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Sleep Disordered Breathing Risk in Childhood Cancer Survivors: An Exploratory Study

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Abstract

Background—Sleep disordered breathing (SDB) is emerging as a significant health condition for children. The purpose of this study is to evaluate SDB symptoms in childhood cancer survivors and identify associations with quality of life (QOL) and psychological symptoms.

Procedure—A sample of 62 survivors aged 8–18 years were recruited during routine survivorship visits. All subjects and their parents completed questionnaires to evaluate sleep, QOL and psychological symptoms; scales included were: Pediatric Sleep Questionnaire, Sleep Disordered Breathing Subscale (PSQ–SDBS), Pediatric Quality of Life Inventory (PedsQL) and Depression Anxiety Stress Scale (DASS-21). Continuous data were used for all scales and a threshold score of >0.33 on the PSA-SDBS was used to identify risk of SDB. The relationships between measures of sleep and independent variables were examined using Pearson correlations and multiple linear regression models for significant associations.

Results—Of the 62 subjects enrolled, underlying diagnoses included 29 leukemias, 30 solid tumors and 3 non-malignant diseases. Nineteen percent of subjects were identified as having SDB risk on the PSQ–SDBS. The lowest mean PedsQL subscale score for parent and child ratings were school QOL; Parent mean 73(±SD 19) and Child mean 71(±SD 20). The severity of SDB per the PSQ was significantly associated with reduced total and school QOL which remained significant after adjusting for stress.

Conclusions—Symptoms suggestive of SDB are common in childhood cancer survivors with negative implications for overall quality of life and school performance.

Keywords

cancer survivor; pediatric; quality of life; sleep disordered breathing

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The authors have full control of all primary data and the journal will be allowed to review the data if requested.

INTRODUCTION

Sleep is essential for good health, and sleep disturbances in children and adolescents are associated with diminished health related quality of life [1]. Sleep disturbances have been associated with comorbidities including insulin resistance and dyslipidemia [2,3]. Neurobehavioral problems including attention deficit/ hyperactivity disorder, reduced academic performance, and cognitive deficits have also been associated with sleep disturbances [4–6].

There are a wide range of sleep disturbances identified in children and adolescents, with a mounting degree of evidence that sleep disordered breathing (SDB), in particular, is associated with increased morbidity and mortality. SDB is defined as a range of sleep-related breathing abnormalities associated with increased upper airway resistance [7]. SDB in childhood has been shown to be associated with cardiovascular complications including Cor pulmonale, heart failure, systemic hypertension, autonomic dysfunction, endothelial dysfunction, and systemic inflammatory responses which may begin in childhood or beyond [8,9]. Symptoms associated with SDB in school age children include excessive day time sleepiness, night terrors, sleepwalking, enuresis, excessive sweating, morning headaches, and frequent repositioning during sleep [10]. The prevalence of SDB in children is estimated to be between 1 and 4 percent but is unknown for children with specific chronic health conditions [11,12].

Although awareness regarding the presence and implication of SDB within the pediatric population has been increasing, the prevalence and impact within childhood cancer survivor patients specifically remain relatively unknown [11,12]. Childhood cancer survivors are a growing population with special health care needs. Sleep disturbances have not been extensively studied in childhood cancer survivors but a large retrospective study found adult survivors of childhood cancer had poorer sleep quality and increased daytime sleepiness when compared to a sibling control group [13]. Few studies have looked at survivors while they are still in childhood and have primarily been limited to populations with a history of central nervous system treatment [14–18]. A study evaluating subjective sleep quality in 62 acute lymphocytic leukemia survivors found that sleep disturbances and fatigue were associated with depression and poorer quality of life in childhood [19]. While no studies have looked at SDB complaints in childhood cancer survivors there is overlap in the complications of SDB and health conditions in childhood cancer survivors making it a logical association to explore. Associations identified in this exploratory study could potentially provide further insights into our understanding of mechanisms and strategies for addressing established sequelae of both cancer survivorship and sleep apnea including neurocognitive deficits, cardiovascular risks, obesity and QOL [20–22]. Therefore, the purpose of this descriptive study was to identify the risk of SDB in childhood cancer survivors and identify associations with quality of life and psychological symptoms

