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Original

Assessment of sleep in pediatric cancer patients

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The purpose of the study is to describe sleep habits, assess the prevalence of sleep disturbances in pediatric cancer patients and healthy controls, and to compare sleep patterns, sleep problems. One hundred-thirty-five patients and 190 healthy controls were evaluated. Healthy children matched for age, sex, economic status, parental education and family structure constituted the control group. Sleep was evaluated by using the Children's Sleep Habits Questionnaire (CSHQ). Sleep problems were detected in half of patients. There were no significant differences in total sleep score and subscale scores between patients and controls. Solely the wake-time was found significantly different between patients and controls. Although our results indicated that neither childhood cancer survivors nor patients with cancer during treatment period had more sleep problems than their healthy peers, sleep problems were not uncommon in whole study group. This study underlines the need to screen, assess and manage sleep problems in children with diagnosis of cancer.

Key words: childhood cancer, sleep disturbances, sleep patterns.

Childhood and adolescent cancers account for less than 2% of all cancer.[1] Treatment has greatly improved over the last decades and survival rates have increased dramatically. Parallel to the improvements in survival rates, there was an increase in number of survivors of childhood cancers and survivorship care has become increasingly important. Treatment may interfere with physiological growth and development in children and adolescent. Besides the health problems as a result of treatment, psychosocial problems should also be considered and evaluated. Children are different from adults in that they are in a progressive course of physical, neurocognitive, social and emotional development. Adequate and good quality sleep is required for optimal growth and development of children and adolescents. Diagnosis, treatment and follow-up periods of cancer affects all these developmental stages of children. Sleep problems are expected to be much more prevalent among medically ill children and adolescents.[2] The patient groups who received cancer treatment in childhood period are affected more seriously than those of other patient groups.[3] The prevalence of sleep problems have been reported in 14% - 16.7% of adult survivors of childhood cancer.[4,5] In early studies sleep disorders have been described particularly in central nervous system (CNS) tumor survivors.[6-9] Sleep related problems can lead to behavioral and neurocognitive impairment in survivors of childhood cancer.[10] Previously, sleep disorders have also been studied in children with diagnosis of acute lymphoblastic leukemia (ALL).[10-15] These studies have demonstrated that there were an association between sleep problems, physical activity, fatigue, quality of life and depression. The objectives of our study were to describe sleep habits and assess the prevalence of sleep disturbances in pediatric cancer patients and survivors, and in healthy controls, and compare sleep outcomes between these groups.

Material and Methods

Study population

This study was conducted at Dr. Behcet Uz

Childrens' Hospital Pediatric Hematology-Oncology Clinic between May 2014 – November 2014. Although 145 children with cancer were eligible 10 of them were excluded because of antidepressant usage. Thus, 135 (85 males, 50 females; 5 – 12 years) children with cancer and 190 healthy controls (105 males, 85 females) were enrolled in the study. The patient group consisted of 104 (77%) children with lymphoproliferative cancer (76 ALL patients, 28 lymphoma patients), and 31 (23%) with a diagnosis of other solid tumor. Oncologic treatment was completed in 100 patients with cancer (Group 1: cancer survivors), treatment was ongoing in the remaining 35 patients (Group 2: patients under ongoing oncologic treatment). The median follow-up time after treatment for cancer was 2.6 years (1 – 12 years). Group 3 consisted from 190 healthy children matched for age, sex, economic status, parental education and family structure; they were selected from the children who visited the "well child outpatient clinic" and the "pediatric hematology clinic for information about thalassemia trait".

