Relationship between Physical Activity and Fatigue and Sleep in Pediatric Brain Tumor Survivors

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Abstract

Research Question: The primary aim of the proposed study is in a cohort of 8-17-year-old brain tumor survivors studied at six months through five years after the completion of their therapy, will physical activity be associated with fatigue, excessive daytime sleepiness, and sleep disruptions.

Background, Significance, and Rational: With improvement in survival rates in children diagnosed with brain tumors, there is an increasing population with potentially long-term health effects due to the tumor and associated treatment. Some of the more common problems experienced by this population include fatigue, daytime sleepiness, psychomotor development, and challenges to be physically active. Levels of physical activity among pediatric brain tumor survivors may be associated with fatigue, excessive daytime sleepiness and other sleep disorders. Analyzing the relationship between these parameters in pediatric brain tumor survivors will contribute to a gap in the literature on the relationship between physical activity and common symptoms survivors will experience.

Materials and Methods: The study is a component of an ongoing larger study conducted by our research team, which is exploring perceived stress, sleep, fatigue, and biomarkers in pediatric brain tumor survivors. A descriptive, cross-sectional, correlation design was used to address the relationships between the variables. In this study, survivors completed the Godin Leisure Time Exercise Questionnaire to evaluate their levels of physical activity. Additionally, data from selected variables from the larger study (e.g., sleep study parameters and reports of perceived fatigue and sleepiness) were available to augment data analysis in this study.

Results: The sample included eight brain tumor survivors, where five were male (62.5%), and all participants were 11 years of age or older, representing an adolescent population. Six different tumor types were represented in the sample, with low grade glioma (37.5%) being the most common. All participants reported physical activity levels considered appropriately active and relatively lower levels of fatigue. While excessive daytime sleepiness was not reported in this sample, most participants had a sleep diagnosis (87.5%), which included primary snoring (62.5%), obstructive sleep apnea (12.5%), and periodic limb movements (12.5%). The Multiple Sleep Latency Test results categorized most participants with daytime sleepiness (71.4%). There were no significant relationships between physical activity and fatigue or sleep measures.

Conclusions and Impact: This study provides information on the relationship between physical activity levels and fatigue and sleep in a young brain tumor survivor population. This information can aid healthcare providers, caregivers, and the patients in understanding the significance of incorporating physical activity into the long-term treatment and symptom management plan. Improved informed care specific to the unique symptoms these survivors experience, will enhance their health-related quality of life.

Research Question

Overall BTS face a range of physical limitations, such as balance impairment and gross motor function, due to the tumor and treatment, and these known limitations may impact activity level.[1] It is important for future research to investigate the benefits of PA during survivorship.[2] A meta-analysis of studies on fitness and exercise among pediatric cancer survivors concluded PA has some association with improved well-being, as well as overall quality of life (QoL).[3] The conclusions recommended further research focused on a clinically related approach when examining the effectiveness of engagement in PA in young survivors.[3] Another study investigating PA levels and sleep quality in pediatric cancer survivors found that higher levels of PA were associated with improved sleep efficiency.[4] This study investigated PA levels and looked for relationships with child and adolescent sleep and fatigue.

The primary research question of the current study is: In a cohort of 8-17-year-old brain tumor survivors (BTS) studied at six months through five years after the completion of their therapy, will physical activity (PA) levels be associated with fatigue, excessive daytime sleepiness, and sleep disturbances.

Hypothesis

The overall hypothesis for the current study is: Pediatric BTS with reported increased PA will experience fewer sleep problems and less fatigue. This hypothesis was tested via the execution of four Specific Aims (SA)., all of which are stated as follows (Fig.1):

Specific Aim 1: Examine the relationship between level of physical activity and self-reported fatigue.

a. The hypothesis tested by this SA is that children with increased levels of physical activity have reduced levels of fatigue. This was evaluated by completing correlation analysis on the measures from the Godin Leisure Time Exercise Questionnaire (GLTEQ) and self-reported outcomes on the PROMIS Fatigue Scale.

Specific Aim 2: Examine the relationship between level of physical activity and self-reported day-time sleepiness.

b. The hypothesis tested by this SA is that children with increased levels of physical activity have reduced levels of daytime sleepiness. This was evaluated by completing correlation analysis on the measures from the GLTEQ and self-reported outcomes on the Epworth Sleepiness Scale (ESS).

Specific Aim 3 (exploratory aim): Explore the relationships between the level of physical activity and daytime sleep latency.

c. The hypothesis tested by this SA is that levels of physical activity are correlated with daytime sleep latency disturbances. This was evaluated by completing correlation analysis on the measures from the GLTEQ and correlating the findings to the data collected on daytime sleep latency from the Multiple Sleep Latency Test (MSLT).

Specific Aim 4 (exploratory aim): Explore the relationships between the level of physical activity and sleep efficiency.

d. The hypothesis tested by this SA is that levels of physical activity are positively correlated with sleep efficiency score. This was evaluated by completing correlation analysis on the measures from the GLTEQ and correlating the findings to the sleep efficiency score collected from the Polysomnography (PSG) test.

