Correlation of Tumor Location and Sleep Disturbance

Subjects: Surgery

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Sleep disturbance can occur when sleep centers of the brain, regions that are responsible for coordinating and generating healthy amounts of sleep, are disrupted by glioma growth or surgical resection. Several disorders cause disruptions to the average duration, quality, or patterns of sleep, resulting in sleep disturbance.

glioma sleep sleep disturbance tumor location

1. Introduction

Among the top concerns for neurosurgeons confronted with a glioma is tumor location [1]. There are several sleep centers in the brain that rely on coordinated communication to generate, perpetuate, and terminate sleep. Understanding of the neurophysiological pathways used to generate sleep and the associated brain regions key to these processes is beneficial when treating patients with glioma. With this understanding, better diagnostic and prognostic decisions can be made that consider the patient's QoL, overall survival, and proper course of treatment. Presenting sleep disturbance symptoms can potentially be one of the first clues pointing to a glioma location. Sleep apnea, hypersomnia, narcolepsy/cataplexy, parasomnia, and insomnia have been linked with tumor location in several case reports and retrospective chart analyses outlined in **Table 1**.

Table 1. Cases with brain tumor diagnosis and sleep disturbance.

Author	Year	Patient Age	Patient Gender	Tumor Location	Tumor Type	Sleep Disturbance
Discolo et al. [2]	2005	71	Male	Right frontal lobe	Glioblastoma Multiforme	Sleep apnea
Osanai et al. [3]	1994	44	Male	Left cerebellar peduncle, medulla	Ganglioglioma	Sleep apnea
Ioos et al. [4]	2016	4	Female	Posterior fossa	Meningioma	Sleep apnea
Greenough et al. [5]	1999	34	Male	Bilateral medulla	Medulloblastoma	Sleep apnea

Author	Year	Patient Age	Patient Gender	Tumor Location	Tumor Type	Sleep Disturbance
Manning and Leiter [6]	2000	18	Female	Medulla	Ganglioglioma	Somnolence, sleep apnea
Ito et al. [7]	1996	12, 6	Male	Medulla, pons	Glioma	Sleep apnea
Kelly et al. [8]	1980	4 weeks	Male	Left middle fossa	Astrocytoma	Sleep apnea
Nakajima et al. [9]	2000	49	Female	Medulla, pons	Astrocytoma	Sleep apnea (Ondine's curse)
Marin-Sanabria [10]	2005	52	Female	Medulla	Glioma	Sleep apnea (Ondine's curse)
Huang et al. [11]	2021	4	Male	Medulla, pons	Glioma	Sleep apnea
Hui et al. [12]	2000	3	Male	Posterior fossa	Pilocytic astrocytoma	Hypersomnia, sleep apnea
Valente et al. [13]	1993	24	Male	Pons	Fibrillary astrocytoma	Sudden awakenings, hypersomnia, sleep apnea
Yen et al. [14]	2022	48	Male	Right side thalamus and midbrain	Glioma	Hypersomnia
Anderson et al. [15]	1977	23	Male	Hypothalamus	Glioma	Narcolepsy, hypersomnia, sleep paralysis
Liao et al. [16]	2020	44	Male	Hippocampal formation	Glioma	Somnolence, Narcolepsy type 2
Laus et al. [17]	2022	3	Male	Optic chiasm	Ganglioglioma	Somnolence, Narcolepsy
Rosen et al. [18]	2003	5–15	Males and Females	Hypothalamus, optic chiasm, brainstem, pineal gland, pituitary gland	Pineoblastoma, craniopharyngioma, medulloblastoma, astrocytoma	Narcolepsy
Butts et al.	2014	53	Male	Corpus callosum	Glioma	Somnolence,

Author	Year	Patient Age	Patient Gender	Tumor Location	Tumor Type	Sleep Disturbance
[19]						Narcolepsy
Mendez [20]	1992	15	Male	Fourth ventricle and brainstem	Astrocytoma	Night terrors
Di Gennaro et al. [21]	2004	48	Female	Right thalamus	Patient refused biopsy	Night terrors
Duffau et al. [22]	2006	38	Female	Right paralimbic region	Oligodendroglioma	Epileptic somnambulism
Reim et al. [23]	2016	29	Female	Right basal ganglia	Astrocytoma	Insomnia
Fukushima et al. [24]	1998	16, 33	Female, Male	Medulla	Hemangioblastoma	Sleep apnea
Prashad. [25]	2013	15	Male	Parietal lobe [7]	Dysembryoplastic neuroepithelial tumor	Sleepwalking
Weil et al. [26]	2017	11	Female	Sellar and suprasellar region	Germinoma	Narcolepsy

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a failure of automatic respiration during the night in which assisted ventilation or death are the prevailing outcomes [27]. This is commonly reported in cases of brainstem tumors in children but can be found in adult cases as well. For example, in a case report by Nakajima et al., a 49 year old woman was found in respiratory arrest that required resuscitation [9]. MRI revealed a glioma in the lower PONS and medulla with subsequent testing revealing Ondine's curse, in which her autonomous respiration ceased during sleep. Treatment required two months of respiratory support and radiation therapy for the glioma.