Children's Sleep Habits Questionnaire

Sleep was evaluated by the validated Turkish version of the Children's Sleep Habits Questionnaire (CSHQ).[16, 17] The CSHQ is a 33-item questionnaire reported by parents to assess the typical sleep patterns of preschool and school-aged children. It also includes three items related with bedtime, wake-up time and total sleep duration (nighttime sleep and daytime nap) over a "typical" recent week. If the patients have an extraordinary event in the week prior to the questionnaire, such as an examination, competition, and so on, parents are asked to fill it according to the nearest typical week. The parents rated the frequency of sleep behavior for the most recent typical week on a three point Likert scale: "usually" (5 to 7 times per week), "sometimes" (2 to 4 times per week), and "rarely" (0 to 1 times per week). Higher scores indicate more frequent sleep disturbances. The CSHQ includes a total sleep disturbance score and eight subscale scores: bedtime resistance (6 items), sleep-onset delay (1 item), sleep duration (3 items), sleep anxiety (4 items), night wakening (3 items), parasomnias (7 items), sleep disorder breathing (3 items) and daytime sleepiness (8 items) (Table I). A total score of ≥41 defines "clinical significant sleep disturbance." Although developers have not established norms for the scale, they determined that a total score of 41 points makes an effective cutoff for screening purposes as it correctly identified 80% of the clinical sample in their initial psychometric study.[16,17]

The study protocol was approved by the Ethics Committee of the Dr. Behcet Uz Children's Hospital (Ethics Committee decision number: 1339918, date May 08, 2014). Parents and children were informed about the scale and the procedure; information concerning consent was taken from parents before performing CSHQ. A parent-reported sleep inventory was applied to all participants. Clinical characteristics and the treatment details of the patients with cancer were recorded from the medical reports of patients. Oncologic diagnosis, oncologic treatment status, history of receiving intrathecal chemotherapy, history of receiving intravenous high dose cytarabine and high dose methotrexate treatments, history of craniospinal surgery and radiotherapy were recorded.

Statistical Analyses

The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) program version 15.0 for Windows was used for all data analyses. For descriptive data analysis, the means and 95% confidence intervals (CI) were calculated. Comparison of the means of quantitative data for dual groups were assessed by using the Student's t-test and Mann-Whitney U- test when appropriate. Chi-square test was used to evaluate the differences in proportions. Children's Sleep Habits Questionnaire total sleep score was compared by gender using the one-way analysis of variance (ANOVA). Inter-correlations between the parameters were computed through the Pearson's correlation analysis for parametric data, Spearman's correlation analysis for nonparametric data. Correlation coefficient indicated low correlation at 0.10 – 0.29, medium correlation at 0.30 – 0.49 and high correlation at ≥0.50. Significance level was set at p values ≤0.05 for all analyses. Internal consistency of the scale was determined by calculating Cronbach's coefficient alpha. Internal consistency reliability Cronbach's coefficient alpha was found to be 0.719 in patient group, 0.781 in control group.

Scales with reliabilities of 0.70 or greater are recommended for comparing the groups.

Results

One hundred thirty-five (85 males, 50 females) children with cancer and cancer survivors and 190 healthy controls (105 males, 85 females) were enrolled in the study. The M/F ratio was 1.7, and the mean age of the patients was 9.8 ± 2.5 years (5 - 12). The M/F ratio was 1.24, and the mean age of the healthy controls was 9.4 ± 2.6 years (5 - 12). There were no significant differences between the patients and the controls (p: 0.172; p: 0.251, respectively) in terms of age and gender. A large majority of parent respondents were mothers (76% in patient group, 71% in control group). The mean age of parents was 37.8 ± 7.5 years (21 – 63) in patient group, 38.5 ± 4.7 years (23 – 55) in control group. No significant differences were found between parents of patients and controls with respect to age, gender and educational level.

The mean bedtime was 11:13 p.m. (range: 08:30 p.m. – 03:00 a.m.) in patients, and 10:27 p.m. (range: 08:30 p.m. – 03:00 a.m.) in healthy controls. The mean wake-time was 08:44 a.m. (range: 05:00 a.m. – 01:00 p.m.) in patients and 08:06 a.m. (range: 05:00 a.m.– 11:00 a.m.) in healthy controls. The wake-time was found significantly different between patients and controls ($p< 0.001$). The mean sleep duration was 9.5 h (95% CI 9.29 – 9.80, range 4 – 14 h) in patients, and 9.4 h (95% CI 9.16 – 9.54; range 4 – 13.5) in healthy controls (p: 0.232). The mean length of waking was 5.3 minutes (95% CI 3.5 – 7.2, range 0 – 90 minutes) in patients, and 4.2 minutes (95% CI 3.2 – 5.3, range 0 – 60 minutes) in healthy controls. There were no statistically significant differences in average bedtime, length of waking and total sleep duration between the groups. Sleep parameters, subscale scores of patients and healthy controls have been summarized in Table II. Additionally, no significant differences of total sleep score and subscale scores existed between the groups. Daytime sleepiness was found significantly different between patients and controls (p: 0.043), however it was not significantly different between survivors and controls, and between patients under ongoing oncologic treatment and controls.

