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Review

Sleep Disorders in Children with Central Nervous System Tumors

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Abstract:

Sleep complaints are common in pediatric patients with central nervous system (CNS) tumors. These problems may result from disruption of normal homeostatic, circadian, neuroendocrine, and cardiorespiratory pathways and vary by tumor location and treatment received. Children with tumors within the hypothalamus and surrounding regions are prone to excessive daytime sleepiness. Sleep-related breathing disorders, especially those involving abnormal control of breathing, may occur in patients with tumors of the brainstem and posterior fossa. Maintaining a high index of suspicion for sleep disorders in children with CNS tumors is essential for early recognition and treatment. In this article, we will review the various sleep problems reported in pediatric brain tumor survivors, explore underlying neurobiological mechanisms, and discuss approaches to screening and diagnosis.

Keywords
CNS tumors; craniopharyngioma; posterior fossa tumors; hypersomnolence; narcolepsy; circadian rhythm disorder; sleep disordered breathing; sleep apnea; sleep-related hypoventilation

1. Background

Sleep is an essential physiologic function for growth, cognition, and physical and emotional well-being. It is particularly important in childhood, when the brain and body are undergoing rapid development. Normal sleep occurs through a complex interplay between homeostatic, circadian, neuroendocrine, and cardiorespiratory pathways. Cancer and cancer treatment may cause disruptions and imbalances in these pathways, resulting in abnormal sleep. Compared to the general population, pediatric cancer survivors are more likely to experience sleep problems. Patients with a history of brain tumors are particularly prone to sleep issues. In this article, we will review the physiology of normal sleep, describe the sleep problems and pathophysiologic mechanisms behind disrupted sleep in children with central nervous system (CNS) tumors, and discuss strategies for screening, diagnosis, and management.

1.1 Sleep Mechanisms and Physiology

Sleep and wakefulness. Sleep is fundamentally important in promoting growth, repair, and neurocognitive functioning. The timing, duration, and quality of sleep depend on complex, balanced interactions between sleep-promoting and wake-promoting pathways. The majority of these pathways are housed in the basal forebrain, diencephalon, and brainstem. The balance between sleep and wakefulness is governed by two distinct biologic processes: sleep-wake homeostasis (Process S) and circadian rhythm (Process C)[1]. Homeostatic drive to sleep intensifies with continued wakefulness over time and subsides as an individual sleeps. During the day, the sleep-dependent homeostatic drive is counteracted by sleep-independent circadian arousal mechanisms. Circadian rhythms are coordinated by an internal pacemaker housed in the bilateral suprachiasmatic nuclei (SCN) of the anterior hypothalamus [1]. The near-24 hour circadian rhythm is externally entrained by the light-dark cycle on Earth through direct input received by the SCN from retinal ganglion cells via the retinohypothalamic tract, which runs through the optic chiasm [2, 3]. Additional input from the intergeniculate leaflet and median raphe nucleus modulate circadian phase shifts [3]. The SCN sends afferents to other regions of the hypothalamus and not only regulates sleep and wakefulness but also body temperature, hormone release, metabolism, and feeding behaviors through complex feedback loops. The primary pathway for circadian regulation of sleep flows from the SCN to the nearby subparaventricular zone, which in turn projects to the dorsomedial hypothalamic nucleus and connects subsequently to the wake-promoting lateral hypothalamus and the sleep-promoting ventrolateral preoptic area [3–5]. The SCN also exerts influence through output to the paraventricular hypothalamic nucleus [3–5]. The paraventricular hypothalamic nucleus in turn sends projections that affect hypothalamic and pituitary hormone release and via a separate pathway, melatonin release from the pineal gland [5].

The diurnal rhythm of melatonin release is essential in maintaining a normal 24-hour sleep-wake cycle [1, 4].

The ascending reticular activating system (ARAS) promotes wakefulness and cortical arousal and is inhibited by input from the sleep-promoting ventrolateral preoptic area. The ARAS originates near the junction between the midbrain and pons then splits into two branches which send projections to nuclei in the thalamus, hypothalamus, basal forebrain, and cerebral cortex [4, 5]. These branches comprise cholinergic and monoaminergic cell populations, as well as neurons containing the excitatory neuropeptide orexin, which is synthesized in the lateral hypothalamus [4, 5]. Orexin-containing neurons in the lateral hypothalamus project to many of the major nuclei involved in sleep and wakefulness and are postulated to play a crucial role in maintaining cortical arousal and stabilizing the sleep-wake balance [4, 5]. Individuals with narcolepsy often have reduced cerebrospinal fluid (CSF) orexin levels and animal models with dysregulated orexin transmission demonstrate sleep-wake and REM sleep derangement [5].

