radiation, and the preliminary frequencies of fatigue and sleep disturbance reported in the 2000 CCSS Follow-up Survey (see appendix 1). Levels of fatigue and sleep disturbance will be assessed in this sub-group using the following scales: the Functional Assessment of Cancer Therapy Fatigue Subscale (FACT-F), the Epworth Sleepiness Scale, and the Pittsburgh Sleep Quality Index (PSQI). These have been compiled into a one page double-sided questionnaire, which takes less than 5 minutes to complete. (See appendix 2 – PSQI questions 1-13, FACT-F question 14, Epworth question 15.)

Hypotheses:

- 1) Excessive fatigue is a prevalent finding in survivors of childhood cancer and will occur more frequently than in sibling controls.
- 2) A significant proportion of fatigue following childhood cancer therapy is related to an underlying sleep disturbance as measured by the PSQI.
- 3) Fatigue following childhood cancer is significantly related to the initial treatment, i.e. chemotherapy, CNS directed radiation therapy, or a combination of these.

- 4) Fatigue is more prevalent in childhood cancer survivors with an earlier age of initial diagnosis.
- 5) Fatigue is significantly related to increased levels of depression and/or anxiety as measured by the Brief Symptom Inventory.
- 6) Major medical complications following treatment; specifically involving the endocrine, pulmonary, or cardiovascular systems; are related to a higher prevalence of fatigue and sleep disturbance.
- 7) Chronic pain contributes to increased levels of fatigue and sleep disturbance in survivors of childhood cancer.

Analysis Framework:

- a. Outcomes of interest from review of existing CCSS data:
 1. Prevalence of fatigue (question 14, CCSS 2000 follow-up survey)
 2. Prevalence of sleep disturbance (question 15, CCSS 2000 follow-up survey)
 3. Relationship of fatigue/sleep disturbance to diagnosis, therapy, age at diagnosis, time since diagnosis, medical complications, depression/anxiety (as measured by the BSI), medications, and pain.
- b. Outcomes of interest from current proposed survey:
 1. Prevalence of fatigue
 2. Prevalence of sleep disturbance
 3. Relationship of fatigue/sleep disturbance to diagnosis (HD, ALL, CNS tumors, bone tumors, soft tissue sarcomas), therapy, age at diagnosis, time since diagnosis, medical complications, depression/anxiety, medications and pain.
- c. Subject population:
 - I. All CCSS cases that responded to the fatigue and sleep questions on the 2000 follow-up survey. The sibling cohort will be analyzed for comparison to the subjects.
 - II. All HD survivors (approximately 1700 individuals) in the CCSS cohort, 400 ALL (½ with history of CNS XRT and ½ without), 400 CNS tumor, 200 bone tumor, and 200 STS survivors. A random sample of 400 from the approximately 776 siblings of these cases will be analyzed for comparison to this sub-group.
- d. Explanatory variables: diagnosis, age, age at diagnosis, time from diagnosis, type of treatment, medical complications (i.e. endocrine, pulmonary, or cardiovascular), depression, anxiety, and pain

d. Type of Analysis:

I. Univariate Analysis

- a. Logistic regression analysis will be performed with the independent variable of fatigue regressed on diagnosis, age, age at diagnosis, time since diagnosis, treatment, medical complications, sleep disturbance and psychosocial variables.

II. Multivariate Analysis

- a. A multivariate analysis will be performed with logistic regression of fatigue on diagnosis, age, age at diagnosis, time since diagnosis, treatment and other significant variables if identified by the univariate analysis.

III. Sibling Analysis

- a. Odds ratios will be calculated comparing the level of fatigue and sleep disturbance in subjects to sibling controls.
b. A multivariate GEE logistic regression will be used for analysis of case data.

e. Specific tables:

I. Demographics of CCSS cases:

- sex
- diagnosis
- age at diagnosis
- age at follow-up
- type of treatment (chemotherapy, radiation, or combination)
- other known medical complications
- BSI score

II. Outcomes:

- frequency of feeling fatigued
- frequency of problems sleeping
- FACT-F score, Epworth Sleepiness Score, PSQI Score

III. Exposures/Risk factors:

- Odd ratios

Special Consideration:

I am a pediatric hematology/oncology/BMT fellow at the University of Minnesota. The analysis of these data will be completed at the University of Minnesota, with input and oversight from the Seattle statistical center as part of a thesis project in a master's degree program in Clinical Research. Dr. Gerald Rosen, a sleep expert from Hennepin County Medical Center, Minneapolis, will assist with interpretation of the sleep data.

These data will be analyzed as part of a master's thesis with the aim of preparing two manuscripts (the first based upon existing CCSS data, the second based upon data acquired from the proposed fatigue/sleep survey) for publication.

Appendix 1

Preliminary Results from 2000 CCSS Follow-up Survey

<u>Diagnosis</u>	<u>Survivors</u> (%)	<u>Fatigue</u>		<u>Sleep Disturbance</u>	
		(%)	<u>OR (95% CI)</u>	(%)	<u>OR (95% CI)</u>
Leukemia	2372 (34.4%)	14.9	--(referent)--	12.0	--(referent)--
CNS	864 (12.5%)	16.8	1.15 (0.93-1.42)	10.4	0.85 (0.66-1.09)
HD	883 (12.8)	19.5	1.38 (1.13-1.69)*	15.5	1.34 (1.08-1.68)*
NHL	491 (7.1%)	16.0	1.09 (0.84-1.43)	10.4	0.85 (0.62-1.16)
Kidney	650 (9.4%)	12.8	0.83 (0.65-1.08)	9.5	0.77 (0.58-1.03)
Neuroblastoma	503 (7.3%)	10.8	0.69 (0.52 0.93)*	8.2	0.65 (0.46-0.92)*
Soft Tissue Sarcoma	602 (8.7%)	19.4	1.38 (1.09-1.73)*	16.3	1.42 (1.11-1.83)*
Bone	525 (7.6%)	18.1	1.26 (0.98-1.62)	17.3	1.54 (1.19-1.99)*
Total	6890	16.0	*p<0.05	12.4	*p<0.05

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