METHODS

A sample of childhood cancer survivors was recruited during routine survivorship visits in a pediatric oncology clinic. Inclusion criteria included prior treatment with surgery, radiation or chemotherapy, being off therapy for at least one year, currently aged 8–18 years and accompanied by parent/guardian familiar with their sleep patterns. Exclusion criteria included patients with a primary cancer of the central nervous system (CNS), leukemia patients with CNS disease were not excluded. Patients meeting inclusion criteria were approached by a member of the study team and completed questionnaires before or immediately after their survivorship visit. Informed consent was obtained for all participants. This study was approved by the Johns Hopkins University Institutional Review Board. Questionnaires were completed by participants that included the follow scales:

The Pediatric Sleep Questionnaire, Sleep Disordered Breathing Subscale (PSQ–SDBS) is a 22 item parent/proxy questionnaire that assesses specific symptoms of SDB including snoring, breathing problems, mouth breathing, daytime sleepiness, and inattention/hyperactivity. The number of items answered positively is divided by the total items answered to give a proportion that ranges from 0.0 to 1.0. Scores >0.33 are considered suggestive of high risk of SDB. Validity for the questionnaire has been established by comparison to polysomnographically defined SDB and reliability with test-retest (mean 36.3 days) Spearman correlation coefficient = 0.75 and internal consistency with a Cronbach alpha = 0.88 [23].

The Pediatric Quality of Life Inventor is a 23 item questionnaire (self-report and proxy versions) that assesses physical, emotional, social and school functioning (child and adolescent and parent versions). Items are scored from 0 (Never) to 4 (Almost Always). Construct validity has been demonstrated in childhood cancer survivors on and off therapy by comparison to healthy children. Internal consistency was demonstrated in each subscale with alpha coefficients exceeding 0.70 [24]. The questionnaire measures five domains of QOL including, Physical Functioning, Emotional Functioning, Social Functioning, Psychosocial and School Functioning using a 0–4 scale (0 = never, 4 = almost always). The mean score for the components and overall score are calculated by transforming the score to a 0–100 scale. Higher scores indicate better QOL.

The DASS-21- Depression Anxiety Stress Scale is a 21 item self-report measure that is designed to measure affective symptoms of depression, anxiety and stress. The 4-point Likert scale encompasses 0 (did not apply to me at all) to 3 (applied to me very much, or most of the time). Internal consistency of the tool has been demonstrated in adults and children >10 years of age with Cronbach Alphas of 0.87 for depression and 0.79 for anxiety. The authors of the DASS-21 have studied whether the three-factor structure of negative affect as defined by the DASS is observable in children (7–14) like it is with adults. They found that while it was not possible to separately observe anxiety and stress syndromes, an observable depression factor was obvious. It is possible to utilize this measure as a screener of negative affect to guide whether there is a need for additional mood assessment [25]. A research assistant was available to answer questions about the measure from subjects while completing the DASS-21 but no parent/proxy input was given. Each component of affect

(depression, anxiety and stress) may have a score ranging from 0 to 21 with higher scores indicating more symptoms. Moderate scores for the depression are >7, Anxiety >6, Stress >10 are based on population norms [26].

Potential Confounding Variables

Anthropometric and treatment information was collected using medical record review including weight to the nearest one tenth of a kilogram on a calibrated digital scale, height with a calibrated stadiometer to the nearest one tenth of a centimeter, and a history of central nervous system radiation. These variables were chosen as they have been shown in the literature to have associations with sleep disturbances [18,27].

Statistical Analysis

Descriptive statistics were calculated for demographic, anthropometric data and questionnaire scores. In addition, the percentage of patients meeting the threshold considered suggestive of SDB on the PSQ-SDBS was calculated. Height and weight were used to calculate body mass index (BMI) and then converted to BMI percentiles using the Center for Disease Control and Prevention calculator (<http://apps.nccd.cdc.gov/dnpabmi/>). *t*-Tests were used to compare survivor total and subscale QOL scores to published healthy normative data. Pearson correlation with Bonferroni-adjusted significance was used to analyze relationships between PSQ-SDBS and selected QOL measures (Parent/Child total and School subscale) and the DASS-21 scores. To identify potential confounders of the PSQ-SDBS and QOL associations, Pearson correlations with Bonferroni-adjusted significance was used to analyze the relationship of variables identified in the literature as possible contributors to sleep disordered breathing (BMI percentile and cranial radiation) and the PSQ-SDBS score. Finally, multiple linear regression analysis for the PSQ-SDBS and QOL associations were conducted adjusting for significant psychological confounders identified by Pearson correlation. A *P*-value of <0.05 was considered to be statistically significant.

