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Excessive Daytime Sleepiness and Sleep-Disordered Breathing Disturbances in Survivors of Childhood Central Nervous System Tumors

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Abstract

Background—Improvements in treatment and management for pediatric central nervous system (CNS) tumors have increased survival rates, allowing clinicians to focus on long-term sequelae, including sleep disorders. The objective of this study was to describe a series of CNS tumor survivors who had sleep evaluations that included polysomnography with attention to sleep disorder in relation to the tumor site.

Procedure—We report on 31 patients who had retrievable reports including an overnight polysomnography (PSG); 17 also underwent multiple sleep latency tests (MSLT) to characterize their sleepiness.

Results—Mean age at tumor diagnosis was 7.4 years, mean age at sleep referral 14.3 years, and a mean time between tumor diagnosis and sleep referral of 6.9 years. The most common tumor location was the suprasellar region, the most common reason for sleep referral was excessive daytime sleepiness (EDS), and the most common sleep diagnosis was obstructive sleep apnea (n = 14) followed by central sleep apnea (n=4), hypersomnia due to medical condition (n= 4) and narcolepsy (n=3). Twenty-six of the 31 subjects were obese/overweight, and among those with the concurrent complaint of EDS, the mean sleep latency on MSLT was 3.16 minutes, consistent with excessive sleepiness.

Conclusions—Suprasellar region tumor survivors who are obese or overweight are more likely to have complaints of EDS and are at greater risk of sleep-disordered breathing. Sleep-related

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CONFLICT OF INTEREST STATEMENT

All Authors disclose no affiliations or other areas of real or perceived conflict of interest that they consider to be relevant and important with any organization that to any author's knowledge has a direct interest, particularly a financial interest, in the subject matter discussed.

symptoms may not be recognized and referral initiated until years after CNS diagnosis. A periodic and thorough sleep history should be taken when caring for CNS tumor survivors.

Keywords

children; adolescents; sleep; CNS tumors

INTRODUCTION

Central nervous system (CNS) tumors are the most common pediatric solid tumors. Patients with these tumors present with a number of neurologic deficits during both treatment and survivorship. Survivors of CNS tumors often endure poorer quality of life and more long-term complications than do survivors of other pediatric tumors. These long-term effects include devastating fatigue and disrupted sleep [1,2], which are rated by pediatric oncology patients as their most distressing symptoms [3,4], and may be related to the primary tumor itself or to the effects of surgery, radiation, chemotherapy, or a combination of these treatments.

Quality sleep is essential for tissue renewal and compensates for energy deficits acquired during daily functions [5,6]. Sleep disturbances are associated with decreased cognitive functioning, increased anxiety and depression, and lower perceived well-being in the general population of children [7,8] and are linked to compromised immune functioning and impaired healing in these patients [9,10].

Although there is limited literature describing sleep disorders specifically in survivors of pediatric CNS tumors, there is a link between the sleep symptoms experienced and the area of the brain affected by the tumor. For example, tumors in the hypothalamic/pituitary region have been linked to the subsequent development of excessive daytime sleepiness (EDS) [11, 12]. Currently there are no screening or treatment guidelines for sleep disturbances in pediatric patients with CNS tumors. However, there are clinical factors and behavioral symptoms such as daytime sleepiness, snoring, fatigue, inattention, impulsivity and obesity that may indicate the need for sleep evaluation and treatment. The objective of this study was to report the results of a large case series of symptomatic pediatric CNS tumor survivors who were referred to a sleep medicine physician and formally evaluated by using polysomnography (PSG). We also describe potential associations between the tumor site, reasons for sleep referral and sleep diagnosis.

METHODS

Study Design

A retrospective chart review was performed on the medical records of all patients who were treated for a CNS tumor at St. Jude Children's Research Hospital and referred for an outside sleep evaluation from 1995 to 2009. The study was approved by the institutional review board at each involved institution. The following data were examined: age at diagnosis of CNS tumor, age and body mass index (BMI) at referral for sleep evaluation, location of tumor, treatment received, endocrine hormone deficiency, reason for sleep referral, and final sleep diagnosis. A total of 35 CNS tumor survivors were referred for a clinical sleep evaluation from 1995 to 2009. Among those referred, 31 patients had retrievable reports including a complete clinical sleep evaluation and polysomnography with/without a multiple sleep latency test performed at 1 of 2 sleep centers.

