Factors Associated With Sleep-Wake Disturbances in Child and Adult Survivors of Pediatric Brain Tumors: A Review

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Purpose/Objectives: To identify factors associated with sleep-wake disturbances in pediatric and adult survivors (aged older than 18 years) of pediatric brain tumors.

Data Sources: A computerized literature search was completed using MEDLINE®, CINAHL®, CancerLit, Dissertation Abstracts International, and PsycINFO. The search and a personal communication with one author discovered 25 English-language research articles and case reports describing sleep-wake patterns in brain tumor survivors from 1966–2008.

Data Synthesis: Disease- and treatment-related factors from direct injury to the hypothalamus results in irregular melatonin secretion and low hypocretin levels. This contributes to decreased daytime alertness, which remains the most reported sleep-wake disturbance in brain tumor survivors. Patients with craniopharyngiomas, radiation dose more than 3,500 cGy, and younger age at time of treatment experienced more severe sleep dysfunction.

Conclusions: Patients with brain tumors experience a disruption of sleep-wake patterns associated with major dysfunction in the hypothalamic-pituitary axis, affecting both Process S (homeostasis) and Process C (circadian) from the Two-Process Model of Sleep Regulation. Various demographic-, disease-, and treatment-related variables are involved in driving the onset of sleep disturbances. Interventions are needed to improve daytime function and decrease the effect of sleep disturbances on quality of life.

Implications for Nursing: Current sleep literature has identified patterns of sleep disturbances in cross-sectional studies of brain tumor survivors. Rigorous longitudinal designs are needed for future studies to detect onset patterns and trajectory of sleep-wake disorders. Intervention studies are needed to impact excessive daytime sleepiness, irregular sleeping and waking patterns, and other identified sleep-wake disorders.

Pediatric brain tumors are the most common solid tumors in pediatric patients (younger than aged 19), with an annual incidence rate of about 3 cases per 100,000 in the United States (Gurney, Smith, & Bunin, 1999). Because of technological advances in radiation therapy and aggressive chemotherapy regimens, the five-year relative survival rates are approaching 75% (Jemal et al., 2006). Invasive surgery and high-dose radiation therapy remain essential components of a long-term cure (Packer, 1999; Packer, Cogen, Vezina, & Rorke, 1999). After these intense cancer treatments, about 50% of brain tumor survivors, in some samples, experienced sleep-wake disturbances as long-term sequelae (Muller, Handewerker, Wollny, Faldum, & Sorenson, 2002; Palm et al., 1992; Van Someren et al., 2004). In follow-up studies of brain tumor survivors, sleep impairment negatively affected quality of life (Anderson et al., 2001; Hudson et al., 2003; Mostow, Byrne, Connelly, & Mulvihill, 1991; Pelletier, Verhoef, Khatri, & Hagen, 2002). To date, little research in adult survivors (aged 19 years and older) of pediatric brain tumors is available to guide sleep interventions and improve daytime functioning. The purpose of this review is the identification of critical factors associated with sleep-wake disturbances in child and adult survivors of pediatric brain tumors.

Background

A key contributor affecting sleep-wake disturbances in brain tumor survivors is destruction of the hypothalamus, a radio-sensitive sleep-wake structure susceptible to long-term damage (Constine et al., 1993; Heikens et al., 1998). Cranial radiation therapy alters the hypothalamic-pituitary axis, with associated hormonal abnormalities and neurocognitive, sensory, and motor defects, as well as impaired sleep patterns (Constine et al.). Radiation dose and age at treatment affect the severity of sequelae (Anderson et al., 2001; Fagioli, Brauner, & Rappaport, 1991; Packer et al., 1999).

Reported sleep disturbances in brain tumor survivors include insomnia, excessive daytime sleepiness, limb movement disorders, sleep apnea, and increased nighttime awakenings (di Gennaro et al., 2004; Marcus, Trescher, Halbower, & Lutz, 2002; Szucs, Bodizs, Barsi, & Halasz, 2001; Zembelis, Paparrigopoulos, & Soldatos, 2002). Impairment of hypocretin-producing cells in the lateral and posterior hypothalamus increases somnolence and promotes secondary narcolepsy in some survivors (Arii et al., 2001; Nishino, Ripley, Overeem, Lammer, & Mignot, 2000; Selbach & Haas, 2006; Taheri,