These various pathways work together in a coordinated pattern of excitation and inhibition to maintain wakefulness and cortical arousal during the day and promote normal restorative sleep at night. Disruption of any one component may throw this intricate system off balance, leading to abnormal or inappropriate sleep. In patients with brain tumors, these disruptions may occur as sequelae of the primary neoplasm or as a consequence of cancer treatment.

Control of breathing and maintenance of ventilation. The primary goal of respiratory control during sleep is maintenance of homeostasis, with regulation of blood gases, to preserve normal function. Central chemoreceptors located along the ventral medulla respond to subtle fluctuations in $PaCO_2$ through changes in pH [3]. Detection of hypercapnia leads to stimulation of breathing, coordinated by the respiratory central pattern generator, which consists of neuronal aggregates housed within the brainstem [3]. When activated, this neuronal circuitry generates rhythmic motor patterns that affect the depth and frequency of ventilatory breaths [3, 6]. Central chemoreceptor activation and response is the primary driver of the ventilatory response to hypercapnia, augmented by smaller contributions from peripheral chemoreceptors [3]. The peripheral chemoreceptors are located at bifurcation of the carotid arteries and are most sensitive to changes in PaO_2. The peripheral chemoreceptors send afferents via the glossopharyngeal nerve to the nucleus of the solitary tract (NTS) in the dorsal medulla, where they converge with afferents from peripheral baroreceptors and pulmonary stretch receptors [7]. The NTS integrates this information to produce coordinated sympathetic, parasympathetic, and respiratory reflex responses via projections to other nuclei within the medulla and pons [7]. The retrotrapezoid nucleus of the ventral medullary group is one of the receiving nuclei and also sends afferents back to the NTS and plays an important role in coordinating respiratory drive [7]. Pontine nuclei receive input from the NTS and send modulatory feedback [7]. Peripheral sensory input is received through stimulation of juxtacapillary (J) receptors of the alveoli by irritation, interstitial fluid, and capillary distention [3]. Signals are then sent to the brainstem via the vagus nerve. These signals elicit rapid shallow breathing or in extreme cases, apnea.

While the majority of the major neurologic processes that coordinate respiratory drive are housed in the brainstem, the cerebellum plays a supporting role. The cerebellum aids in rhythmic pattern generation and motor coordination, supporting the cyclical act of breathing [8–11]. It helps synchronize contraction of the muscles that maintain upper airway patency with diaphragmatic contraction, supporting optimal inspiratory flow [9].The deep nuclei of the

cerebellum, particularly the fastigial and medial nuclei, may help coordinate motor responses to the respiratory stimuli [10, 11].

In normal individuals, central respiratory drive and ventilatory muscle power work in conjunction to sufficiently overcome the respiratory load and maintain adequate ventilation. During sleep the body is vulnerable to respiratory insufficiency as a result of normal sleep-related physiologic changes in breathing mechanisms. During normal sleep minute ventilation decreases, resulting in an approximately 20% decline in alveolar ventilation [3]. The ventilatory responses to hypoxia and hypercapnia are blunted, requiring larger deviations from baseline to evoke a ventilatory response [3]. Upon initiation of sleep and withdrawal of the wakefulness stimulus, upper airway tone decreases and airway resistance increases, leading to decreased air flow and lower minute ventilation [3, 12]. Despite these physiologic variables which decrease ventilation during sleep, normal individuals continue to maintain adequate ventilation in the absence of additional impairment. However, tumors of the brainstem, cerebellum, and nearby regions may disrupt the neuromotor pathways that maintain respiratory drive and response to chemosensory input. This additional insult may provoke abnormal breathing and respiratory insufficiency during the already-vulnerable sleep state. Specific sleep related breathing disorders and their anatomic tumor associations will be discussed later in this review.

1.2 Assessment Tools for Pediatric Sleep Complaints

Clinicians have a variety of tools available to aid in assessing sleep complaints, characterizing sleep patterns, and evaluating for sleep-related breathing disorders. Validated questionnaires use patient or parent-reported information to identify specific symptoms of concern and determine their severity. Patients may be asked to keep a sleep diary to record sleep quality and duration from day to day. When sleep problems are identified, further objective testing may be indicated in order to determine symptom etiology. An individual's baseline sleep-wake pattern can be assessed through the use of an actigraph, a wearable device that continuously detects level of activity and uses an algorithm to determine sleep duration and quality from day to day [13]. Overnight polysomnography provides a comprehensive assessment of a single night's sleep, including information on sleep architecture, respiratory function, and abnormal movements or behaviors [14]. Multiple sleep latency testing (MSLT) in conjunction with polysomnography is used to evaluate for narcolepsy in individuals complaining of excessive daytime sleepiness. The MSLT consists of four to five 20-minute nap opportunities set apart in two-hour intervals, with the goal of defining time to onset of sleep (sleep latency) and sleep-onset rapid-eye movement sleep (SOREM)[15]. Maintenance of wakefulness testing is similar to MSLT but instead measures the ability to stay awake in a sleep-promoting environment [15]. The application of these tests in assessment and diagnosis of specific sleep disorders will be covered later in this review.