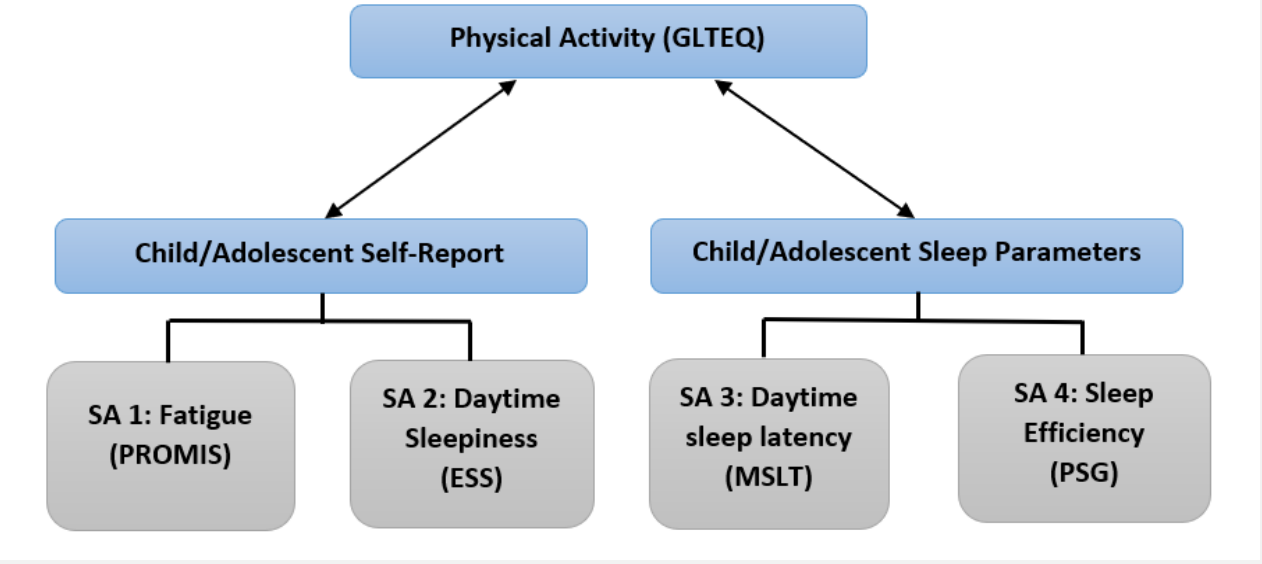

Figure 1. Hypothesis test organized by Specific Aims
Each Specific Aim (SA) will use an individual variable from the larger study (green boxes) and explore the relationship to physical activity levels.

Introduction

Background

Approximately 28,000 children birth through 19 years are diagnosed with cancer including central nervous system (CNS) tumors and primary brain tumors, which are the second most reported cancer in children, after leukemia, and the most common solid tumor of childhood in the United States.[5] Survival rates are improving, and among children diagnosed with CNS tumors are nearing 75% survival five years after being diagnosed.[5] Advanced medical treatments have given rise to an increase in the number of survivors in this population, however despite these improved rates, this subset of pediatric cancer survivors is experiencing adverse psychological and physiological side effects.[6] The impact of the tumor or treatment type, including surgery, or other treatments such as radiation and/or chemotherapy are known to contribute to the brain injury and cognitive deficits seen in this population.[7] These improved survivorship rates among pediatric brain tumor survivors (PBTS) are significant, and increased attention is needed to address the long-term consequences these survivors may experience and necessary intervention strategies in order to improve their health-related quality of life (HRQoL).

Fatigue during survivorship, frequently referred to as cancer-related fatigue (CRF), is one of the most frequent and devastating symptoms in cancer survivors, and it can impair performance in school and work-related settings.[8] CRF includes symptoms such as diminished energy and mental capacity. It has been demonstrated in studies that fatigue and reduced quality of sleep are common late effects encountered by childhood cancer survivors, and survivors of childhood brain tumor report more fatigue compared to that of a population-based control.[9] Causes for the symptoms of fatigue and sleep disturbances among young pediatric BTS population are poorly understood, and are likely multifactorial.[8] Additionally, childhood survivors of cancer mostly do not meet the weekly physical activity recommendations[3], and this is an addressable factor when considering the long-term symptoms of fatigue and sleepiness experienced by survivors. Engaging in physical activity has been correlated with improved well-being in pediatric cancer subpopulations[3], moreover, physical activity interventions studied in pediatric BTS are considered safe and has potential to decrease reported fatigue in patients.[10]

Significance

HRQoL is multidimensional and includes assessments of physical functioning which are sensitive to the developmental changes in children and adolescents.[11] A study focused on HRQoL in childhood cancer survivors was conducted to identify factors related to poor quality of life outcomes and found survivors who reported more fatigue experienced poorer outcomes.[12] Among factors potentially related to fatigue is sleepiness. Fatigue is specified by lower levels of energy and weariness, while sleepiness is a regular feeling of needing to sleep and may be classified as a disorder when sleep occurs too often (excessive daytime sleepiness) or too infrequent (insomnia). Within the pediatric cancer population, pediatric brain tumor patients are at a higher risk for insomnia and sleepiness because of direct damage to brain structures by the tumor, the treatment, or both.[13,14]

Contributing factors to increased levels of fatigue and sleepiness in pediatric cancer survivors is persistence of disrupted sleep patterns and habits, such as decreased levels of PA and disruption of regular sleep-wake cycle during treatment.[4] Levels of PA during survivorship may be expected to increase, however several studies have indicated that childhood survivors of cancer often have lower levels of PA than their peers.[3,8,10,13] A study evaluated the relationship between PA and sleep in children undergoing treatment for their cancer (23 leukemia/lymphoma, five brain tumor, and eight solid tumor), and found that increased levels of PA was meaningfully associated with improved quantity and efficiency of sleep.[4] Thus, PA may be regarded as a potential modifiable factor to decrease abnormal sleep patterns that may contribute to fatigue.