RESULTS

Sample Characteristics

Sixty two subjects were enrolled over a 10 month period. Underlying diagnoses included 29 leukemia, 12 Wilm's tumor, 7 lymphoma, 5 sarcoma, 3 neuroblastoma, 2 hepatoblastoma, 1 pleuropulmonary blastoma, and 3 non-malignant diseases. The non-malignant diseases included aplastic anemia (two subjects) and X-linked autoimmunity-allergic dysregulation disorder (one subject) treated with chemotherapy and followed in the survivorship program. No subjects were actively being treated for a sleep disorder at the time of enrollment and no subjects approached declined participation. Table I further describes the sample characteristics.

PSQ-SDBS

The mean score for on the PSQ-SDBS was 0.19 ($\pm$ SD 0.18, range 0–0.72). Nineteen percent scored above the threshold for SDB risk on the PSQ-SDBS (>0.33).

Quality of Life Scores

The lowest mean subscale score for both the parent and child QOL was in the school QOL domain (parent score mean 73 [$\pm$ SD 19], child 71 [$\pm$ SD 20]) [28]. Total QOL and school QOL (parent and child) were selected for further analysis and model building. Table II displays the mean and standard deviations for survivor total and subscale scores as well as published healthy normative data. *t*-Test comparing survivors to healthy norms revealed significantly lower self-report QOL for the subscales of psychosocial and school QOL in the survivor group and marginal significance for total QOL score. For the parent proxy rating survivors scored significantly lower than healthy norms for total and all subscales QOL using *t*-tests.

DASS-21 Scores

The mean ($\pm$ SD) scores for depression was 3.0 ($\pm$ SD 4.1), Anxiety 4.5 ($\pm$ SD 5.2) and Stress 7.5 ($\pm$ SD 6.9). Seventeen percent (10/62) scored >7 on the depression scale, 19% (12/62) scored >6 on the anxiety scale and 21% (13/62) scored >10 on the stress scale (thresholds for moderate symptoms for each scale using population norms).

Quality of Life, Psychological Symptoms and SDB Risk

Table III displays the Pearson Correlations and *P* values between PSQ-SDBS and QOL and DASS scores. Total QOL was chosen for analysis because it encompasses all domains and school QOL was chosen because it had the lowest mean scores in the study sample and was significantly lower than healthy norm scores for both self-report and parent proxy. Scores on the PSQ-SDBS had significant negative correlations with all selected QOL measures. Score on the PSQ-SDBS had a significant positive correlation with only the stress score on the DASS.

Pearson Correlations and Potential Contributing Variables

No statistically significant associations were identified for BMI percentile and CNS radiation and the measure of SDB using Pearson correlations.

Multiple Linear Regression Models

Four models were analyzed to evaluate the association between the PSQ-SDBS and the selected QOL scores adjusting for stress scores. In all four models the statistically significant negative association between PSQ-SDBS remained when controlling for stress.

DISCUSSION

Providers caring for childhood cancer survivors have many competing health care concerns to address. Screening recommendations exist for this population that include follow up on 136 therapeutic exposures (such as chemotherapy, radiation, and surgery) with potential long term complications [29]. As survival rates of childhood cancer have reached 80%, there has been an increased recognition of these long term complications and the need for careful surveillance for morbidity in this vulnerable population [30]. Sleep disturbances are emerging as a potential complication with broad health and QOL implications for childhood

cancer survivors. To our knowledge ours is the first study to assess the risk for SDB in childhood cancer survivors <18 years of age, not including children with CNS primary disease. The current study provides insights on sleep in the childhood cancer survivor population. We found that 19% of survivors in this study scored above the threshold for risk of SDB on the PSQ/SDBS. The threshold score of 0.33 on the PSQ/SDBS that was used in our study has shown strong sensitivity (0.83) and specificity (0.87) for identifying children and adolescents who were diagnosed as having SDB identified by polysomnography [23]. Moreover, the prevalence rate of 19% suggested by the PSQ–SDBS tool used in our study sample is significantly higher than the 0–5.7% prevalence of SDB in the general childhood population as reported by the American Academy of Pediatrics [31].