1.3 Pediatric CNS Tumor Prevalence, Morbidity, and Mortality

Childhood cancer encompasses a wide variety of malignancies that vary in prevalence by age and sex. CNS tumors represent 26% of all childhood cancers, second only to leukemia [16]. The most common pediatric CNS tumors are astrocytomas, which may arise throughout the CNS and vary in grade and medulloblastomas, which develop in the posterior fossa and are always malignant [17]. While cancer remains the second leading cause of death in children,

improvements in detection and treatment have led to marked improvement in survivorship [16, 17]. However, as cancer survivors, pediatric brain tumor patients have the highest prevalence of long-term morbidities [18]. CNS tumor management is guided by location, size, histology, and grade of the neoplasm. Resection, chemotherapy, and/or cranial radiation therapy (CRT) are the cornerstones of treatment. These treatments, in addition to damage from the tumor itself, can lead to long-term physical sequelae, including motor, sensory, and cognitive deficits, hydrocephalus, seizures, and endocrinopathies [19, 20]. Complications vary by primary tumor location and type of treatment received. Cranial radiation exposure independently increases risk of subsequent neoplasms, seizures, neurologic deficits, and neurocognitive impairment [19]. Patients with tumors within or near the hypothalamus, especially those who have undergone radiation therapy, are prone to neuroendocrine dysfunction and obesity due to disruption of the hypothalamic-pituitary axis. In addition to physical sequelae, pediatric CNS tumor survivors are at higher risk for psychological distress, depression, and lower quality of life than their peers [19, 20]. While data in children are lacking, adult childhood cancer survivors are more likely than their healthy siblings to report fatigue, disrupted sleep, and daytime sleepiness [21]. The presence of sleep issues in cancer survivors is associated with lower health-related quality of life [21, 22]. Thus, early recognition and treatment of sleep problems in pediatric cancer survivors is important not only for physical health and healing but also for preserving mental health and emotional well-being.

1.4 Pediatric Brain Tumors and Sleep

From its onset through survivorship, cancer has the ability to negatively impact sleep through disruption of normal circadian, homeostatic, cardiorespiratory, hormonal, and behavioral influences. Cancer-related psychological distress may also elicit or augment sleep disturbances. There is a greater prevalence of sleep complaints in children with a history of CNS tumors compared to those with other childhood cancers [23–25]. Children with tumors near the hypothalamus, thalamus, and brainstem are the most likely to experience sleep disturbances [23–27]. In 2011, Rosen et al reported that out of 70 pediatric cancer patients referred for sleep problems, 68% had a history of CNS malignancies [24]. Out of all referred patients with CNS neoplasms 73% had hypothalamic, thalamic, or brainstem tumors. In another report of pediatric CNS tumor survivors referred for sleep problems, Mandrell and colleagues found that 55% of referred patients had tumors of the hypothalamus or nearby regions [26]. As previously discussed, a multitude of neurochemical processes controlling sleep are housed within the basal forebrain, diencephalon, and brainstem. In brain cancer patients, the primary tumor, surgical resection, chemotherapy, and radiation may damage and disrupt these pathways, leading to inadequate, ineffective, or dysregulated sleep [23, 25, 27]. Exposure to cranial radiation therapy is associated in a dose-dependent manner with sleep-wake disturbances both during therapy and into adulthood [21, 28, 29]. Neuroendocrine dysfunction may result from disruption of the hypothalamic-pituitary axis and lead to obesity, snoring, and obstructive sleep apnea [23, 26]. Damage to structures in the brainstem and posterior fossa involved in control of breathing may lead to central sleep apnea and hypoventilation [8, 30, 31]. Sleep problems are a significant factor negatively impacting quality of life in cancer survivors but often go under recognized and under reported [21, 32]. In the following sections, we will review the prevalence and etiologies of various

sleep problems reported by children with CNS tumors and discuss our approach to screening, diagnosis, and management.