Zeitzer, & Mignot, 2002). In addition, after surgery for craniopharyngioma, reduced erratic melatonin secretion, a key endocrine hormone for sleep regulation, promotes irregular sleep patterns and excessive daytime sleepiness (Chakrabarti, Amar, Couldwell, & Weiss, 2005). Therefore, impaired daytime alertness and insomnia negatively influence brain tumor survivors' ability to engage in usual activities such as school or work. Daytime napping and other coping strategies reduce the time and quality of social interaction and affect role function for survivors (Poretti, Grotzer, Ribi, Schonle, & Boltshauser, 2004). This review of the literature identifies factors associated with sleep-wake disturbances in child and adult survivors of pediatric brain tumors.

Sleep-wake conceptual models specific to patients with cancer are evolving. Vena, Parker, Cunningham, Clark, and McMillan (2004) identified variables contributing to sleep disturbances in patients with cancer. These concepts extend the Two Process Model of Sleep Regulation by identifying the affect of demographic, disease-related, lifestyle, psychological, and treatment-related factors on circadian and homeostatic processes. For instance, disease-related factors might include pain, hormone irregularities or deficiencies, and cytokine production. Lifestyle factors such as poor sleep hygiene, caffeine and alcohol intake, or smoking may affect sleep-wake patterns (see Figure 2). The factors identified by Vena et al. have clinical and empirical use for brain tumor survivors, as multiple disease and treatment-

Conceptual Models of Sleep Regulation

The Two-Process Model of Sleep Regulation forms the foundation for this review. This model hypothesizes sleep regulation as a homeostatic process identifying sleep debt and a circadian process following the linear function of time. Process S (the homeostatic process) increases during wakefulness and declines during sleep. This process defines a sleep threshold, the point at which sleep debt is such that sleep onset must occur to assure function during a wakeful state. Process C (circadian process) is controlled by the suprachiasmatic nuclei in the hypothalamus. The thresholds run in parallel and vary rhythmically with time of day (Borbely & Achermann, 1999). Damage to the hypocretin cells in the hypothalamus during brain tumor treatment affects the arousal mechanisms of Process S. The circadian process (Process C) is affected when brain tumors or their treatment destroy the suprachiasmatic cells, eliminating the 24-hour periodicity required for normal sleep patterns. Other variables affected by cancer treatments, such as pain, stress, and infection, also can affect the timing of sleep (Beersma, 1998) (see Figure 1).