Polysomnography

Comprehensive, attended, nocturnal PSG was performed either at the Le Bonheur Pediatric and Adolescent Sleep Disorders Center or at the Methodist Healthcare Sleep Disorders Center, both accredited by the American Academy of Sleep Medicine (AASM). Studies were conducted by experienced polysomnographic technologists and interpreted by sleep medicine physicians Board-certified in sleep medicine. PSG was initiated within one hour of the patient's usual bedtime. The following records were made during PSG: electroencephalograms (2-4 channels); electro-oculograms (2 channels); submental electromyograms (one channel); electrocardiograms; electromyograms or accelerometry of the anterior tibialis to assess limb movements; audio recordings to detect snoring and other obstructive sounds; and video tape recordings to document movements and behaviors during sleep. The following measurements were also taken during PSG testing: respiratory effort of the chest and abdomen (2 channels); air flow as assessed by using oronasal thermistors and, in most cases, nasal pressure transducers; pulse oximetry; and end-tidal CO₂ pressure. PSG testing was performed for 6 to 10 hours.

Sleep/wake scoring was performed by using the standardized techniques and scoring criteria described by Rechtschaffen and Kales [13] for studies performed before 2007 and by using AASM scoring criteria [14] for studies performed after 2007. Obstructive apneas were scored when air-flow registration decreased by 90% to 100% with continued respiratory effort, with at least 2 respiratory cycles for patients younger than 18 years and at least 10 seconds for patients older than 18 years. Hypopneas were scored when air-flow registration was decreased by at least 30% from baseline either in association with a 3% drop in oxygen saturation values or in association with an arousal; the duration criteria used were the same as those used to diagnose obstructive apnea. Arousals were scored by using the American Sleep Disorders Association's criteria [15].

Multiple Sleep Latency Test

The MSLT is an objective, in-laboratory assessment of the patient's tendency to fall asleep under standardized conditions and was performed after the nocturnal PSG in 17 patients. The MSLT was performed according to guidelines developed by Carskadon et al. [16] and subsequently adapted by the AASM [17]. Whenever possible, patients were tapered off central nervous system-acting medications 10 to 14 days prior to the MSLT. Patients were given 4 or 5 nap opportunities at 2-hour intervals throughout the day, and were observed and not allowed to sleep between nap opportunities. If sleep onset occurred, patients were allowed to sleep 15 minutes and then awakened by the technologist. If no sleep occurred after 20 minutes, the nap opportunity ended and sleep latency was recorded as 20 minutes. The mean sleep latency was calculated as the arithmetic mean of all nap opportunities; the number of naps and the corresponding sleep stages were also recorded. Diagnostic criteria used for hypersomnia due to medical condition and narcolepsy due to medical condition are identical to those listed in the International Classification of Sleep Disorders, 2nd edition [18]. Criteria for hypersomnia due to medical condition include a complaint of excessive sleepiness present almost daily for at least three months, a mean sleep latency on MSLT of less than eight minutes, with no more than one sleep-onset REM period. Criteria for narcolepsy due to medical condition include a complaint of excessive sleepiness present almost daily for at least three months, a mean sleep latency on MSLT of less than eight minutes, and presence of two or more sleep-onset REM periods despite sufficient nocturnal sleep prior to the test.

RESULTS

Patients' Characteristics

Physicians at St. Jude's After Completion of Therapy clinic referred 7 females and 24 males for sleep evaluation. Table I details each patient's age at CNS tumor diagnosis, location of the tumor, treatment, and associated endocrine hormone deficiencies. The mean age at tumor diagnosis was 7.4 years (range, <1 month to 17.7 years). The most common CNS tumor location was sellar/parasellar/hypothalamic (n=17). Diagnoses included glioma (n=11); craniopharyngioma (n=10), ependymoma (n=4), medulloblastoma (n=4), germ cell tumor (n=1), and neurocytoma (n=1). Almost half of the patients had hydrocephalus requiring a ventriculoperitoneal shunt, and radiation therapy was the most commonly prescribed treatment.