Rationale

A previous but related study, Perceived Stress, and the Fatigue Symptom Cluster in Childhood Brain Tumor Survivors[15], used a cross-sectional method to measure sleep-wake disturbances (SWD) and fatigue in school age survivors in their first five years post treatment. The collection of sleep-wake parameters using actigraphy was not feasible, however, the study did find the parents reported SWD and children reported fatigue. The results from this study indicated the need for further investigation of the relationship between variables to develop a better understanding of the young survivor experience. While this study did not investigate PA in the participants, further research related to PA is suggested because it is thought to be important, given evidence for inadequate activity in childhood BTS.[15] This study contributes to the information gap regarding PA and its relationship to the contributing factors to sleepiness and fatigue.

The goal of the current study was to explore the relationships between PA levels and fatigue, excessive daytime sleepiness, and sleep disturbances in 8-17-year-old BTS, 6 months through 5 years from completion of therapy. The study was conducted as a companion investigation to an ongoing larger research study investigating relationships between factors of fatigue and sleepiness such as perceived stress, sleep/wake parameters, and stress/sleep biomarkers in childhood BTS. The investigation provided the foundational underpinning which enabled the generation of the research question for this companion study, as well as, provided baseline information that has the potential to enrich the analysis of data obtained from the companion investigation. The outcomes of these analyses are useful in understanding the clinical impact PA may have on fatigue, sleepiness, and sleep, and ultimately the HRQoL in this patient population. Therefore, this research may be significant in better informing health-care providers, caregivers, and patients on designing a long-term treatment plan which can enhance the HRQoL of these patients.

Materials and Methods

General Study Details and Resources

This study is a companion study which is a component of a larger study that is exploring the relationships between perceived stress, sleep, fatigue, and biomarkers in childhood BTS. The companion study utilized data collected from the larger study where survivors participate in a Polysomnography (PSG) test and complete several questionnaires to measure their perceived

stress levels, sleepiness, and fatigue. In addition to the larger study's data collection, the companion study included obtaining PA levels in childhood BTS. The data on fatigue, sleepiness, and sleep retrieved from the larger study contributes to the exploration of the relationship between sleepiness and fatigue variables and PA in this study.

This is a single group, single arm study design using convenience sampling. The larger study recruited 25 participants from the Cook Children's Medical Center (CCMC) in the Neurosciences Program and the Life After Cancer Program (LACP). Eight participants from the larger study who completed the PA questionnaire are included in this study.

Subject identification

All participants for the study, established by the larger study, were identified using the Electronic Health Records system. Inclusion and exclusion criteria were applied to potential study participants during the initial identification process of the larger study.

All participants were recruited in the outpatient setting. The target population for this study are children and adolescents ages 8 to 17 years who are free of active or recurrent disease from tumor or cancer (may have stable residual tumor) at the time of recruitment, and who are at least 6 months and less than 6 years from the completion of all treatment for a malignant or nonmalignant brain tumor. Exclusion criteria included non-English language and inability of child or parent to complete study requirements.

A password-protected Excel master list was kept logging all contact with potentially eligible participants, their date of birth, telephone number(s), address, and email address, which was maintained on the Team Site for the Hematology and Oncology Program at Cook Children's Medical Center. Email addresses were only used following their signing of the Agreement and Consent for Cook Children's Physician/Participant Email Communications from participants wanting to communicate and receive documents by email. Each eligible participant was assigned a code, and the password protected master list served as the document allowing for matching the participant to the code. This study was conducted in compliance with the protocol, Good Clinical Practice, and all Institutional Review Board regulatory requirements.

Measures

I. Physical Activity Questionnaire

Physical activity (PA) was measured using the Leisure Score Index (LSI) from the Godin-Leisure-Time Exercise Questionnaire (GLTEQ). It is a four-item self-administered questionnaire asking participants to recall the type (mild, moderate, strenuous) and amount/frequency of exercise they engage in for at least 15 minutes during a typical week.[16] One question asks how often the participant engages in any regular activity long enough to work up a sweat or make their heartbeat rapidly in a 7-day period. A total score for the week is calculated by using the participant responses to the three other questions regarding frequency engaging in the three different levels of activity and multiplying each frequency by an estimated intensity guided metabolic equivalents (METs). The levels of activity include mild, moderate, and strenuous

exercise and is multiplied by three, five, and nine respectively, and the final score is calculated by summing each weighted frequency.[16] To calculate, the equation appears as follows; (3* mild frequency* duration) + (5* moderate frequency*duration) + (9* strenuous frequency* duration).