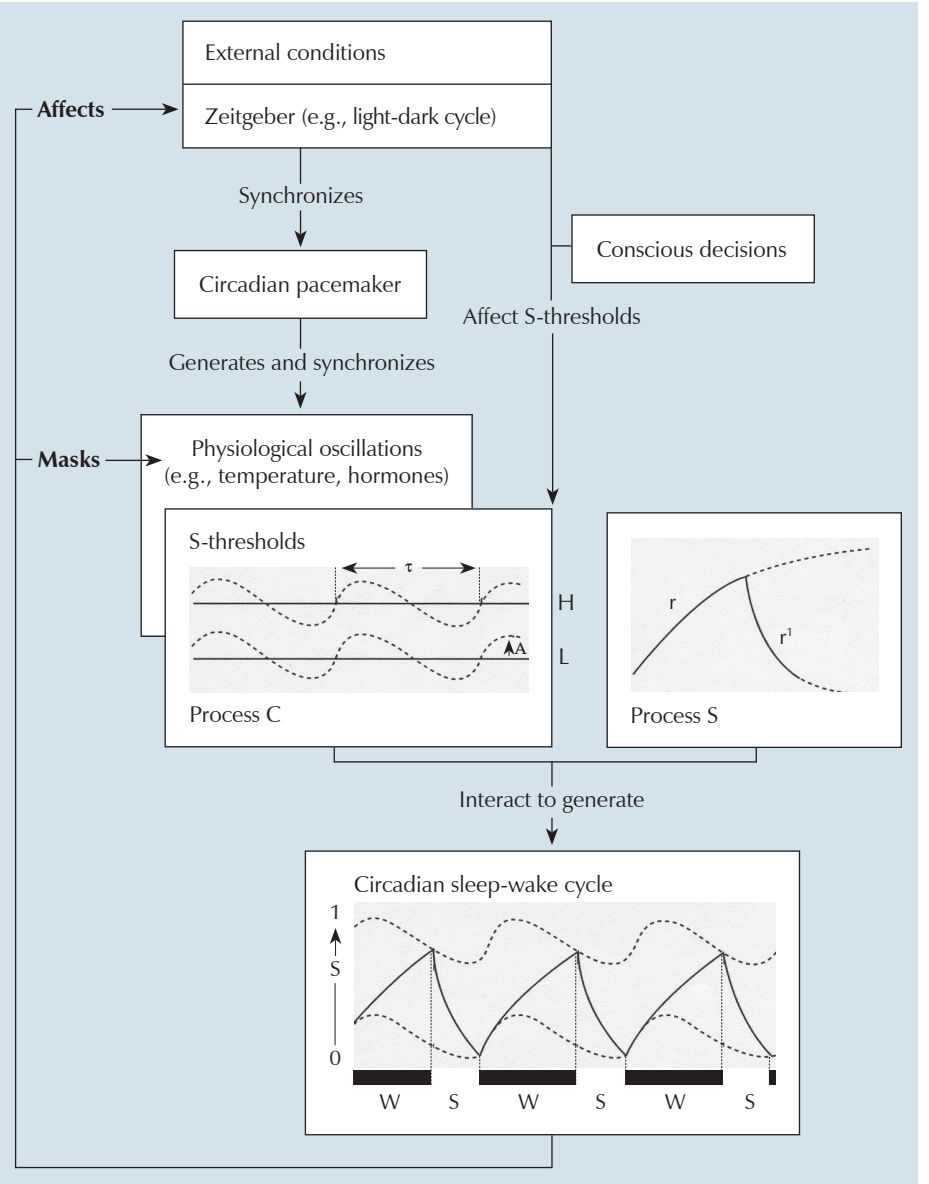

Figure 1. Two-Process Model of Sleep Regulation

Note. From "Models of Human Sleep Regulation," by D.G.M. Beersma, 1998, *Sleep Medicine Reviews, 2*(1), p. 33. Copyright 1998 by Elsevier. Reprinted with permission.

related factors continue long after acute treatment ends, dramatically affecting sleep-wake cycles.

Search Strategy

The initial literature search encompassed research or case studies describing factors associated with sleep-wake disturbances in the target population of adult survivors of pediatric brain tumors only. To expand the number of articles, the second phase included studies of sleep disturbances in pediatric survivors (younger than age 18 years) with brain tumors.

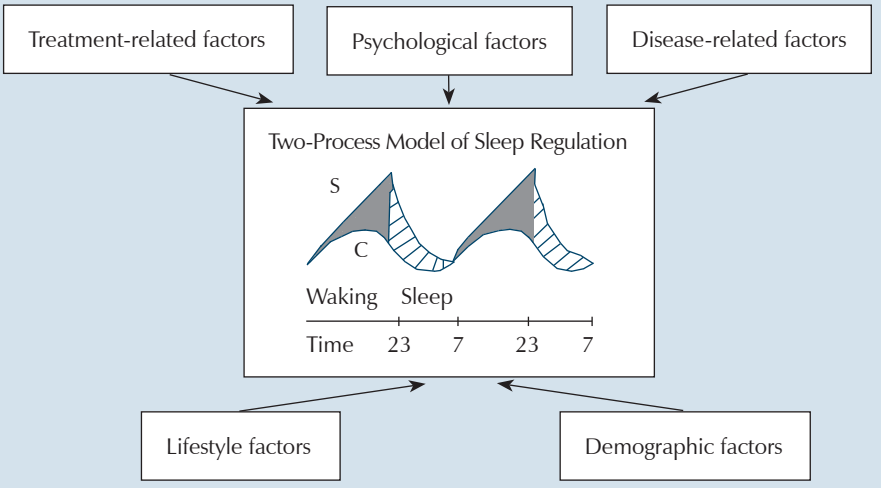

Figure 2. Cancer-Related Factors Model Affecting Sleep

Note. Based on information from Vena et al., 2004.

Sleep-Wake Disturbances in Adult Survivors of Pediatric Brain Tumors

A computerized literature search was completed using MEDLINE®, CINAHL®, CancerLit, Dissertation Abstracts International, and PsycInfo. Search terms included *brain neoplasm* or *brain tumor* combined with *sleep*, *sleep disorders*, *sleep disturbance*, *sleep regulation*, *sleepiness*, *daytime sleepiness*, *circadian rhythm*, *survivor*, *adult*, *childhood*, and *cancer*. The time period searched was 1966–2008 because treatment for malignant brain tumors with radiation therapy became common in this era.