Endocrine Deficiencies

In 22 of the patients, 2 or more endocrine hormone deficiencies were noted, with hypothyroidism being the most common (Table I). Among those with hypothyroidism, 18 had concurrent growth hormone deficiencies, and 13 had concurrent growth and cortisol deficiency. Of the 7 patients with sex hormone deficiency, all had concurrent hypothyroidism, growth hormone, and cortisol deficiency. Patients with tumors in either the sellar, parasellar, or hypothalamic region had the most substantial endocrine deficiencies. Additionally, 9 patients were not diagnosed with an endocrine deficiency, and all but 1 had tumor located outside the sellar, parasellar, or hypothalamic region. Follow up for all patients included monitoring and hormone replacement as indicated by the endocrine service.

Reason for Sleep Referral, and Diagnosis

Table II describes age and BMI at sleep referral, tumor location, reason for sleep referral, and sleep diagnosis. The mean time from tumor diagnosis to sleep referral was 6.9 years, with the mean age at sleep referral being 14.3 years (range, 1.2 to 25.5 years). The mean body mass index (BMI) was 28.8 kg/m² at the time of sleep referral, with 26 of the 31 being obese or overweight. The 31 patients had a total of 42 sleep symptoms at the time of referral, with 10 patients having more than 1. The most common reason for referral was the complaint of EDS as reported by 19 patients, followed by clinical symptoms of irregular breathing during sleep with referral to rule out sleep apnea. The most common sleep diagnosis was OSA (n=14) followed by central sleep apnea (n=4), hypersomnia (n=4), and narcolepsy (n=3) due to medical condition.

Suprasellar/hypothalamic region—Seventeen patients had tumors of the suprasellar/hypothalamic region and were most often referred for a sleep evaluation with the complaint of EDS, followed by irregular breathing during sleep, snoring, and fatigue. Among these 17 patients, 9 were diagnosed with obstructive sleep apnea (OSA). Narcolepsy without cataplexy was diagnosed in 3 of the patients and hypersomnia was diagnosed in 3 others, all having the sole complaint of EDS. Somniloquy was diagnosed in an additional patient with a suprasellar tumor who complained of snoring and symptoms of irregular breathing during sleep, and another patient in this tumor group complained of EDS with symptoms of irregular breathing during sleep, but did not meet diagnostic criteria.

Posterior fossa and fourth ventricle—Tumors of the posterior fossa and fourth ventricle were present in 4 patients each. Among those with posterior fossa tumors, the most common reason for referral was symptoms of irregular breathing during sleep and the complaint of snoring, with OSA diagnosed in one such patient. Another with the complaint of EDS did not meet diagnostic criteria for OSA, and central sleep apnea was diagnosed in

the third. The fourth patient was referred for assistance with weaning from the nighttime ventilator and was diagnosed with central hypoventilation. Those with fourth ventricle tumors had reasons for referral that included complaints of snoring and EDS; 2 had OSA, 1, central apnea, and 1, periodic limb-movement disorder.

Other tumor locations—Two patients had optic nerve tumors. Obstructive sleep apnea was diagnosed in the one patient who was referred with the complaint of snoring and fatigue. Diagnostic criteria were not met for any sleep disorder for the other patient who was referred for EDS. The following diagnoses were also made: OSA in a patient with a pineal tumor who was referred for symptoms of irregular breathing during sleep, EDS, and fatigue; hypersomnia was diagnosed in a patient with a thalamic tumor who was referred for the complaint of EDS; and central sleep apnea was diagnosed in both a patient with a brainstem tumor and a patient with a spinal tumor who was referred for symptoms of irregular breathing during sleep.

DISCUSSION

Among children with cancer who are referred to sleep centers, more than 60% have brain tumors, and more than 90% of these brain tumors are located in the hypothalamus, thalamus, or brain stem [19]. Concordant with previous reports in the literature, our cohort of CNS tumor survivors referred for sleep evaluation most often had tumors of the suprasellar region, which includes the hypothalamus. Furthermore, those with suprasellar tumors were more likely to complain of EDS and required long-term hormonal replacement. Likewise, Rosen et al. [11, 12] found EDS to be the most common sleep complaint in their cohort, and children with the most severe sleepiness had evidence of hypothalamic/pituitary injury with hormonal deficiencies. Our findings support the hypothesis of Rosen et al. [11, 12] that the location of brain tumor lesion has a strong effect on the nature and severity of sleep disturbance.