This summation is called the Leisure Score Index (LSI), where scores can be used to evaluate the individual's engagement in PA, from lowest to highest. These scores are also used to classify participants, determined by the North American public health PA guidelines, which are as follows: LSI 24 units or more is considered active, LSI 14 to 23 units is considered moderately active, and less than 14 units is considered insufficiently active/sedentary.[18]

The GLTEQ is commonly used in oncology research and the total score, LSI, can be used for ranking individuals from the lowest to highest exercise levels, with a LSI directly correlating to activity level.[17] There are findings to support the use of the scale and the interpretation of the LSI for assessing relative change in exercise among cancer survivors.[18] The GLTEQ measures have been validated and have proven reliability in a cancer population study and specifically teenagers and young adults (TYA) living with cancer or as cancer survivors.[19,20] Additionally, GLTEQ has a test-retest coefficient of 0.81 in children and adolescents.[21]

II. Fatigue Questionnaire

Self-reported fatigue was evaluated with the PROMIS-Pediatric Fatigue questionnaire. The pediatric PROMIS fatigue item short form includes 10 items measuring specific fields of participant energy and capacity for physical functioning, psychosocial effects, as well as anemia-specific concerns. The PROMIS fatigue measure for pediatrics demonstrates validity in oncology by differentiating between 8- to 17-year-olds who are on treatment versus survivorship[21] and is the recommended assessment tool for CRF per the National Cancer Institute Clinical Trials Planning Committee. Reliability in a pediatric oncology sample of 200 participants ages 8 to 17 with leukemia, brain tumors, and solid tumors was 85%, and feasibility was reflected in a 92% completion rate.[22] The PROMIS-Pediatric Fatigue questionnaire raw scores are converted to standardized t scores, and a t score of 50 is considered normal. Scores above or below 50 in increments of 10 are scored as standard deviation scores above or below average levels of fatigue.

III. Daytime Sleepiness Questionnaire

The Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) was used to evaluate for self-reported excessive daytime sleepiness (EDS) in participants. This questionnaire was developed from the need to assess accurately sleepiness in young children and adolescents. The ESS-CHAD was originally a modification of the original ESS scale editing items 3 and 7 and adding an additional item to the ESS-CHAD.

A study conducted with 297 adolescents within two independent schools with ages ranging from 12-18 years indicated the ESS-CHAD is both reliable and valid when using in this population.[23] Independent samples *t*- test was used initially to ascertain if there were any differences between the two schools where data was collected. Internal validity of the ESS-CHAD was measured

using item-total Pearson correlations and Rasch analysis. Inter-item correlations and Cronbach's α were conducted to establish reliability of the measure.

Following test-retest data from a small subgroup of 29 students in one school provided an intraclass correlation coefficient of 0.89. For the whole sample of 297 adolescents, the ESS-CHAD showed moderate to strong correlations and Cronbach α of 0.73.[23] However, the ESS-CHAD requires further investigation to establish validity in children less than 12 years age. The ESS-CHAD has not yet been widely studied in the populations to which it was designed to assess. The ESS-CHAD has a possible range of 0-24 and scored using any score >= 10 considered excessive daytime sleepiness and scores >= 16 indicating severe excessive daytime sleepiness.

IV. Sleep Study (Sleep Diagnosis, Sleep Efficiency, and Multiple Sleep Latency Test)

Polysomnography (PSG) provides electrophysiological sleep data of participants, including sleep stages and sleep efficiency. PSG is the accepted gold standard for sleep assessment has been shown to be a reliable method of evaluating sleep in children as it is in adults.[24] PSG is used in children with suspected OSAS (obstructive sleep apnea syndrome), central apnea, neuromuscular disorders, chronic lung disease, parasomnias, restless legs syndrome, and excessive daytime sleepiness.[25] Sleep Efficiency (SE) scores were computed based on the results from the PSG study for each participant. SE scores equal to or greater than 80 percent are considered appropriately efficient.

The Multiple Sleep Latency Test (MSLT), focusing on REM Sleep Onset (REMSO) during naps, is typically performed following the PSG to assess objective information on excessive daytime sleepiness.[26] The REMSO mean time (in minutes) was used to categorize participants into three groups: narcolepsy for a mean REMSO 10 minutes or less, sleepy for a mean REMSO 11 to 19 minutes, and normal for a mean RESOM equal to or greater than 20 minutes. The procedure for MSLT begins 1.5-3 hours after morning awakening following PSG and includes a series of 4-5 opportunities for the child to sleep for a period of two hours in an environment similar to nighttime sleep. To ensure reliability of the daytime sleep measurements, calibration of the EEG leads to identify REM is conducted with the patient prior to all nap events.

Data Collection

I. Recruitment and Consent

Identified participants were recruited using several methods including being approached by an investigator during routine clinic visits, receiving a flyer sent via postal mail with a consent for email communication, or receiving a scripted telephone call from an investigator. All telephone calls were made by the student investigator using a phone script to explain the study, and a formal consent/assent was obtained prior to any data collection procedures. The student investigator ensured the participants provided both informed consent and assent prior to any consent procedures. Information shared included a discussion of the purpose of the study, procedures to be followed, the duration of participation, and the risks and benefits of participation, as described in the consent form. A signed consent form was obtained from a

parent/LAR, and written assent from a minor aged 13 to 17 years and verbal assent from a minor aged 8 to 12 years.