The inclusion criteria were human subjects diagnosed with a brain tumor when they were aged 18 years or younger, English language articles, case study or original research, and measurement of sleep disturbance in the sample. Exclusion criteria were articles describing hormonal deficiencies in brain tumor survivors without the use of concurrent sleep measures in the population. No attempt was made to identify unpublished studies by searching conference proceedings. However, one article (Mulrooney et al., 2008) was retrieved in January 2008 after discussion with researchers from the Children's Cancer Survivor's Study. Also included in the search were textbooks on sleep and sleep medicine and chapters from oncology nursing textbooks. Manuscript reference lists were searched for pertinent sources.

Assessment of Methodologic Quality

The criteria for review focused on the methodologic quality of the study. Because of the very small number of articles retrieved, all research articles or case studies meeting the inclusion criteria were reviewed, even if sample size or design were not ideal. Methodologic criteria and the strength of evidence hierarchy were adapted from Fink (2005) to include definition of major variables and terms, psychometrics of measurement instruments in the brain tumor population, prospective data collection, randomized sampling strategies, an adequate description of the sample, adequacy of response rates, and conclusions. Each article was examined and placed in one of the following five categories.

- Category A: Randomized, controlled trials
- Category B: Prospective, nonrandomized, controlled trials or cross-sectional studies
- Category C: Retrospective studies with clearly defined sources of information
- Category D: Retrospective trials with unspecified or unclear data sources
- Category E: Case reports

Results

This review describes associated factors for sleep-wake disturbances in adult and pediatric survivors of pediatric brain tumors. A total of 34 articles were identified and evaluated from the electronic and reference article search. Twenty articles, including samples of adult and pediatric survivors of pediatric brain tumors, met the search criteria and were critiqued for the review. Also included was an article describing pediatric cancer survivors from the Children's Cancer Survivor's Study with varying types of cancer, including brain tumors. In addition, four articles on somnolence syndrome after radiation therapy advantaged the final synthesis by identifying potential precipitating factors of sleep disturbances. Thirteen of the 34 articles retrieved were not included as the authors did not measure sleep disturbance in the sample. The final review consisted of 25 articles divided into categories including mixed samples of adult and pediatric survivors of pediatric brain tumors, pediatric survivors of brain

tumors, or adult survivors of brain tumors. Repeatedly, the factors most strongly associated with sleep issues were hypothalamic damage resulting in excessive daytime sleepiness, melatonin and hypocretin defects contributing to poor arousal mechanisms, and damage to suprachiasmatic nuclei affecting circadian rhythm. Patients with hypothalamic tumors or craniopharyngiomas, with doses of radiation greater than 3,500 cGy affecting the region of the hypothalamus, and aged younger than 5 years at radiation therapy were more likely to suffer severe sleep dysfunction. The literature is summarized in Table 1.

Factors Associated With Sleep Disturbances in Adult Survivors of Pediatric Brain Tumors

Damage to the hypothalamus: Early sleep-wake disturbances in adults and children with brain tumors are associated with radiation therapy. Evidence exists of a "somnolence syndrome" emerging in about 60%–75% of children with acute lymphoblastic leukemia or non-Hodgkin lymphoma treated with prophylactic radiation to the central nervous system. In addition, adults with primary brain tumors have been found to experience the same syndrome. About four to six weeks after initial treatment with cranial radiation, the symptoms of sleepiness, abnormal sleep-wake schedules, anorexia, lethargy, fever, and cataplexy appear. The syndrome is dose dependent with an indicated symptom threshold of 3,500 cGy and with radiation fractions given over shorter time periods. Use of steroids during therapy has demonstrated improvement in the syndrome (Faithful, 1991; Faithful & Brada, 1998; Parker et al., 1978; Uzal et al., 1998). The long-term effect of this acute syndrome is unknown; however, damage to the specialized cells which stimulate melatonin production or hypocretin proteins or to suprachiasmatic nuclei may be responsible for long-term loss of function.