2. Sleep Problems in Children with CNS Tumors

2.1. Excessive Daytime Sleepiness and Narcolepsy

Excessive daytime sleepiness (EDS) is the most prevalent sleep complaint in pediatric cancer survivors and is more common after brain tumors than other pediatric malignancies [24, 31, 33]. It is the most common reason for referral to a sleep specialist in children with a history of CNS tumors [24, 26, 31]. Several retrospective studies of pediatric CNS tumor survivors have suggested a link between EDS prevalence and CNS tumor location, with a greater proportion of patients having possessed tumors within or near the hypothalamus [24, 26, 31, 34]. However, data remains mixed, as recent prospective surveys of pediatric brain tumor survivors found no association between tumor location and EDS [33, 35]. Other reported risk factors for development of EDS include obesity [26, 36], exposure to cranial radiation therapy [32, 34], and use of antiepileptic medications [34].

Excessive daytime sleepiness often represents the final common manifestation of an array of disorders affecting normal initiation and maintenance of sleep. EDS may be the result of a central neurologic process such as narcolepsy or occur secondary to sleep deprivation from insufficient sleep or sufficient but interrupted sleep. Inadequate sleep in cancer patients and cancer survivors can result from an innumerable host of physiologic, behavioral, and psychologic issues, including sleep-related breathing disorders, circadian rhythm disorders, insomnia, poor sleep hygiene, pain, anxiety, depression, and medication side effect. Subjective indicators of EDS include inappropriately falling asleep during routine daytime activities and new-onset daytime napping. It should be delineated from fatigue, which is characterized by lack of physical or mental energy [37]. EDS is objectively defined by the inability to maintain wakefulness and alertness during normal waking hours, with unintentional or inappropriate sleep occurring daily for three months or more [37].

When pediatric CNS tumor patients exhibit excessive daytime sleepiness in the absence of identifiable secondary contributors, narcolepsy and hypersomnia due to medical condition should be suspected. Narcolepsy is objectively defined by excessive daytime sleepiness plus sleep latency ≤ 8 minutes and two or more episodes of sleep-onset rapid-eye movement sleep (SOREM) on a multiple sleep latency test (MSLT)[37]. Narcolepsy is further classified as type 1 or type 2, with diagnosis of type 1 narcolepsy requiring presence of cataplexy and/or a reduced concentration of orexin in the CSF [37]. Hypersomnia is also defined by presence of excessive daytime sleepiness and MLST demonstrating sleep latency ≤ 8 minutes. Multiple episodes of SOREM are not present [37].

Secondary narcolepsy and hypersomnia due to medical condition are not uncommon in children with CNS tumors and may emerge near time of tumor diagnosis or during treatment and survivorship [26, 31, 38–40]. Patients with tumors of the sellar/parasellar and suprasellar/hypothalamic regions, particularly craniopharyngiomas, are especially vulnerable to developing these disorders [26, 38–41]. Mandrell and colleagues reported 31 pediatric patients with a history of brain tumors referred for sleep complaints [26]. Seventeen underwent MSLT and

seven were subsequently diagnosed with hypersomnia or narcolepsy. All seven patients had a history of sellar/parasellar, hypothalamic, or thalamic tumors. Weil et al recently reviewed 26 cases of narcolepsy associated with brain tumors within or near the hypothalamus [40]. Tumor types included craniopharyngiomas, adenomas, gliomas, and germinomas. Ten patients had narcolepsy with cataplexy. Four of five patients who underwent measurement of CSF orexin had abnormally low orexin levels. Twelve of the 26 total patients were symptomatic at the time of tumor diagnosis, while 13 developed narcolepsy after surgery, and one developed narcolepsy after cranial radiation therapy. Most of the patients who developed narcolepsy after surgery had craniopharyngiomas, which are often difficult to resect with significant risk for hypothalamic injury. The patients who did not require extensive surgical resection of the tumor were more likely to have improvement in their narcolepsy symptoms during the treatment course.

In patients with brain tumors damage to orexin-mediated arousal pathways is likely the driving mechanism underlying the development of secondary narcolepsy and hypersomnolence. This is supported by these disorders' association with tumors in the vicinity of the hypothalamus and the finding of low CSF orexin in some affected patients [26, 40, 41]. Damage to the orexin-containing neurons of the lateral hypothalamus may occur as a result of tumor invasion, during surgical resection, and/or after cranial radiation therapy. The particular association between narcolepsy and craniopharyngiomas is likely attributable to both the proximity of the mass to the hypothalamus and the propensity for hypothalamic injury to occur during resection [40]. We recommend that a high index of suspicion for narcolepsy be maintained in all children with brain tumors near the hypothalamus. In these patients the threshold for objective evaluation of EDS with polysomnography and MSLT should be low.