Within our cohort, those with the complaint of EDS, followed by irregular breathing during sleep and snoring were more likely to be given a diagnosis of OSA. While these complaints are commonly associated with OSA in adults [20, 21], the complaint of EDS among pediatric patients is not common with parental concern for EDS present only in a minority of children with OSA [22, 23]. The discrepancy in the complaint of EDS between children and adults may occur because of developmental or maturational differences in how sleepiness is manifest. Children may manifest sleepiness through inattentiveness, distractibility, or impulsivity, while adults complain of daytime sleepiness. Additionally, among general pediatric patients the prevalence of sleep apnea is 2% to 3% and peaks between 2 and 8 years of age [24]. However, the prevalence of sleep apnea is higher among neurologically impaired children because of hypotonia and weakness of the pharyngeal/respiratory muscles coupled with an inability to change position during sleep [25].

Obesity is thought to play a significant role in sleep-disordered breathing and EDS in tumors of the sellar/parasellar/hypothalamic region, with 26 of the 31 CNS survivors found to be obese or overweight at the time of their sleep referral. As with our cohort, a previous report indicates that subjective complaints of EDS are associated with obesity in children with varying degrees of OSA [26]. Redline et al. [27] found that the risk for sleep-disordered breathing in obese children is increased fourfold to fivefold, with the risk of OSA increasing 12% for every increase in BMI of 1 kg/m² beyond the mean for age and gender. While another study found significantly more EDS in the overweight/obese group with moderate sleep-disordered breathing [28]. The complaint of EDS and concurrent obesity among these CNS tumor survivors is further exacerbated by disruption of the circadian clock in the suprachiasmatic nucleus, secondary to tumor location. Proper function of the

suprachiasmatic nucleus is required for the circadian responses including release of melatonin, corticosteroid secretion and feeding. In patients with tumors within the hypothalamus-pituitary axis, decreased nocturnal salivary melatonin levels have been associated with increased BMI and daytime sleepiness [29].

Sleep-disordered breathing among CNS tumor survivors is problematic, not only because it interferes with normal sleep patterns and increases daytime sleepiness, but also because it may further impair cognitive and social functioning. Children with symptoms of sleep-disordered breathing experience a range of neuropsychological dysfunction including problems with cognition [30], hyperactivity [31], memory [32], executive function [33], and school performance [34, 35]. Along with neurocognitive morbidity, OSA and obesity create a chronic low grade inflammatory process resulting in an increased risk for metabolic and cardiovascular disease [24, 26, 36]. One may presume that CNS tumor survivors with sleep disorders may experience an additive effect resulting in even greater vulnerability to these disturbances.

Among general pediatric patient complaints, insomnia and parasomnia are common complaints; however, these complaints were not elicited from our cohort. In the study by Rosen et al. [12], 17 of 70 children had a complaint of sleep maintenance insomnia and most were on active therapy for a hematologic cancer receiving corticosteroid treatment, while a small number had insomnia related to pain. Insomnia and parasomnia were not found to be complaints among those with CNS tumors.

Limitations to this study include its retrospective method and its skewed sample of CNS tumor survivors referred to a sleep disorders center. Although this sample allows for conclusions related to the most common sleep disorders in this sample, it does not permit analyses of the rates of sleep disturbance in a larger subset of pediatric CNS tumor survivors. Ongoing, prospective studies of sleep concerns in pediatric CNS tumor survivors should provide more insight into the rates of sleep disturbance in this group of patients.