Melatonin secretion defects: Damage to the hypothalamus results in irregular melatonin secretion, increased body mass index (BMI), and excessive daytime sleepiness, which has been well studied in craniopharyngioma survivors with self-reports indicating insomnia, excessive daytime sleepiness, and secondary narcolepsy. While not malignant, craniopharyngiomas arise in the hypothalamic-pituitary axis and are treated with surgical excision, making the patients an excellent model in which to study the effects of damage to the hypothalamus. About 95% of patients with craniopharyngioma have significant hypothalamic pituitary damage related to the tumor itself (Ullrich, Scott, & Pomeroy, 2005). German researchers evaluated a group of patients with hypothalamic pilocytic astrocytomas and craniopharyngiomas, comparing them to healthy controls. They reported craniopharyngioma survivors with severe obesity (BMI Standard Deviation Scale of greater than four) had higher scores on the Epworth Sleepiness Scale (greater than 10) than normal weight or less-obese survivors. Decreased nocturnal melatonin levels correlated with excessive daytime sleepiness and obesity (Muller et al., 2002).

Other studies with craniopharyngioma survivors have indicated that damage to the hypothalamus results in significant sleep issues. Higher scores on the Epworth Sleepiness Scale, with corresponding obesity and lower quality of life, were reported by Poretti et al. (2004). Similarly, shortened sleep periods and multiple awakenings with a decreased nighttime melatonin production were observed in a 14-year-old boy with a pineal tumor (Etzioni et al., 1996). In one study of craniopharyngioma survivors, the frequent awakenings were severe enough to be classified as a disorder of maintaining sleep according to the Association of Sleep Disorders Centers 1979 Classifications (Palm et al., 1992).

A report from the Children's Cancer Survivors Study with a large sample of 2,645 cancer survivors, including 398 with a variety of pediatric brain tumors, identified that 16.7% of the total sample and 15.7% of the brain tumor survivors self-reported disrupted sleep on the Pittsburgh Sleep Quality Index (PSQI). More brain tumor survivors reported daytime sleepiness (16.4%) compared to 14% of the total sample. Obese survivors with any cancer diagnosis were more likely to experience daytime sleepiness and sleep disruptions. Survivors with soft tissue sarcoma reported more significant sleep disturbances (22%) than survivors with other cancer diagnoses. Survivors reporting sleep disturbance and daytime sleepiness had lower physical functioning, role performance, and general health scores. Although survivors with a history of radiation therapy were more likely to have higher fatigue scores, no relationship between radiation therapy dose and sleep disturbance was detected in the brain tumor survivors in their sample (Mulrooney et al., 2008).

Intervention studies with small sample sizes have supported the hypotheses implicating hypothalamic injury with decreased nocturnal melatonin levels as a predictor of excessive daytime sleepiness. Muller, Handwerker, et al. (2006) administered a 6 mg evening melatonin substitution to seven adult and three pediatric survivors of pediatric craniopharyngioma and pilocytic astrocytoma experiencing the most severe excessive daytime sleepiness from the study. All 10 patients had Epworth Sleepiness Scale scores greater than 10. In addition, the severely obese patients had lower melatonin concentrations at nighttime than other subjects. In all 10 survivors receiving melatonin supplementation, the degree of excessive daytime sleepiness improved significantly based on activity diaries, administration of the Epworth Sleepiness Scale (median score of seven while under treatment), self-assessment questionnaires, and actigraphy. Other studies also demonstrated improvement

Table 1. Key Features and Supporting Literature for Sleep Disturbances in Adult Survivors of Pediatric Brain Tumors