Comparisons of sleep parameters, subscale scores of patient groups and healthy controls have been summarized in Table III. No significant gender difference in total sleep scores, scores of subscales, bedtime, wake-up time and sleep duration were observed in all

Table I. Components of the Subscales of the Children's Sleep Habits Questionnaire.

Subscales	Items
Bedtime resistance	Goes to bed at same time / Falls asleep in own bed / Falls asleep in other's bed / Needs parent in room to sleep / Struggles at bedtime / Afraid of sleeping alone.
Sleep-onset delay	Falls asleep in 20 minutes
Sleep duration	Sleeps too little / Sleeps the right amount / Sleeps same amount each day.
Sleep anxiety	Needs parent in room to sleep / Afraid of sleeping in the dark / Afraid of sleeping alone / Trouble sleeping away
Night wakening	Moves to other's bed in the night / Awakes once during night / Awakes more than once
Parasomnias	Wets the bed at night / Talks during sleep / Restless and moves a lot / Sleepwalks / Grinds teeth during sleep / Awakens screaming, sweating / Alarmed by a scary dream
Sleep disorder breathing	Snores loudly / Stops breathing / Snorts and gasps
Daytime sleepiness	Wakes by himself / Wakes up in negative mood / Others wake child / Hard time getting out of bed / Takes long time to be alert / Seems tired / Falls asleep watching TV / riding in car

three groups.

The scores of the subscales were not different between males and females in all three groups. Younger age was correlated with longer duration of sleep in all three groups (Group 1, r: –0.448, p< 0.001; Group 2 r: –0.369, p: 0.029; and Group 3 r: –0.357, p< 0.001), and correlated with higher rates of total sleep scores only in healthy controls (r: –0.161, p:0.026). In healthy control group, 55 percent of 5-10 years old group (106 children) and 36 percent of 11-12 years old group (84 children) had sleep disorders (p:0.013). There was no significant difference between 5-10 years and 10-11 years old children in both patient groups (Group 1, Group 2) in terms of sleep disorder rates. Younger age was associated with higher rates of bedtime resistance (G1, r: –0.285, p:0.004; G2, r: –0.568, p< 0.001, G3, r: –0.374, p< 0.001) and sleep anxiety (G1, r: –0.277, p< 0.001, G2, r: –0.472, p:0.004, G3, r: –0.336, p< 0.001) in both patient and healthy control groups, and older age was associated with higher rates of sleep onset delay (G1, r: 0.320, p:0.001) in survivors (Group 1). Sleep duration and daytime sleepiness were inversely correlated in healthy controls (r: –0.151, p:0.037)

Relationship between sleep behaviors and characteristics of cancer survivors (Group 1)

Sleep problems were detected in 51% (n:51) of survivors; 50% of 74 patients with lymphoproliferative tumor, and 54% of 26 patients with solid tumor had sleep disorders (p: 0.821). Total sleep scores and scores of the subscales were not significantly different in patients with lymphoproliferative tumors and solid tumors Table IV. There were 54 patients with ALL and 12 patients with non-B NHL whose anticancer treatments were the same protocol. So these 66 patients were analyzed together as ALL group: 50% of 66 patients with ALL had sleep problems and there was no significant difference between patients with solid tumor (p: 0.819). There was not a significant correlation between follow-up time without treatment and total sleep score (r: -0.098, p:0.332), however follow-up time and duration of sleep were inversely correlated (r: -0.283, p:0.004). There were no significant difference between patients who had follow up time of more than five years (n: 70) and less than five years (n: 30) in terms of total sleep scores and scores of the subscales. Also there were no difference between the patients who received intrathecal chemotherapy (n: 66) or not (n: 34); who received intravenous high dose cytarabine (n: 23) or not (n: 77); who received intravenous high dose methotrexate (n: 37) or not (n:63). These analyses were also performed in the lymphoproliferative tumor group (n: 74), and in the ALL group (n: 66), and no significant difference was found. There were 66 patients with ALL and 18 of them received craniospinal radiotherapy; total sleep scores and scores of the subscales were not significantly different between the patients who received radiotherapy or not. There were 91 patients with ALL in whole group, 50% of ALL survivors (n:66) and 56% of patients under

Table II. Sleep Parameters of Patients and Controls.