2.2 Circadian Rhythm Sleep Disorders

Circadian rhythm sleep disorders are characterized by misalignment between an individual's sleep pattern and the sleep pattern that is considered normal or desired [37]. Circadian rhythm sleep disorders occur through alterations in the circadian timing system [37]. These disorders can be diagnosed through the use of sleep logs or actigraphy and are classified into subgroups based on sleep pattern. Patients with delayed sleep-wake phase disorder fall asleep and wake up two or more hours later than is considered normal, while patients with advanced sleep-wake phase disorder go to bed and wake up earlier [37]. Delayed sleep-wake phase disorder is common in healthy adolescents and young adults with an estimated prevalence of 7-16%, while advanced sleep-wake phase disorder more often occurs in the elderly [37]. Non-24-hour sleep-wake disorder occurs when an individual operates on a sleep-wake cycle greater than 24 hours, leading to progressive delay in sleep and wake from day to day [37]. This disorder is thought to represent failure of 24-hour circadian entrainment due to the absence of photic light-dark input. Most individuals with non-24-hour sleep-wake disorder are blind, though sighted individuals can be affected. Irregular sleep-wake rhythm disorder is characterized by intermittent bouts of sleep throughout the day and night with no discernible rhythm [37]. Periods of sleep typically last less than four hours and patients often complain of excessive sleepiness and/or insomnia depending on the time of day. Irregular sleep-wake rhythm disorder typically occurs in individuals with neurocognitive or neurodegenerative disease and rarely affects healthy children [37].

There is a paucity of data on circadian rhythm sleep disorders in childhood cancer and it is difficult to speculate on the prevalence in patients with CNS tumors. Delayed sleep-wake phase disorder may presumably occur in adolescent CNS tumor patients given its prevalence in the healthy adolescent population. Children with brain tumors that compromise visual pathways are at risk for blindness and thus at risk for developing non-24 hour sleep-wake disorder [19, 42]. In Rosen and colleagues' 2011 study, three of 70 pediatric cancer patients were diagnosed with a circadian rhythm disorder [24]. Two of the three had CNS tumors involving the brainstem or hypothalamus. One was an adolescent diagnosed with delayed sleep-wake phase disorder and the other was blind with a likely diagnosis of non-24 hour sleep-wake disorder. Irregular sleep-wake rhythm disorder has been reported in patients with tumors of the pituitary and hypothalamic regions and may be present at time of diagnosis or after tumor treatment [43–47]. These irregular sleep-wake patterns may be attributable to disruption in normal diurnal melatonin secretion. Altered patterns of melatonin secretion with shifted or absent nocturnal peak and/or inadequate daytime suppression have been demonstrated in some patients with tumors of the sellar/parasellar, suprasellar/hypothalamic, and pineal regions [46–52]. The specific melatonin-regulating circadian pathway affected varies with tumor location. Tumors affecting the optic chiasm may interrupt photoneural input to the SCN travelling via the retinohypothalamic tract [51]. Sellar and suprasellar tumors may directly damage the SCN or its melatonin-regulating afferents [47, 50]. Pineal tumors may disrupt the distal end of the melatonin pathway, impairing melatonin release from the pineal gland [52].

The therapeutic approach to circadian rhythm sleep disorders includes interventions to aid in entrainment to the normal 24-hour circadian cycle and exogenous melatonin administration to shift an individual's current circadian phase in the desired direction [53]. Strategically timed oral melatonin administration is the cornerstone of therapy, with additional behavioral interventions such as prescribed sleep-wake scheduling and deliberate periods of light avoidance and exposure [53]. This approach may be successfully applied to affected patients with CNS tumors [49, 52]. In one study, melatonin substitution in pediatric patients with craniopharyngiomas not only resulted in better diurnal variation in salivary melatonin but also yielded improvements in daytime sleepiness and physical activity [49].

2.3 Insomnia and Interrupted Sleep

Insomnia is characterized by difficulty initiating and maintaining sleep or experiencing non-restorative sleep. This disruption occurs despite adequate opportunities for sleep and leads to impairment in daytime function [37]. Insomnia often co-occurs with excessive daytime sleepiness and fatigue and like EDS, may have a multitude of secondary causes. Insomnia is purported to be the most common sleep problem in adults with cancer, including those with primary brain tumors [32, 54]. Insomnia and interrupted sleep are common complaints in children still receiving cancer therapy but are less often reported than other sleep complaints in cancer survivors [24, 55]. In Rosen et al's 2011 study 17 out of 70 pediatric cancer patients were referred for insomnia, most of whom were still receiving cancer therapy [24]. The prevalence of insomnia in patients with brain tumors was not significantly different from those with non-CNS malignancies. Identified etiologies included behavioral issues, pain, and high-dose corticosteroid therapy. Robertson and colleagues also identified ongoing corticosteroid therapy to be associated with insomnia in adult patients

with CNS tumors but notably found a lack of association between insomnia and tumor location or use of other medications such as antidepressants, antipsychotics, and stimulants [56].