Authors	Study Type	Sample
Damage to hypothalamic-pituitary axis (key feature: excessive daytime sleepiness)		
Arii et al., 2001	Case report	Girl aged 16 years
Etzioni et al., 1996	Case report	Boy aged 14 years
Marcus et al., 2002	Case reports	3 children
Muller et al., 2002[a]	Quasi-experimental	98 ASCBT and children, 1 control
Muller, Handwerker, et al., 2006[a]	Quasi-experimental	10 ASCBT
Muller, Muller-Stover, et al., 2006[a]	Cross-sectional survey	115 ASCBT and children, 1 control
Mulrooney et al., 2008	Retrospective cohort	2,645 survivors, 398 ASCBT
Palm et al., 1991[a]	Quasi-experimental	10 patients and 18 controls; 5 patients were ASCBT
Poretti et al., 2004[a]	Retrospective series	25 ASCBT and children
Rosen et al., 2003	Retrospective case reviews	14 children
Loss of suprachiasmatic nuclei cells (key feature: irregular sleep-wake patterns)		
Borodkin et al., 2005	Case report	Man aged 21 years
Kubota et al., 1991	Case report	2 adults
Damage to brainstem and thalamic nuclei (key feature: sleep apnea and increased slow-wave sleep)		
Frieboes et al., 1998	Quasi-experimental	7 adults and 7 controls
Ioos et al., 2001	Case report	Girl aged 4 years
Ito et al., 1996	Case reports	Children aged 7–12 years
Van Someren et al., 2004[a]	Quasi-experimental	25 ASCBT and 34 controls
Disruption of cortical cells on side of lesion (key feature: sleep spindle disruption or night terrors)		
Daly, 1968	Descriptive series	78 adults
Di Gennaro et al., 2004	Case report	Woman aged 48 years
Ohgami, 1973	Descriptive series	52 adults and 15 controls
Reeves & Klass, 1998	Case report	Boy aged 12 years

[a] Original articles that met the search criteria
ASCBT—adult survivor of childhood brain tumor
Note. Four articles on somnolence syndrome are not included in this table.

with melatonin supplementation or the use of stimulants (Etzioni et al., 1996; Marcus et al., 2002).

Damage to hypocretin cells: Retrospective research designs have identified excessive daytime sleepiness from damage to hypocretin cells within the hypothalamus. The cells are crucial for arousal mechanisms, and loss of these specialized neurons may result in secondary narcolepsy. In 14 children with brain tumors evaluated at a sleep clinic, Rosen, Bendel, Neglia, Moertel, & Mahowald (2003) identified excessive daytime sleepiness exhibited by one or more of the following.

- Increase in total sleep time per 24 hours
- Increased daytime naps previously discontinued at a younger age
- Inability to awaken in the morning to begin usual activities
- Inability to remain awake during daytime activities, such as school.

Children with the most severe sleepiness had evidence of hypothalamic-pituitary injury with deficiencies in both anterior and posterior pituitary hormones.

Van Someren et al. (2004) identified increased sleepiness and difficulty transitioning to wakefulness during the last hour of sleep in a mixed sample of 25 adult and pediatric survivors of pediatric brain tumors compared to healthy volunteers. Analysis revealed significantly longer sleep duration (increased slow wave or deep sleep) and lower levels of morning activity in the brain tumor group versus the control group. Young age and higher dosage of radiation was associated with increased difficulty in overcoming sleepiness. A case report supporting the effects of hypocretin cell loss after surgery described excessive daytime sleepiness and increased rapid-eye movement (REM) sleep with a low cerebrospinal fluid hypocretin level in a 16-year-old girl after removal of a pilocytic astrocytoma (Arii et al., 2001).

In a study by Muller et al. (2002), craniopharyngioma survivors' self-report scores on the Epworth Sleepiness Scale were correlated with sleep laboratory testing (polysomnography and multiple sleep latency testing). Survivors with scores greater than 10 had sleep-onset REM activity, a classic criterion for narcolepsy. Another group of investigators (Marcus et al., 2002) also described secondary narcolepsy in three children with brain tumors. Each of the tumors caused widespread

damage to the hypothalamus. One of the children experienced cataplexy, a classic sign of narcolepsy.

Damage to the suprachiasmatic nuclei: Irregular sleep-wake patterns related to circadian disturbances in suprachiasmatic nuclei of the hypothalamus were identified in two case reports. The first, by Kubota, Shinozaki, Nagata, & Sasaki (1991), described two young men, aged 17 and 19 years, with hypothalamic brain tumors and dysfunctional rhythmicity. The patients experienced disturbance in slow-wave sleep and dispersed sleep patterns throughout the 24-hour cycle. Similarly, Borodkin, Ayalon, Kanety, & Dagan (2005) reported a 21-year-old patient with difficulty in sleep onset and awakening after a diagnosis of a prolactin-secreting pituitary microadenoma. Actigraphic monitoring revealed irregularity in rest-activity patterns with sleep onset time advanced by about one hour per day. The circadian oral temperature, salivary melatonin, and sleep-wake rhythms were desynchronized. The final diagnosis was circadian rhythm discord originating between the ultradian and circadian components of the sleep regulatory system.