A possible explanation for a potential increased prevalence of SDB in our study population may be adenotonsillar or anatomical abnormalities. These abnormalities are closely associated with SDB in children and adolescents [32]. We are not aware of definitive evidence that adenotonsillar abnormalities are seen more frequently in the cancer survivor population, in one case series 20% of childhood cancer survivors referred to a pediatric sleep clinic required adenotonsillectomy for treatment of their obstructive sleep apnea, this is in contrast to the general childhood population where adenotonsillectomy is the most common intervention used for the treatment of obstructive sleep apnea [33,34].

An additional anatomical hypothesis for the possible increased risk of SDB in childhood cancer survivors is deep cervical lymph node hypertrophy. Larger volumes of cervical, jugular and retropharyngeal nodes as measured by magnetic resonance imaging are seen in children with obstructive sleep apnea as compared to controls [35]. This finding is suggested as evidence as to why up to 1/3 of children continue to have sleep apnea after adenotonsillectomy [36]. Prolonged immunosuppression and recurrent infections are not uncommon during treatment for childhood cancer and could potentially contribute to increased lymph node volumes in this population. Further research is needed to determine if lymph node hypertrophy or other anatomical abnormalities in childhood cancer survivors contributes to SDB.

Obesity/central adiposity is also closely associated with SDB in children, and SDB has been reported to occur in 26–33% of obese children [37]. The American Academy of Pediatrics rated the evidence as level I (strongest evidence) that obesity is an independent risk factor for SDB. Several mechanism impact the effect of obesity on SDB including increased pressure on upper airway structures from adipose tissue, decreased lung volumes seen in obese children, abnormal central nervous system ventilatory responses, and neurohormonal control defects including leptin resistance [31]. Mounting evidence indicates childhood cancer survivors are at risk of developing obesity [38–40]. Risk factors and the etiology of obesity in childhood cancer survivors are multifactorial and may include changes in normal gut flora leading to pro-inflammatory states, rebound weight gain after therapy and epigenetic influences on metabolic systems resulting from chemotherapy or radiation [41]. In the current study, BMI percentile was not significantly associated with SDB measures, which may indicate that obesity is not the driving factor for SDB risk in this childhood cancer survivor population. We did not have a measure of central adiposity which limits our ability to fully evaluate the association between SDB and obesity in this sample, but our

findings do suggest that using obesity as a proxy for SDB risk may not be appropriate for childhood cancer survivors.

The hypothalamic pituitary adrenocortical axis (HPA) is intimately involved in both sleep and weight control [42,43]. Disruption of the HPA is a well-recognized complication of surgery, chemotherapy and radiation to the central nervous system (CNS) and long term disruption has been identified in leukemia survivors treated with glucocorticoids [19]. The treatment of childhood cancer with interventions that affect the CNS has been associated with endocrinopathies, sleep disturbances and diminished QOL [20,44]. While no association has been shown between SDB and HPA disruption in childhood cancer survivors a theoretical risk may be considered. In our study did not find a significant association between cranial radiation and SDB risk. A possible explanation for this lack of association is that while 19% of our sample received cranial radiation, none of the patients were diagnosed with a CNS primary and therefore received lower doses of radiation resulting in less impact on the HPA. Further investigation is necessary to identify the dose effect of cranial radiation as well as other impacts of childhood cancer therapy on the HPA.