Initial consent/assent procedures for this study were done concurrently with the larger study data collection for participants. For this study, recruitment of past participants who already completed data collection procedures of the larger study was completed by identifying participants using the contact information provided in password-protected excel master list. Re-consent/assent by participants was obtained when carrying out telephone recruitment for participants.

Participants were surveyed either by telephone (if already completed larger study visit) or by pencil and paper questionnaire at the time of data collection for the study. If surveyed by telephone, the participant (or legally authorized guardian) was contacted via the phone number provided in password-protected excel master list. Re-consent/assent by participants was obtained when carrying out the telephone call with participants, as it is an addition to the previously consented research study.

II. Recording

Data collection was from survivors (13-17 years) who were able to verbally respond and give an accurate self-assessment to questions without their legally authorized guardians, or from the patient's legally authorized guardians from those survivors (8-12 years) who were unable to verbally respond and give an accurate self-assessment of their physical activity levels, fatigue, and sleepiness.

The recruited participants for this study completed the questionnaires using pencil and paper when they came onsite for their scheduled day of participation for the larger, primary study, as the two investigations were run simultaneously. The participants completed the paper questionnaire, if they could provide an accurate self-assessment, or with the assistance of the participant's legal parent or guardian if the participant was not capable of providing an accurate self-assessment. Demographic information on the participants was collected from the medical records and parental report.

Statistical Analysis, Clinical Characteristics, and Sample Size

Statistical analysis was performed using both descriptive and inferential statistics to explore relationships among the variables of PA, fatigue, sleepiness, and sleep. Several of the measures are designed to categorize outcomes, including the LSI, ESD, and MSLT, rather than to apply to a continuous spectrum. Spearman's Rho was used for analysis of correlations between the nonparametric variables for the following specific aims:

Specific Aim 1: Examine the relationship between level of physical activity and self-reported fatigue.

e. The hypothesis tested by this SA is that children with increased levels of physical activity have reduced levels of fatigue. This was tested by completing correlation analysis on the measures from the Godin Leisure Time Exercise Questionnaire (GLTEQ) and self-reported outcomes on the PROMIS Fatigue Scale.

Specific Aim 2: Examine the relationship between level of physical activity and self-reported day-time sleepiness.

f. The hypothesis tested by this SA is that children with increased levels of physical activity have reduced levels of daytime sleepiness. This was evaluated by completing correlation analysis on the measures from the GLTEQ and self-reported outcomes on the Epworth Sleepiness Scale (ESS).

Specific Aim 3 (exploratory aim): Explore the relationships between the level of physical activity and daytime sleep latency.

g. The hypothesis tested by this SA is that levels of physical activity is correlated with daytime sleep latency disturbances. This was evaluated by completing correlation analysis on the measures from the GLTEQ and the findings to the data collected on daytime sleep latency from the Multiple Sleep Latency Test (MSLT).

Specific Aim 4 (exploratory aim): Explore the relationships between the level of physical activity and sleep efficiency.

h. The hypothesis tested by this SA is that levels of physical activity is positively correlated with sleep efficiency score. This was evaluated by completing correlation analysis on the measures from the GLTEQ and the findings to the sleep efficiency score collected from the Polysomnography (PSG) test.

All field data was appraised for completeness, and any missing information was acquired on site. Data analyses was completed utilizing [IBM SPSS 27.0 (SPSS Inc, Chicago, IL, U.S.A.)]. All statistical tests were two-sided with a critical alpha level of 0.05 indicating statistical significance. There is no randomization in this correlational study. G-Power 3 was used to calculate the sample size necessary to have a power of 0.8 or greater for this study with a moderate effect.[27] A sample size of 60 was desired and based on the pilot study[15] was feasible.

Results

Recruitment and Enrollment

At completion of enrollment, the larger study included 25 participants who completed the study protocol, and of these participants, eight participants completed the PA questionnaire. Enrollment for participation was paused for several months at the start of the COVID-19 pandemic. Prior to January 2020 we had 19 participants enrolled in the larger study and two of these participants had completed the PA questionnaire. After COVID-19 restrictions were removed from the study site, the last few months of recruitment included only six participants who enrolled and completed the study protocol. The participants completed the PA questionnaire on site, along with the larger study protocol.

Participant Characteristics

Descriptive statistics of the sample included frequencies for gender, age, tumor type, treatment type, time since completion of treatment, and sleep diagnosis (See Table 1). The study sample included eight BTS, five males and three females with an age range of 11 to 17 years at the time

of enrollment. This sample represented six different brain tumor diagnoses, including three low grade glioma tumors, one astrocytoma, one medulloblastoma, one nongerminomatus germ cell tumor (GCT), one mature teratoma, and one craniopharyngioma. Treatment within this sample included four participants (50%) who received surgery only, one who received surgery and radiation, one who received surgery, radiation, and laser ablation, one who received radiation only, and one who received chemotherapy only. At the time of enrollment, the time since completion of treatment for participants ranged from 12 months to 69 months. Five out of the eight participants (62.5%) were less than two years from the completion of their treatment.