These findings as well as others [11, 12] support the need to incorporate a comprehensive sleep evaluation with both subjective and objective components into the care of long-term survivors of childhood brain tumors, most specifically those whose tumor involves the suprasellar/hypothalamic region. Although EDS can have various manifestations, which may include excessive napping, sleeping in unusual positions, or inattention, it is an important indicator of sleep disturbance in neurologically impaired children including CNS tumor survivors. Methods used to subjectively measure EDS within this population should include a validated tool such as the 4-item Pediatric Sleep Questionnaire-Sleepiness Subscale, which has been found to correlate well with the objective MSLT [37], or the modified Epworth Sleepiness Scale for Children [38]. Although sleep concerns are common in patients with brain tumors, the extended time between the diagnosis of a brain tumor and referral for a sleep evaluation highlights the importance of considering sleep disorders earlier in the trajectory of anti-brain tumor treatment. Longitudinal follow-up of these patients will help define the natural history of sleep disturbance in this population and will address the effects of sleep disturbance on neurocognitive function, behavior, and quality of life.

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Table I

Patients' Age at Diagnosis, Tumor Location, Treatment and Endocrine Deficiency

Patient	Age at Diagnosis	Tumor/Location	Treatment	Endocrine Deficiency
1	1.0	Posterior fossa	NTR, RT, shunt, chemo	Thyroid, growth
2	2.2	Sellar/parasellar/hypothalamic	NTR, RT	Thyroid, growth, sex, cortisol
3	3.2	Optic nerve-bilateral	RT, chemo	Thyroid, growth, sex, cortisol
4	2.8	Sellar/parasellar/hypothalamic	RT, shunt, chemo	Thyroid, growth, sex, cortisol
5	7.4	4 th ventricle	NTR, RT, shunt, chemo	Thyroid, growth, cortisol
6	10.2	Pineal	GTR, RT, shunt, chemo	Thyroid, growth
7	10.1	Sellar/parasellar/hypothalamic	PR, RT	Thyroid, cortisol
8	14.1	Sellar/parasellar/hypothalamic	NTR, RT, chemo	Thyroid, growth
9	1.0	4 th ventricle	RT, shunt, chemo	None
10	0.1	4 th ventricle	GTR, RT, chemo	Thyroid, growth, cortisol
11	17.7	Thalamus	RT, shunt	None
12	16.4	Sellar/parasellar/hypothalamic	NTR, RT	Thyroid, cortisol
13	5.4	Sellar/parasellar/hypothalamic	RT, shunt	Thyroid, growth, cortisol
14	1.4	Brainstem	RT, chemo	None
15	11.8	Sellar/parasellar/hypothalamic	NTR, RT	Thyroid, growth, sex, cortisol
16	16.8	Sellar/parasellar/hypothalamic	RT	Thyroid, growth, sex, cortisol
17	7.9	Sellar/parasellar/hypothalamic	PR, shunt	Thyroid, growth, sex, cortisol
18	7.8	Sellar/parasellar/hypothalamic	RT, shunt	Thyroid, growth, cortisol
19	3.6	Sellar/parasellar/hypothalamic	NTR, RT, shunt	Thyroid, cortisol
20	4.5	Optic nerve-bilateral	RT, chemo, shunt	None
21	9.6	Sellar/parasellar/hypothalamic	PR, RT	Thyroid, growth, cortisol
22	9.4	Sellar/parasellar/hypothalamic	GTR, RT, shunt	None
23	0.7	Posterior fossa	PR, RT, shunt, chemo	None
24	9.8	Posterior fossa	PR, RT, chemo	Thyroid, growth
25	11.4	Sellar/parasellar/hypothalamic	NTR, RT, shunt	Thyroid, growth, sex, cortisol
26	4.6	4 th ventricle	Multiple surgeries, RT, chemo	None
27	12.0	Sellar/parasellar/hypothalamic	NTR, RT, shunt	Thyroid, growth, cortisol
28	6.6	Sellar/parasellar/hypothalamic	RT, shunt	Thyroid, growth
29	6.7	Posterior fossa	RT, chemo	None
30	4.8	Sellar/parasellar/hypothalamic	NTR, RT	Thyroid, cortisol
31	8.8	Spinal	RT	None

NTR, near total resection; PR, partial resection; GTR, gross total resection; RT, radiation therapy

Table II
Patient Age at Diagnosis, Age at Sleep Referral, BMI, Tumor Location, Reason for Sleep Referral and Sleep Diagnosis