A unique and thought-provoking finding of our study is the association of SDB risk and parent/child rated school QOL. The parent and children ratings for school QOL was the lowest scoring QOL domain and a significant negative correlation was identified between school QOL and SDB risk for both. Neurocognitive deficits are a well-documented complication of the treatment of childhood cancer. The etiology and interventions for this complication continue to unfold [45]. The effects of SDB and other sleep disturbances on school performance are well-documented in the general population [6]. Reduced attention, hyperactivity, increased aggression, irritability, emotional issues, peer difficulties, and somatic complaints are among the behavioral issues that have been associated the SDB and may impact school QOL [46]. Neurocognitive impairments may be attributed to SDB, even in children for whom primary snoring is the only abnormality seen on polysomnography [47]. Moreover improvements in cognitive function are seen after interventions to improve sleep in the general population [48]. Objective sleep and neuropsychological measures are needed to elicit the exact effect that sleep may have on neurocognitive outcomes for childhood cancer survivors and should be a priority for researchers in this area.

Limitations of our study include the heterogeneous sample of underlying conditions for which the survivors received treatment which limits our ability to identify associations with specific childhood malignancies and SDB risk. Larger sample size or homogeneous populations are needed to establish these associations. Additionally, the measure of SDB risk is made by questionnaire only and not confirmed with objective sleep study evaluations. Future studies should include objective measures of SDB to confirm the prevalence in the childhood cancer survivor population. The PSQ-SDBS is not a validated screening tool and is currently recommended only for clinical research. Further, it should be noted that previous investigators have suggested that SDBS may be effective in predicting cross-sectional morbidity because some parents rate their children high, in a nonspecific manner, for any pathological finding [49]. This could explain the significant correlations between the SDBS scale and the parent QOL measures as well as the Peds QOL and DASS-21 observed in this study.

At the current rates of incidence and cure, it is projected that by 2020 there will be nearly 500,000 survivors of childhood cancer in the United States [50]. The understanding of late complications of treatment continues to evolve as this population grows and matures. The evidence that sleep disturbances may impact and contribute to late complications and QOL for childhood cancer survivors has just scratched the surface. In this paper, we reported a potentially higher prevalence of SDB in childhood cancer survivors compared to the general population and consider some of the possible contributing factors. Further research is clearly needed to fully understand the prevalence and contributing factors for SDB in this population. Given the potential for improving late complications by addressing SDB, continued inquiry should be a priority. Our findings point to an interesting association between SDB risk and school related QOL, suggesting that research addressing interventions to improve sleep could positively impact the neurocognitive outcomes for this population.

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TABLE I**Subject Characteristics (n = 62)**

Age in years (mean/s.d.)	13.1 (3.1)
Years off therapy (mean/s.d.)	6.1 (4.2)
Male (%)	55%
BMI percentile (mean/s.d.)	61.0 (30.9)
Cranial radiation (%)	19%

TABLE II
Unpaired *t*-Test Comparing Survivor Total and Subscale Scores to Published Healthy Norms¹

Scale	Cancer Survivor			Healthy Norms			P-value
	N	Mean	sd	N	Mean	sd	
Self-Report							
Total score	61	79.37	12.33	401	83.00	14.79	0.069
Physical	61	82.52	12.50	400	84.41	17.26	0.411
Psychosocial	61	77.69	13.65	399	82.38	15.51	0.026
Emotional	61	77.05	20.22	400	80.86	19.64	0.161
Social	61	85.16	14.97	399	87.42	17.18	0.331
School	61	70.98	19.58	386	78.63	20.53	0.007
Parent Proxy							
Total score	62	77.83	16.34	717	87.61	12.33	<0.001
Physical	62	80.83	19.98	717	89.32	16.35	<0.001
Psychosocial	62	76.28	16.38	717	86.58	12.79	<0.001
Emotional	62	74.52	19.73	718	82.64	17.54	<0.001
Social	62	85.16	22.78	716	91.56	14.20	<0.001
School	62	73.43	18.82	611	85.47	17.61	<0.001

¹Varni, J.W., M. Seid, and P.S. Kurtin. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care*, 2001; 39(8): p. 800-812.

TABLE III

Pearson Correlations for PSQ-SDBS, Selected QOL and DASS*

Risk score (PSQ-SDBS)	Pearson Correlation (<i>P</i> -value)
Select QOL	
Parent total	−0.59 (<0.001)
Parent school	−0.43 (0.013)
Child total	−0.47 (0.004)
Child School	−0.43 (0.015)
DASS	
Depression	0.22 (NS)
Anxiety	0.25 (NS)
Stress	0.44 (0.008)

* Bonferroni-adjusted, alpha <0.05.