Table 1. Participant Characteristics (n = 8)

Characteristic	n	%
Gender		
Male	5	62.5
Female	3	37.5
Age (years)		
11	2	25
13	1	12.5
14	1	12.5
15	2	25
16	1	12.5
17	1	12.5
Tumor Type		
Low Grade Glioma	3	37.5
Astrocytoma	1	12.5
Medulloblastoma	1	12.5
Nongerminomatus GCT	1	12.5
Mature Teratoma	1	12.5
Craniopharyngioma	1	12.5
Treatment Type		
Surgery Only	4	50
Surgery + Radiation	1	12.5
Surgery + Radiation + Laser Ablation	1	12.5
Radiation Only	1	12.5
Chemotherapy Only	1	12.5
Time since completion (months)		
12	1	12.5
15	2	25
21	1	12.5
22	1	12.5
37	1	12.5
39	1	12.5
69	1	12.5

Godin Leisure Time Exercise Questionnaire

Results from participants completing the GLTEQ included a median LSI score at 78.5 and a range with a minimum LSI at 36 to a maximum LSI at 90. All participants scored at or above 24 and met criteria to be classified as active according to the North American public health guidelines.[28] The mean LSI for all eight participants was 75, with a standard deviation of 17.1.

Self-reported Fatigue

The median for the total score on the PROMIS Fatigue Scale in this sample was 40.9, with scores ranging from 30.30 to 57.30 units. The minimum score represents the least fatigue, and the maximum score represents the most fatigue in this sample. This sample mean is 42.85 (SD 8.84) and approaches one standard deviation below the mean fatigue score (50, SD 10) when compared to a standard population.

Self-reported Sleepiness

Self-reported sleepiness was recorded using the Epworth Sleepiness Scale (ESS). The median total score on the ESS was 5, ranging from 0 to 8 in our sample. All participants reported daytime sleepiness under 10 which categorizes them in the normal range. Scores above 10 on the ESS represent excessive daytime sleepiness (EDS), and scores above 16 represent narcolepsy. None of the eight participants in our sample met criteria for EDS or narcolepsy on this scale.

Sleep

PSG revealed sleep symptoms in seven out of the eight participants (87.5%), including primary snoring in five participants, obstructive sleep apnea in one participant, and periodic limb movements in one participant. Sleep efficiency (SE) scores equal to or greater than 80 percent are considered appropriately efficient. In this sample, the median SE was 84.6, ranging from a minimum 71.70 to 93.20. Two participants' scores were less than 80 and considered less efficient.

The MSLT used REM Sleep Onset (REMSO) results to record the objective measure of excessive daytime sleepiness. Reported results were used to categorize participants into three separate groups, classified as follows: narcolepsy for a mean REMSO 10 minutes or less, sleepy for a mean REMSO 11 to 19 minutes, and normal for a mean RESOM equal to or greater than 20 minutes. Seven out of the eight participants completed the MSLT. Within the sample of seven participants, five were categorized as sleepy (71.4%), and two were categorized as normal.

Correlations

Due to a small sample size, effect sizes were utilized to convey the magnitude of relationships between variables. Spearman's rho correlation coefficient was used to categorize effect sizes into small, medium, and large. For Spearman's Rho (r), the closer the value is to 0, the smaller the effect size, and a value closer to 1 indicates a higher effect size. A small effect size is categorized as $r = .1$ to .3, a medium effect size is categorized as $r = 0.3$ to 0.5, and a large effect size is

categorized as 0.5 or greater. The results of nonparametric correlations between variables are found in Table 2.

I. GLTEQ and PROMIS Fatigue Scale

The Spearman's rho coefficient revealed a medium effect size of the association between the LSI total score and the PROMIS fatigue scale total score (r = .301, 95% CI [-.531, .838]). The results indicate a medium effect size between PA and perceived fatigue.

II. GLTEQ and Epworth Sleepiness Scale

The Spearman's rho coefficient revealed a small effect size of the association between the LSI total score and ESS total score *(*r = -.282, 95% CI [-.831, .546]). The results indicate a small effect size between PA and perceived daytime sleepiness.

III. GLTEQ and Multiple Sleep Latency Test

The Spearman's rho coefficient revealed minimal association between the LSI total score and the REMSO time *(*r = .071, 95% CI [-.734, .793]). The results indicate that there is not a reportable effect size between PA and daytime sleepiness.

IV. GLTEQ and Sleep Efficiency

The Spearman's rho coefficient revealed a medium effect size of the association between the LSI total score and the SE percentage *(*r = -.310, 95% CI [-.840, .524]). The results indicate a medium effect size between PA and SE.