Pt	Age at Diagnosis	Age at sleep referral	BMI at sleep study referral	Tumor Location	Reason for Sleep Referral	Sleep Study Diagnosis
1	1.0	21.9	32.6	Posterior fossa	EDS, snoring	Suspected SRBS not confirmed by PSG
2	2.2	17.2	35.2	Sellar/parasellar/hypothalamic	Concern Sleep Apnea , snoring	Other-Somniloquy
3	3.2	14.5	38.9	Optic nerve-bilateral	Fatigue, snoring	Obstructive Sleep Apnea
4	2.8	17.2	28.9	Sellar/parasellar/hypothalamic	Concern Sleep Apnea , EDS	Obstructive Sleep Apnea
5	7.4	18.2	21.7	4 th ventricle	EDS, snoring	Obstructive Sleep Apnea
6	10.2	19.1	39.9	Pineal	Concern Sleep Apnea ,fatigue,EDS	Obstructive Sleep Apnea
7	10.1	23.2	34.6	Sellar/parasellar/hypothalamic	EDS	Narcolepsy due to medical condition w/o cataplexy
8	14.1	23.2	36.9	Sellar/parasellar/hypothalamic	Concern Sleep apnea	Obstructive Sleep Apnea
9	1.0	9.6	26.3	4 th ventricle	Snoring	Periodic limb movement disorder
10	0.0	9.5	15.9	4 th ventricle	Concern Sleep apnea, EDS	Central sleep apnea
11	17.7	25.5	22.2	Thalamus	EDS	Hypersomnia due to medical condition
12	16.4	23.8	20.6	Sellar/parasellar/hypothalamic	EDS	Hypersomnia due to medical condition
13	5.4	11.7	35.7	Sellar/parasellar/hypothalamic	EDS	Suspected SRBS not confirmed by PSG
14	1.4	4.1	21.3	Brainstem	Concern Sleep apnea	Central sleep apnea
15	11.8	18.4	37	Sellar/parasellar/hypothalamic	EDS	Narcolepsy due to medical condition w/o cataplexy
16	16.8	24.1	31.9	Sellar/parasellar/hypothalamic	EDS	Hypersomnia due to medical condition
17	7.9	14.7	29.2	Sellar/parasellar/hypothalamic	Concern Sleep apnea	Obstructive Sleep Apnea
18	7.8	12.6	24.9	Sellar/parasellar/hypothalamic	EDS	Narcolepsy due to medical condition w/o cataplexy
19	3.6	8.0	24.5	Sellar/parasellar/hypothalamic	EDS	Hypersomnia due to medical condition
20	4.5	8.2	21.1	Optic nerve-bilateral	EDS	Normal
21	9.6	18.6	45.8	Sellar/parasellar/hypothalamic	EDS	Obstructive sleep apnea
22	9.4	14.8	44.2	Sellar/parasellar/hypothalamic	Snoring	Obstructive sleep apnea
23	0.7	1.2	13.4	Posterior fossa	Concern Sleep apnea	Central sleep apnea
24	9.8	12.0	25.4	Posterior fossa	Concern Sleep apnea, snoring	Obstructive sleep apnea
25	11.4	15.0	34.7	Sellar/parasellar/hypothalamic	Concern Sleep apnea, EDS	Obstructive sleep apnea

Pt	Age at Diagnosis	Age at sleep referral	BMI at sleep study referral	Tumor Location	Reason for Sleep Referral	Sleep Study Diagnosis
26	4.6	6.7	18.5	4 th ventricle	Snoring	Obstructive sleep apnea
27	12.0	14.6	41.1	Sellar/parasellar/hypothalamic	Fatigue, EDS	Obstructive sleep apnea
28	6.6	10.9	38.2	Sellar/parasellar/hypothalamic	EDS	Obstructive sleep apnea
29	6.7	8.0	23.1	Posterior fossa	Wean nighttime ventilator	Central hypoventilation
30	4.8	10.9	28.3	Sellar/parasellar/hypothalamic	Concern Sleep apnea, EDS	Obstructive sleep apnea
31	8.8	9.2	19.3	Spinal	Concern Sleep apnea	Central sleep apnea

EDS, excessive daytime sleepiness; IBDS, irregular breathing during sleep, SRBD, sleep related breathing disorder, BMI, body mass index