	Patients with cancer (n:135)	Healthy controls (n:190)	p-value
Total sleep score	42.6 (41.4 – 43.7)	43.7 (42.6 – 44.8)	0.178
Subscales			
Bedtime resistance	8.5 (8.0 – 8.9)	9.1 (8.6 – 9.6)	0.063
Sleep onset delay	1.3 (1.2 – 1.4)	1.3 (1.2 – 1.4)	0.911
Sleep duration	3.7 (3.4 – 3.9)	3.7 (3.5 – 3.9)	0.763
Sleep anxiety	6.1 (5.8 – 6.5)	6.1 (5.8 – 6.5)	0.971
Night wakening	4.1 (3.9 – 4.2)	4.0 (3.8 – 4.1)	0.401
Parasomnias	8.5 (8.2 – 8.8)	8.4 (8.2 – 8.6)	0.557
Sleep-disordered breathing	3.3 (3.1 – 3.4)	3.3 (3.2 – 3.4)	0.519
Day-time sleepiness	10.1 (9.6 – 10.7)	10.9 (10.4 – 11.3)	0.043

Data is presented as mean (95% confidence interval)

ongoing oncologic treatment (n:25) had sleep problems, indicating no significant difference (p: 0.645).

Sleep problems were detected in one patient with a CNS tumor who had history of surgery and radiotherapy. There were eight patients with late sequela and four of them had sleep problems. Oncologic diagnosis and late sequela of these four patients with sleep problems were pelvic rhabdomyosarcoma with urinary incontinence (n: 1), bilateral retinoblastoma and blindness (n:1), osteosarcoma who had limb prothesis (n: 1), non-Hodgkin lymphoma with urinary incontinence (n: 1).

Relationship between sleep behaviors and characteristics of patients under ongoing oncologic treatment

Sleep problems were detected in 51% (n: 18) of all 35 patients. There were 22 patients with ALL and 3 patients with non B NHL whose anticancer treatments were the same protocol. Thus all of 25 patients were analyzed as ALL group (20 patients were on maintenance treatment, 5 patients were on induction therapy) and 56% (n: 14) of them had sleep problems. Patients were divided into subgroups. Comparison results of sleep duration, total sleep scores and scores of subscales according to presence or absence of receiving intrathecal chemotherapy, intravenous HD cytarabine and intravenous HD methotrexate were evaluated. Thus there were no significant differences between groups in terms of most of the sleep parameters. However, night-wakening of the patients who received intrathecal chemotherapy and intravenous HD cytarabine were lower than that of other patients who didn't receive these treatments. Craniospinal radiotherapy had been performed in five patients (one with medulloblastoma) and three of them had sleep problems.

Discussion

This is the first study to compare sleep patterns and sleep problems of preschool and school

Table III. Subscale Comparisons Between Patients with Cancer and Healthy Controls.