Damage to the brainstem and thalamus: Brain lesions affecting the brainstem and thalamus are associated with EEG and sleep abnormalities. Frieboes, Murck, Stalla, Antonijevic, & Steiger (1998) compared patients with prolactinomas to healthy age- and sex-matched controls. All prolactinoma patients' EEGs demonstrated significantly longer duration of slow-wave sleep (stages 3 and 4), yet reported no subjective sleep disturbances.

Commonly, brainstem lesions cause central sleep apneas, reduction of total sleep time, variable sleep stages, and disruption of REM sleep. Sleep apnea results in microarousals and desaturations creating a fragmented sleep episode. Ito, Murofushi, Mizuno, & Smeba (1996) reported two children, aged 7 and 12 years, with brainstem gliomas resulting in central sleep apnea. Polysomnography revealed 40 apneas during five hours of sleep with an apnea index of eight. All apneas were central and lasted longer than 10 seconds. Similarly, Ioos, Estournet-Mathiaud, Pinard, and Cheliout-Heraut (2001) described a case report of a 4-year-old girl with a brainstem lesion requiring tracheotomy and nocturnal ventilation. A polysomnographic study demonstrated disordered sleep stages, increased microarousals, and more than eight apneic episodes per hour. Others have reported disrupted REM sleep, reduction of total sleep time, and sleep apneas with brainstem lesions (Markand & Dyken, 1976; Valledeoriola, Santamaria, Graus, & Tolosa, 1993).

Alterations in EEGs of patients with brain tumors have been recognized since the late 1930s (Daly, 1968; Ohgami, 1973; Reeves & Klass, 1998). Although previous authors identified EEG abnormalities alone, di Gennaro et al. (2004) were first to describe a patient with EEG abnormalities and night terrors possibly initiated by an abnormal deep sleep (arousal disorder) with fragmentation of slow-wave sleep. The patient, a 48-year-old woman with a right thalamic tumor, regularly experienced 10-minute episodes of night terrors with screaming and terrified expressions during non-REM sleep. Sleep fragmentation and arousals were evident during a sleep study. Sleep spindles were decreased on the affected side (di Gennaro et al.).

Discussion

This review explores factors associated with sleep-wake disturbances in adult survivors of pediatric brain tumors, with about 70% reporting excessive daytime sleepiness in some samples, a significant late effect of both the tumor and its treatment that was experienced by only 0.5%–13.3% of the general population (Benbadis, Perry, Sundstad, & Wolgamuth, 1999; D'Alessandro, Rinaldi, Cristina, Gamberini, & Lugaresi, 1995). The evidence is based on heterogeneous small sample sizes, poor sample descriptions, and inadequate control groups, creating difficulty in identifying the factors most strongly associated with sleep-wake disturbances among brain tumor survivors. However, the literature does provide some insight into factors affecting insomnia and decreased daytime alertness among brain tumor survivors.

The frameworks for this review are Borbely and Achermann's (1999) Two Process Model of Sleep Regulation, and Vena et al.'s (2004) Cancer-Related Factors Affecting Sleep. In support of both conceptual models, a review of the literature identified that disease- and treatment-related factors affect sleep processes and are linked to sleep-wake disturbances. This suggests the Two Process Model of Sleep Regulation is affected by sleep disruptions or irregular sleep patterns arising from insufficient melatonin secretion, resulting in erratic Process C circadian patterns. This results from damage to the suprachiasmatic nuclei, a clock-like mechanism in the hypothalamus. Certain tumor types located near the hypothalamus, such as craniopharyngiomas, elicit predictable Process S sleep disturbances and daytime sleepiness severe enough to be classified as secondary narcolepsy. Initial small intervention studies with craniopharyngioma survivors demonstrate less sleepiness and improved quality of life with melatonin supplementation.

Interestingly, the largest study reviewed, which included more than 350 pediatric survivors of malignant brain tumors, demonstrated a lower rate of sleep disturbance in the sample with no link to radiation therapy treatment or dose of radiation. Mulrooney et al. (2008) does not include significant numbers of patients with craniopharyngiomas (a benign tumor) and might provide an inadvertent comparison to the studies of craniopharyngioma survivors. Certainly, survivors with extensive damage to the hypothalamus, such as those

with craniopharyngioma, self-report more extensive issues with obesity and excessive daytime sleepiness than survivors from Mulrooney et al. with a variety of malignant brain tumors. Additional stratification of tumor types or comparisons of brain tumor survivors might prove helpful in identifying specific causal mechanisms related to sleep disturbances.