Insomnia during cancer treatment may occur as a result of numerous physiologic, environmental, and psychologic factors which may negatively impact sleep; however, knowledge of insomnia prevalence and associations among pediatric brain tumor survivors remains limited. Nolan and colleagues compared adult survivors of childhood CNS tumors to matched controls and found no significant difference in overall sleep quality between the two groups, although survivors were nearly three times more likely to take longer to fall asleep [57]. Zhou et al reported insomnia in 25 of 98 adult childhood CNS tumor survivors but identified no statistically significant associations, including cancer diagnosis, cancer recurrence, type of treatment received, or presence of depression/anxiety [58]. Thus while it seems pediatric brain tumor survivors may experience more symptoms of insomnia than the general population, the etiology remains unclear.

2.4 Parasomnias and Sleep Related Movement Disorders

Parasomnias represent a heterogeneous category of sleep disorders involving undesirable physical behaviors or experiences that occur during sleep onset, within sleep, or during arousal from sleep [37]. Consciousness consists of three distinct states: wake, rapid eye movement (REM) sleep, and non-REM sleep. Normal transitions between these states arise through the coordinated interplay of various sleep and wake pathways. Parasomnias are thought to occur as a result of dysfunctional state-to-state transitions which leave the individual in an unstable, dissociated state of consciousness. Disinhibition of physiologic functions that are normally suppressed during sleep leads to abnormal behaviors [37]. Examples of these disorders include somnambulism, sleep-related eating, sleep terrors, and dream-enacting behaviors [37]. Video polysomnography is helpful in diagnosis by allowing characterization of the abnormal event and determining the sleep stage in which it occurs [37].

There is insufficient data to determine the prevalence of parasomnias in children with brain cancer compared to healthy children or children with other malignancies. There are isolated case reports of patients experiencing parasomnias as a presenting symptom leading to tumor diagnosis [59–62]. Pilotto and colleagues conducted a retrospective study of comparing 29 pediatric CNS tumor survivors to healthy controls and identified an increased frequency of parasomnias in patients [63]. However, the study was inadequately powered to detect associations with tumor location or treatment type. Which specific disorders were detected within the category of parasomnias was not reported by the authors.

Sleep related movement disorders are a group of conditions characterized by stereotypic movements that occur during sleep [37]. Sleep related movement disorders are distinguished from parasomnias by the simplicity of the abnormal movement. Disorders that fall into this category include bruxism, restless legs syndrome, periodic limb movement disorder, and sleep-related rhythmic movement disorder [37]. There is a paucity of data on prevalence of these disorders in cancer patients and even less in pediatric patients with CNS tumors. Some reports suggest that high-dose chemotherapy in cancer patients may be associated with restless leg syndrome and increased periodic limb movements during sleep [64, 65]. Ostacoli and colleagues reported a restless leg syndrome prevalence of 18.3% in adult patients undergoing therapy [64]. Restless leg syndrome was associated with anxiety, depression, and lower quality of life. Further

research is needed to determine the prevalence of restless leg syndrome and other sleep related movement disorders in children with cancer, including those with CNS tumors, to promote early detection and treatment.

2.5 Sleep Related Breathing Disorders

Sleep related breathing disorders encompass a wide variety of issues affecting ventilation during sleep, including obstructive sleep apnea (OSA), central sleep apnea (CSA), sleep-related hypoxemia, and central hypoventilation [37]. Children with sleep related breathing disorders may present with labored breathing or witnessed apneas during sleep, snoring, excessive daytime sleepiness, non-restorative sleep, daytime hyperactivity, and behavioral issues. Polysomnography is required for diagnosis and should be scored using the most contemporary American Academy of Sleep Medicine (AASM) criteria [37, 66]. Children with CNS tumors may experience damage to the neurochemical and neuromotor pathways that coordinate breathing or develop conditions which lead to increased airway resistance, predisposing them to abnormal breathing during sleep [24, 26, 30, 31, 67]. It is difficult to estimate the overall prevalence of all sleep related breathing disorders in pediatric patients with CNS tumors. In Rosen's 2011 study, sleep related breathing disorders were diagnosed in 28 out of 70 pediatric cancer patients, 20 of whom had CNS tumors [24]. Diagnoses included OSA, CSA, and sleep-related hypoxemia. Multiple sleep related breathing disorders may co-occur in patients with tumors of the brainstem and posterior fossa [8, 9, 68]. Fujimoto et al recently reported a 12 year-old obese male presenting with OSA, CSA, and sleep-related hypoventilation who was found to have a tumor within the medulla [68]. Lee and colleagues described four pediatric patients with medulloblastomas involving the fourth ventricle without brainstem invasion, all who developed symptoms of sleep-disordered breathing years after resection, chemotherapy, and radiation [8]. All four patients demonstrated obstructive sleep apnea, central sleep apnea, and hypoventilation on polysomnography. Thus it is important to maintain a high suspicion for sleep related breathing disorders in patients with posterior fossa tumors from diagnosis through survivorship, even when no brainstem involvement is suspected.