	Group 1 Cancer survivors (n:100)	Group 2 Patients under ongoing treatment (n:35)	Group 3 Healthy controls (n:190)	p-value G 1–2/G 2–3/G 1–3
Sleep Patterns				
Average bedtime	11:08 p.m. (08:30 pm-03:00 am)	11:30 p.m. (09:30 pm-02:00 am)	10:49 p.m. (08:30 pm–03:00 am)	0.323/0.099/0.225
Average wake-up time	08:34 a.m. (05:00 am–00:30 pm)	09:12 a.m. (06:30 am–01:00 pm)	08:06 a.m. (05:00 am–11:00 am)	0.041/<0.001/0.013
Length of waking (min)	5.6 (3.3 – 7.9)	4.6 (2.2 – 7.0)	4.2 (3.2 – 5.3)	0.549/0.783/0.294
Total sleep duration (hour)	9.2 (9.1 – 9.7)	9.9 (9.3 – 10.4)	9.4 (9.16 – 9.54)	0.144/0.068/0.665
Total sleep score	42.6 (41.3–44.0)	42.5 (40.4 – 44.5)	43.7 (42.6 – 44.8)	0.883/0.301/0.246
Subscales				
Bedtime resistance	8.4 (7.9 – 9.0)	8.6 (7.6 – 9.6)	9.1 (8.6 – 9.6)	0.788/0.359/0.064
Sleep onset delay	1.3 (1.2 – 1.4)	1.3 (1.1 – 1.5)	1.3 (1.2 – 1.4)	0.783/0.771/0.995
Sleep duration	3.7 (3.5 – 3.9)	3.6 (3.0 – 4.3)	3.7 (3.5 – 3.9)	0.899/0.809/0.819
Sleep anxiety	6.1 (5.7 – 6.5)	6.3 (5.5 – 7.2)	6.1 (5.8 – 6.5)	0.618/0.685/0.848
Night wakening	4.1 (3.9 – 4.3)	4.0 (3.7 – 4.3)	4.0 (3.8 – 4.1)	0.665/0.824/0.366
Parasomnias	8.6 (8.2 – 8.9)	8.3 (7.8 – 8.8)	8.4 (8.2 – 8.6)	0.479/0.856/0.440
Sleep-disordered breathing	3.3 (3.2 – 3.5)	3.1 (3.0 – 3.3)	3.3 (3.2 – 3.4)	0.061/0.033/0.954
Day-time sleepiness	10.1 (9.4–10.8)	10.2 (9.2 – 11.1)	10.9 (10.4 – 11.3)	0.892/0.208/0.067

Data is presented as mean (95% confidence interval)

Table IV. Subscale Comparisons Between Patients with Lymphoproliferative Tumors and Patients with Solid Tumors Among Cancer Survivors.

	Cancer survivors			p-value LPT-ST/ALL-ST
	LPT group (n:74)	ST group (n:26)	ALL group (n:66)	
Total sleep scores	42.6 (31.0–74.0)	42.6 (34.0–57.0)	42.3 (33.0 – 74.0)	0.95 / 0.87
Subscales				
Bedtime resistance	8.4 (6.0 – 15.0)	8.3 (6.0 – 16.0)	8.3 (6.0 – 15.0)	0.99 / 0.95
Sleep onset delay	1.3 (1.0 – 3.0)	1.2 (1.0 – 3.0)	1.3 (1.0 – 3.0)	0.68 / 0.97
Sleep duration	3.8 (3.0 – 7.0)	3.5 (3.0 – 7.0)	3.7 (3.0 – 7.0)	0.23 / 0.26
Sleep anxiety	6.1 (4.0 – 12.0)	6.0 (4.0 – 11.0)	6.0 (4.0 – 12.0)	0.74 / 0.79
Night wakening	4.0 (3.0 – 8.0)	4.3 (3.0 – 8.0)	4.0 (3.0 – 8.0)	0.27 / 0.25
Parasomnias	8.6 (6.0 – 18.0)	8.6 (7.0 – 16.0)	8.7 (7.0 – 18.0)	0.90 / 0.87
Sleep-disordered breathing	3.4 (3.0 – 7.0)	3.2 (3.0 – 5.0)	3.3 (3.0 – 7.0)	0.25 / 0.22
Day-time sleepiness	10.1 (6.0 – 20.0)	10.2 (6.0–20.0)	9.9 (6.0 – 20.0)	0.92 / 0.93
Problem sleepers	50%	54%	50%	

ALL group: patients with ALL and non B NHL, LPT group: patients with lymphoproliferative tumor, ST group: patients with solid tumor
Data is presented as mean (95% confidence interval)

aged children between patients with cancer and healthy controls in Turkey using the Turkish version of the CSHQ. In this study, children's sleep problems and sleep patterns were reported by parents. Sleep problems were detected in half of our patients with cancer, parallel with the previous studies.[7, 18]

The results of our study indicated that neither childhood cancer survivors nor patients with cancer during the treatment period had more sleep problems than their healthy peers. In our study sleep problems were identified in 46% of 5 to 12 years old healthy Turkish children. However, in several previous studies, sleep problems of healthy children were reported as 20-30%.[19,20] Unalan et al.[21] reported that sleep disturbances existed in 31 – 48% of 1966 elementary school Turkish children [difficulty in waking up (48%), sleepy all day long (31%), having nightmares (45%)]. Kilincaslan et al.[22] found that nearly one quarter of 3,485 high school Turkish adolescents had sleep problems. Higher rates of sleep problems were commonly seen in healthy school aged Turkish children compared to different populations. It has been reported that cultural differences play an important role in sleep habits.[2] Higher rates of sleep problems might be related to the cultural differences, sociocultural structure of family, life conditions, education and employment status of parents, and structure of primary school education system in Turkey.