Sleep apneas and abnormal EEG patterns often follow disease- and treatment-related factors, such as surgical resection or tumor damage to the brain stem and thalamus. The physiologic mechanisms and their relationship to EEG changes are not well documented. Apnea related to brain stem damage can prevent normal Process S (homeostasis) sleep patterns because of frequent microarousals, and some of these patients may require mechanical ventilation. Many cases involve interrupted sleep and decreased total sleep time with the appearance of slow-wave sleep abnormalities.

Continuing evidence appears to exist for use of the Two Process Model of Sleep Regulation to explain homeostatic (Process S) and circadian processes (Process C). The interruption of sleep mechanisms by brain tumor physiology and treatment clearly affected both parts of the model. When considering Vena et al.'s (2004) framework, no studies were found that researched specific sleep disturbances affected by differences in demographic (age, gender, socioeconomic status), lifestyle (diet, exercise), or psychologic (previous mental health) factors. Instead, many treatment- and disease-related factors were commonly identified as indicators associated with sleep disturbance. Of interest would be additional exploration related to demographic, lifestyle, or psychologic factors to determine their exact contribution to sleep disturbances and quality of life in brain tumor survivors.

Potential Biases and Limitations

Bias inherent within the search relates to exclusion of articles published in a language other than English. Also, the population of patients with brain tumors worldwide is relatively small, yielding small sample sizes or even case reports, in comparison to other groups of patients with cancer (Arii et al., 2001; Borodkin et al., 2005; di Gennaro et al., 2004; Etzioni et al., 1996; Frieboes et al., 1998; Ioos et al., 2001; Ito et al., 1996; Kubota et al., 1991; Marcus et al., 2002). In addition, studies available on this population tend to be published from the same institutions and repeatedly use the same brain tumor populations (Muller et al., 2002; Muller, Handwerker, et al., 2006; Muller, Muller-Stover, et al., 2006; Mulrooney et al., 2008). A potential bias exists for publication of positive findings (Mulrooney et al.). Limitations of this review include change in the original search criteria to gain an adequate sample of articles. In addition, one study included cancer survivors with brain tumors as well as other hematologic and solid tumor cancer diagnoses (Mulrooney et al.).

Implications for Nursing Research and Practice

Care of patients suffering from late effects of cancer and its treatment, including sleep-wake disturbances, should be focused and intent on relieving symptoms that affect quality of life. This article identifies potential factors associated with sleep disturbances, such as excessive daytime sleepiness and insomnia, which the practicing nurse can explore with brain tumor survivors at follow-up visits. A thorough history of sleep-wake patterns, which identify sleep issues affecting the patient's daily functioning, is important. Additional referral, evaluation, and diagnosis of sleep dysfunction may be required in the brain tumor survivor population to maximize their functional potential.

Exploration of factors associated with sleep-wake disturbances using prospective longitudinal and repeated-measures designs, descriptions of particular sleep disorders in the brain tumor population, improvement of measurement instruments, identification of appropriate outcome criteria, and development and evaluation of successful interventions in this population are needed. Additional testing of the Two Process Model of Sleep Regulation and expansion of the model to test Vena et al.'s (2004) cancer-related framework of demographic, lifestyle, psychological, disease, and treatment-related factors would contribute to professional understanding. Nursing researchers interested in sleep disturbances could contribute additional evidence for patterns of sleep disturbances; successful interventions to ameliorate the issues and their consequences on daytime functioning, productivity, and interpersonal relationships; and ultimately improve quality of life for brain tumor survivors.

Conclusion

This article synthesized available literature identifying sleep-wake disturbances in adult survivors of pediatric brain tumors. These patients experience disruption of sleep-wake patterns associated with major dysfunction in the hypothalamic-pituitary axis related to disease- and treatment-related damage. Neuroendocrine deficiencies create fluctuating levels of regulatory sleep hormones that drive the onset of sleep disturbances and are associated with adverse health implications and symptoms, such as excessive daytime sleepiness. Future research must include an expanded conceptual model, rigorous longitudinal research designs, and larger samples to promote additional understanding of sleep-wake disturbances in this population.

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