Table 2. *Correlations between Physical Activity, Fatigue, and Sleep*

			LSI	Fatigue	ESS	MSLT	Sleep Efficiency
Spearman's rho	**LSI**	Correlation Coefficient	1.000	.301	-.282	.071	-.310
		Sig. (2-tailed)	.	.468	.498	.879	.456
		N	8	8	8	7	8
	Fatigue	Correlation Coefficient	.301	1.000	.578	-.018	-.024
		Sig. (2-tailed)	.468	.	.134	.969	.955
		N	8	8	8	7	8
	ESS	Correlation Coefficient	-.282	.578	1.000	-.145	.331
		Sig. (2-tailed)	.498	.134	.	.756	.423
		N	8	8	8	7	8
	MSLT	Correlation Coefficient	.071	-.018	-.145	1.000	-.679
		Sig. (2-tailed)	.879	.969	.756	.	.094
		N	7	7	7	7	7
	Sleep Efficiency	Correlation Coefficient	-.310	-.024	.331	-.679	1.000
		Sig. (2-tailed)	.456	.955	.423	.094	.
		N	8	8	8	7	8

Note. LSI- Leisure Score Index; ESS- Epworth Sleepiness Scale; MSLT- Multiple Sleep Latency Test-Sleep Latency outcome. Sleep Efficiency was scored from polysomnography testing.

Discussion and Innovation

This study on pediatric BTS investigated the relationship between perceived daytime sleepiness, fatigue, sleep parameters, and their levels of physical activity. With improving survivorship rates among this population, it is essential more attention is put towards the young survivor experience and ways to improve their overall quality of life (QoL). A recent systematic review on adolescent and young adult BTS reveal that there is currently insufficient knowledge of what this population specifically needs as supportive care despite these survivors experiencing unique long-term issues related to impaired daily and cognitive functioning that are integral to their QoL.[29] There are many variables that play a role in the QoL of a pediatric BTS and understanding the role of increased PA levels in this population is just one component that may be a significant factor to their outcome.

Interestingly, the PA levels reported in this sample were considered appropriately active in all eight participants based on the categorization of the LSI score. This is a surprising finding, as we expected an increased number of participants to be categorized as insufficiently active. It is known that pediatric BTS face many physical limitations after treatment and are less able to participate in PA and age-appropriate activities when compared to other childhood cancer survivors.[29-33] Many of the late effects that can contribute to physical limitations seen in this population may be associated with exposure to cranial radiation and cardiotoxicity secondary to

chemotherapeutic medications.[30,33,34] A notable feature to our sample of BTS is that 50% received surgical treatment only, therefore the sample had limited exposure to chemotherapy and radiation. It is possible that a sample less exposed to chemotherapy and radiation may exhibit fewer physical limitations, and consequently exhibit greater levels of PA than one expects in this population. Furthermore, physical activity levels were self-reported by our sample and their engagement in physical activity could have been over reported.

The relationship between self-reported PA levels and self-reported fatigue was not significant, however, this sample was considered appropriately active and reported relatively lower levels of fatigue. This may suggest that increased levels of PA levels are associated with lower levels of fatigue symptoms. It is encouraging to see a sample of pediatric BTS who may enjoy being physically active and find ways to stay engaged. However, increased fatigue experienced by this population is expected, and it is possible that they could be underreporting the fatigue they experience. Another consideration for higher-than-expected activity levels in this sample may be associated with the use of the GLTEQ to record physical activity levels.

Although the use of GLTEQ and the interpretation of the relative changes in PA of cancer survivors has been supported the scores (LSI),[18] the interpretation of mild, moderate, and strenuous exercise may differ between participants. A study completed on the accuracy of perceived PA levels among childhood cancer survivors found that many survivors were incorrect in perceiving whether their PA levels were appropriate and many survivors in this sample overestimated their activity levels.[32]

We are interested in the sleep symptoms of pediatric BTS because they are at increased risk of sleep disorders and there is a need for investigating potential modifiable confounders.[35] As anticipated in this population, most of our participants were found to have a sleep diagnosis. The sleep study also revealed a high percentage of our participants objectively experience daytime sleepiness, which aligns with research reporting an increased risk of EDS in children with cancer.[14,35] Despite a high percentage of this sample exhibiting sleep symptoms, we were intrigued to find that the participants' SE averaged on the lower end of normal for this age-group and they lacked subjective reporting of daytime sleepiness. The lack of self-reported EDS in this population may suggest that this population often under-reports their symptoms, considering the objective daytime sleepiness measure counters these findings.

With the various unique sleep findings in our sample, it is challenging to appreciate how PA levels may contribute to the sleep findings. A recent systematic review on PA intervention trials completed in pediatric BTS supports the need to study the effects of exercise on fatigue, as well as sleep in this population to better aid in managing specific impairments.[36] The relationship between sleep variables and PA in this study did not show meaningful relationships, and future research on the association between PA and subjective and objective sleep measures are warranted to understand how PA may be a modifiable confounder.

The participant characteristics of this sample described primarily a young adolescent group of BTS who represented various types of brain tumor types and were, on average, less than two years since the completion of their brain tumor treatment. Because most participants were early in their survivorship, the reported symptoms such as fatigue and daytime sleepiness, may differ

from a sample presenting late in their survivorship. Additionally, when considering PA levels in a sample including primarily adolescents, the survivors may have different opportunities or choices to engage in various forms of exercise or sports in school and after school. It is important to recognize the significant role the child's age may play in PA participation, as it is recognized that PA inclination may differ by age groups, as well as the knowledge of the benefits of PA.[37] Although we did not survey the type of exercise participants were engaging in, it would be encouraging to learn that young BTS are finding preferred ways to engage in PA.