Obstructive sleep apnea. Obstructive sleep apnea (OSA) is the most common sleep related breathing disorder in children, affecting up to 5% of the pediatric population with a peak incidence from two to six years of age [69]. OSA occurs as a result of complete or partial airway obstruction leading to intermittent episodes of reduced or absent airflow during sleep [37, 69]. In healthy children, OSA is most often attributable to enlarged tonsils and adenoids. Other conditions that contribute to airway obstruction include obesity and craniofacial abnormalities as well as neurologic impairment, which may lead to hypotonia and weakness of airway and ventilatory muscles [69–72].

Similar to healthy children, OSA in pediatric patients with CNS tumors may be multifactorial. Obesity is a significant risk factor for OSA and may occur through unique mechanisms specific to brain tumor patients. Children with brain tumors may develop obesity as a side effect of medications such as corticosteroids, from reduced caloric expenditure in the setting of physical morbidity, or as a result of neuroendocrine derangement. Examples of neuroendocrine abnormalities that may cause weight gain include hypothyroidism, Cushing's disease, and hypothalamic obesity. Hypothalamic obesity results from damage to the hypothalamic pathways regulating satiety and energy balance and is characterized by hyperphagia, decreased metabolic

rate, and rapid weight gain even after caloric restriction [73]. This damage may be the result of tumor invasion, surgical injury, or radiation therapy [73]. Mandrell and colleagues retrospectively reviewed 31 pediatric CNS tumor survivors who underwent polysomnography and found that 14 had OSA, the majority of whom were obese [26]. Nine of the 14 patients had tumors of the sellar/parasellar and hypothalamic regions. Other tumor locations included the posterior fossa, pineal gland, and optic nerve. Independent of obesity, OSA may occur due to impaired contraction of the pharyngeal dilator muscles involved in maintaining upper airway patency [23, 67]. Normal function requires neuromotor input from the glossopharyngeal, vagus, and hypoglossal nerves, which exit the medulla just below the inferior cerebellar peduncles. These neural pathways may be disrupted by posterior fossa tumors, leading to discoordination or weakness of the affected muscle groups [67].

Treatment of OSA in healthy children and children with CNS tumors involves supporting airway patency through the use of positive airway pressure and interventions to alleviate the source of airway obstruction. Adenotonsillectomy should be considered in those with enlarged tonsils and adenoids, although in the presence of other tumor-related factors, OSA may persist despite surgery. Continuous positive airway pressure (CPAP) is an appropriate treatment for OSA in children without central sleep apnea or hypoventilation [74]. CPAP initiation and management should be overseen by a sleep physician or pulmonologist working in conjunction with a multidisciplinary team consisting of a respiratory therapist, nurse, and psychologist to aid in equipment fitting, habituation, and adherence [74]. Acclimatization techniques should be utilized to improve compliance and include trial of different mask types to determine best comfort and fit, use of mask during the day to accustom the child to the sensation, and use of ramp mode at the beginning of sleep to gradually increase the delivered pressure to goal. Weight loss should be encouraged in obese patients. Management of secondary obesity due to neuroendocrine dysfunction by an experienced endocrinologist is critical [75]. More research is needed to identify differences in treatment response and prognosis for improvement in children with CNS tumors and OSA compared to other children.

Central sleep apnea and sleep-related hypoventilation. Central sleep apnea (CSA) occurs when ventilatory control pathways fail to initiate respiratory effort, leading to pauses in breathing [37]. In patients with CNS tumors abnormal respiratory drive results from acquired injury to the pathways controlling ventilation, which may occur through direct tumor invasion or surgical resection [8, 9, 30, 31, 76]. While injury to the respiratory centers of the medulla is of particular concern, tumors in other regions of the brainstem, posterior fossa, and surrounding areas may also damage of key pathways and result in CSA [8, 9, 24, 26, 30, 31, 76]. Sleep related central hypoventilation represents a separate type of sleep related breathing disorder that often co-occurs with CSA and arises through similar mechanisms [8, 37, 77]. Like CSA, it is usually reported in relation to tumors of the brain stem and posterior fossa [8, 76, 78, 79].