There was no considerable difference in sleep patterns of the children receiving treatment for cancer and survivors and healthy controls, except for the wake-up times. This difference may be explained by the period of preparation before going to school in the morning. The patients with cancer reported lower scores of day-time sleepiness when compared to healthy controls. However, when we compared survivors and patients with cancer during treatment period to healthy controls, the difference about day-time sleepiness was not statistically significant. In our study, there were 20 children with ALL who had been receiving maintenance treatment and 50% of them had sleep problems. In the literature, this ratio had been reported up to 87%.[14]

In the previous studies it was suggested that dexamethasone treatment, drug induced neurotoxicity, history of radiotherapy may contribute to the sleep problems in children with cancer.[4,23,24] It has been reported that dexamethasone alters most sleep parameters in pediatric patients with ALL, particularly

associated with increases in sleep duration, actual sleep duration, total daily sleep duration, and total daily nap length and with decreased nocturnal awakenings according to the actigraphy measurements.[23] In this study no statistically significant difference was found between patients who were divided into groups according to receive or not intrathecal chemotherapy, high dose (HD) methotrexate, HD cytarabine, and craniospinal radiotherapy after and during treatment in terms of in sleep scores and sleep characteristics. There were only two patients with CNS tumor and two of them had sleep problems. Rosen et al.[7] reported that excessive daytime sleepiness was the most common sleep problem and seen in 60% of children with cancer, and in 80% of children with CNS neoplasms.

Sanford et al.[25] reported gender differences in the sleep of children with ALL after controlling for differences in age, treatment and risk group. However, we did not observe any gender difference in the sleep scores and the sleep patterns among children with cancer and healthy controls. One possible limitation of our study is a relatively small number of patients under ongoing oncologic treatment. Olson[26] systematically reviewed sleep related problems included difficulty initiating sleep, fragmented sleep, disordered breathing, parasomnias, napping, daytime sleepiness/fatigue among adolescents with cancer. Sleep disturbances are also common in adolescents with cancer. However, 13-18 years old adolescent patients were not included into our study since a validated Turkish version of the Adolescent Sleep Habits Questionnaire (ASHQ) (adapted adolescent version of the CSHQ) was not available.

Healthy sleep is a vital function, and an essential periodic state of rest for the mind and body. Sleep disturbances should be assessed routinely in children and adolescents with cancer. Sleep is influenced by many different factors including characteristics and development of children, psychosocial conditions, emotional distress, anxiety, depression, pain, symptoms related to anticancer therapy (dexamethasone etc.), traumatic events, family factors, education and employment status of parents, social and environmental factors, ethnic and cultural structure of society, etc. Although we have no facilities to perform further evaluations of patients with sleep problems in our center, patients with sleep problems can be referred to more specialized centers. Comprehensive and more objective assessments of sleep disturbances in children and adolescents with cancer can be done in specialized sleep laboratories and pediatric sleep centers. The routinely performed measurements include polysomnogram (PSG), multiple sleep latency test (MSLT), and actigraphy.[6,27,28] Sleep problems can be defined and managed according to the International Classification of Sleep Disorders (ICSD).[28] Firstly, comfortable sleep environment should be provided and behavioral therapeutic approaches should be applied to prevent and treat sleep problems in children. More complex sleep problems should be managed and treated in the pediatric sleep centers. Treating sleep may help prevent chronic medical conditions.

Adequate and good quality sleep is very important for children. Sleep impacts children's growth and development, and also cognitive functions, learnings and attention.[29-31] Although our results indicated that neither childhood cancer survivors nor patients with cancer during treatment period had no more sleep problems than their healthy peers, sleep problems were not uncommon in whole study group. Sleep problems were identified in about half of children with cancer and also healthy controls.

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