While this study did not reveal significant relationships between PA levels and symptoms such as fatigue and sleep, analysis revealed medium magnitude of the relationships between PA and fatigue and sleep efficiency. These relationships may represent clinical significance. Engaging in PA is recognized as a safe and healthy lifestyle choice that has the potential to improve the overall QoL of pediatric BTS. Further research on the impacts of PA on common long-term health consequences experienced by survivors, as well as on the QoL of pediatric BTS is necessary to help inform their survivorship care.

Study Limitations

This study has several limitations. One of the study's primary limitations includes the small sample size. Following COVID-19 study restrictions, there were few participants who completed the study protocol with the PA questionnaire. This study was a companion study of a larger study that had already been implemented prior to COVID-19, and many of the participants had already completed the study requirements without the PA questionnaire. Additionally, participants who already completed study requirements were unable to be reconsented to this study because of a lack of communication or the participants became ineligible.

Another limitation recognized includes the outcome measures used to report PA levels, fatigue, and perceived daytime sleepiness. All these measures are self-reported by participants, so there is a possibility measures could be over-reported or under-reported. The GLTEQ was used to report PA levels, however the type and amount of PA that the participants reported engaging on a weekly basis may not be completely accurate due to differences in interpretation. We measured EDS with self-reported measures, as well as with objective measures, and our findings suggest that it is possible our participants are under reporting their symptoms. In future studies, it would be important to study the relationship between select variables with multiple modalities, such as using objective measures of PA levels, to understand how they are related.

Future Directions

Although our hypotheses testing did not have significant findings, we encourage further exploration of the effects of increased PA level on fatigue and sleep in this population. Further research would offer a better understanding of expectations of QoL in each patient and how we can best maximize it for the individual. In our sample, we had a relatively active group of pediatric BTS and mild self-reported fatigue and excessive daytime sleepiness, which may suggest that these survivors benefit from their increased PA levels. It would be significant to expand on the literature on how to design an ideal treatment plan for each pediatric BTS.

One consideration on how to improve the study includes using actigraphy to measure PA levels and sleep patterns in participants. Actigraphy uses electrophysiologic wristwatch-like movement monitoring which could record both daytime activity levels and movement during sleep. This modality to measure PA levels would be of interest because it would be an objective measure of activity levels, rather than the subjective reports on the GLTEQ, thus may provide a more accurate interpretation of how active the participant is throughout the week. The device has been correlated with the gold standard polysomnography and validated in adults and children.[19]

We encourage future research to investigate the use of PA as an intervention to improve outcomes in pediatric BTS. In 2021, the National Comprehensive Cancer Network (NCCN) and the American Society for Clinical Oncology (ASCO) published guidelines for cancer survivors with recommendations for survivors to be physically active as possible.[38,39] Although it is recognized that exercise and increased PA levels have associated health benefits in the general population, as well as in the adult cancer population, there are gaps in the literature on the benefits in the pediatric BTS population. Further information on the impact of PA as an intervention in this survivor population can help survivors and their healthcare providers better understand their unique healthcare needs, thus improving health-related symptoms and their overall QoL.

Conclusions

This study investigated physical activity levels, perceived fatigue and daytime sleepiness, and objective sleep parameters (sleep efficiency and EDS) in pediatric BTS. While the study did not reveal significant relationships between physical activity and fatigue or sleep measures, the findings did display a population who had relatively lower levels of fatigue and engaged in surprisingly appropriate levels of physical activity, despite experiencing daytime sleepiness and a variety of sleep disorders. Although the pediatric BTS population is increasing, and cancer-related fatigue and sleep disorders are well documented problems in this population, there is a gap in the literature regarding specific lifestyle modifications, such as engaging in physical activity, that can improve these cancer-related symptoms.

Although there is limited information on how fatigue and sleep may be impacted by physical activity in this population, there is growing evidence of that supports potential health benefits related to promoting physical activity in a pediatric cancer survivor population. Furthermore, participating in physical activity is safe for survivors and as represented in this sample, pediatric BTS are already engaging in physical activity. Understanding how physical activity relates to cancer-related symptoms will ultimately contribute to a holistic care plan for the patient that can improve their survivorship. Advancing our knowledge on the impacts of enhanced PA on pediatric BTS symptoms can provide guidance to both the caregivers and patient on intervention strategies and symptom management plans that will improve the patient's health and well-being. The possibility to expand on this aspect of the literature offers an opportunity to develop more refined and unique interventions in a patient's plan of care. Overall, comprehensive survivorship care for pediatric BTS is necessary for an improved quality of life.

Compliance Plan

The research was approved by Cook Children's Health Care System (CCHCS) IRB. This study did not require any consideration or approval from IACUC. I completed all required CITI training by CCHCS and Texas Christian University at this time.

I. CITI Training
   a. Cook Children's Health Care System
   b. Biomedical Investigators and KSP
   c. Good Clinical Practice

II. Texas Christian University
   a. Human Subjects Researcher (biomedical)
   b. Responsible Conduct of Research for Health
   c. Social and Behavioral Responsible Conduct of Research

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