Treatment of CSA and sleep-related hypoventilation is often challenging. Surgical tumor resection may lead to improvement in symptoms but does not guarantee complete resolution [78]. Patients may require long-term positive pressure ventilation during sleep, either non-invasively using bilevel positive pressure ventilation (BPAP) or invasively via tracheostomy and home mechanical ventilation. As with CPAP, initiation of BPAP should begin with mask fitting and acclimatization under the guidance of a multidisciplinary team. An age-appropriate backup rate should be used in all patients with central hypoventilation, bradypnea, or those that are unable to

reliably trigger spontaneous breaths [80]. Patients should undergo titration of BPAP settings via polysomnography to determine the optimal settings for adequate gas exchange per AASM guidelines [80]. Tracheostomy and mechanical ventilation should be considered in those with central apneas, bradypnea, or hypoventilation while awake. It should also be considered in those with intolerance to BPAP or poor treatment response. Treatment decisions should be made through bidirectional communication between the patient's family and medical providers. These choices should be guided by the patient's clinical status, presence of comorbid conditions, prognosis, and overall goals of care.

3. Screening and Diagnostic Approach

Given the prevalence of sleep complaints in children with CNS tumors, we recommend that the patient's primary pediatrician or oncologist inquire about sleep problems during routine visits. The interview should elicit information on sleep-wake timing, sleep latency, excessive sleepiness, nighttime awakenings, perceived sleep quality, and daytime sleep habits. If significant sleep complaints are identified, referral to a pediatric sleep specialist should be considered. Preliminary evaluation of sleep-wake disturbances can begin with the use of validated questionnaires and patient sleep logs. Because of the age variation and the heterogeneous nature of sleep complaints, no single questionnaire is adequate for all patients. The Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaires on Pediatric Sleep Disturbance and Sleep-Related Impairment may be used to obtain a subjective assessment of daytime sleepiness, impairment in daily function, and difficulties with sleep onset and maintenance [81, 82]. The Pittsburgh Sleep Quality Index (PSQI) is a validated and widely used tool to evaluate sleep timing, sleep quality, and sleep efficiency [83]. Questionnaires that aid specifically in evaluating excessive daytime sleepiness in children include the Epworth Sleepiness Scale (ESS)[84] and the Pediatric Daytime Sleepiness Scale (PDSS)[85]. The ESS assesses severity of daytime sleepiness through self-reported propensity to fall asleep during various activities. The PDSS measures daytime sleepiness in relation to school performance to determine degree of impairment. Actigraphy should be considered in patients with symptoms of excessive daytime sleepiness, insomnia, or difficulty initiating and maintaining sleep [13]. Actigraphy is useful in assessing for abnormal sleep patterns caused by circadian rhythm sleep-wake disorders and central disorders of hypersomnolence. Patients with severe hypersomnolence or excessive daytime sleepiness, especially those with tumors of the hypothalamus and surrounding regions, should undergo polysomnography with a multiple sleep latency test to assess for narcolepsy. Evaluation for parasomnias with video polysomnography may be indicated in patients with frequent nighttime awakenings or abnormal sleep behaviors. Patient or parental reports of daytime sleepiness, hyperactivity, non-restorative sleep, snoring, irregular breathing, and/or witnessed apneas are concerning for sleep-disordered breathing and should prompt timely assessment with polysomnography.

4. Conclusions

Children with brain tumors are at increased risk for experiencing abnormal sleep from the time of tumor diagnosis, through treatment, and during survivorship. They may be affected by an array of pathologic sleep conditions including sleep related breathing disorders, narcolepsy, circadian rhythm sleep-wake disorders, insomnia, parasomnias, and sleep-related movement disorders.

Recognizing associations between these disorders and tumor location or type of treatment received may aid in prompt diagnosis and intervention. Due to their propensity to negatively impact overall health and quality of life, screening for sleep problems should be part of anticipatory care in children with CNS tumors.

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Author Contributions

Dr. Maloney performed the literature review. She conceptualized and wrote the majority of the manuscript. Dr. Lewinter assisted in reviewing the literature and writing the manuscript. Dr. Davidson Ward reviewed and edited the manuscript for concept, content, and clarity. Dr. Perez conceptualized the manuscript topic and scope. She guided the literature review and supervised the manuscript writing process. She reviewed and edited the final manuscript.

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Competing Interests

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