While tumoral disruption of the medulla and PONS are the overwhelming cause of tumor-associated sleep apnea, tumors in the frontal lobe have also been correlated with sleep apnea, specifically OSA. In a drastically different mechanism to the brainstem, tumor growth in the frontal lobe disrupts control of the phrenic and intercostal musculature nerves, reducing the motor function necessary to take breaths [2]. Tumors in the frontal lobe and brainstem also result in other serious motor deficits that can obscure the discovery of sleep apnea as a presenting symptom. In contrast to other sleep disorders that can potentially mimic or be caused by other consequences of a poor night's sleep, sleep apnea is a relatively unique and easily definable disorder. As a result of this, identification of sleep apnea as a presenting or recurring symptom of glioma is more readily accomplished by those without expertise in sleep medicine.

3. Hypersomnia

Diurnal drowsiness or hypersomnia is another condition that can be correlated with gliomas found in the posterior fossa, hypothalamus, and thalamus/midbrain [6][12][13][14][15][16]. Hypersomnia is characterized by excessive daytime sleepiness that can impact academic or work performance. Hypersomnias are tracked, diagnosed, and classified

by their reported sleep quality, diurnal sleep, and the overall restfulness a patient feels after sleep [28]. Somnolence is also another term that falls under the umbrella of hypersomnia and describes a strong desire to fall asleep or constant state of drowsiness that has been well-characterized as a side effect of radiation therapy [29]. A specific case report by Anderson and Salmon details a 23-year-old man who had hypersomnia as a presenting symptom [15]. The hypersomnia seen in this patient progressed to narcolepsy, followed by attacks of sleep paralysis. Exploration of the brain found a glioma in the right-side hypothalamus. No treatment was given for the glioma, but medications to aid with nocturnal sleep were given with no success. Diurnal drowsiness and hypersomnias can be difficult to characterize because they need to be separated from other sleep or mood disorders with extensive testing [30]. Once it is clear that excessive diurnal sleepiness is negatively impacting everyday living, or that a sudden/unusual onset of diurnal sleepiness has occurred, the presentation of this symptom can indicate an underlying condition such as glioma. Treatment of hypersomnia in glioma patients includes medication or scheduled daily naps to improve daily functioning.

4. Narcolepsy

Narcolepsy is another presenting symptom in patients with glioma. This is especially well researched in pediatric cases and is often associated with concurrent cataplexy. Narcolepsy, which can either be type 1 (with cataplexy and low levels of hypocretin) or type 2 (without cataplexy and normal hypocretin), is excessive daytime sleepiness affecting daytime functioning [31]. Narcolepsy with cataplexy results in sudden loss of muscle tone due to strong emotions [31]. Case reports show that the onset of narcolepsy can be correlated with tumoral infiltration in or near the hypothalamus, optic chiasm, sellar and suprasellar region, and hippocampus [15][16][17][18]. Among the top consequences for this type of sleep disturbance are poor QoL and reduced academic success for children where narcolepsy impacts their ability to function normally. Rosen et al. described 14 cases of children aged 5 months to 15 years, both males and females, detailing narcolepsy symptoms in many different types of gliomas located in the optic chiasm, brainstem, pituitary gland, pineal gland, frontal lobe, and posterior fossa. Treatment of gliomas included gross total resection, radiation treatment, chemotherapy, and shunt placement depending on the individual patient. Treatment for narcolepsy symptoms in these patients was heavily focused on stimulant medications. This retrospective chart review, along with other case reports of glioma, germinoma, stroke, and TBI discussed in later sections, provide excellent evidence to suggest that presenting narcolepsy symptoms can be varied but are often localized to only a few deep brain regions.

Treatment of narcolepsy in glioma patients is based on stimulant medication used to reduce excessive daytime sleepiness. One case of glioma with concurrent narcolepsy found that stimulant medication is effective at treating narcolepsy symptoms, but required a larger than normal dose with symptoms returning when the medication is stopped [19]. A trial of a popular stimulant medication, modafinil, in primary tumor patients found that symptoms were not improved compared to placebo patients [32]. These results indicate that the effects from stimulant drugs could potentially be dose-dependent or be impacted by tumor location and severity; an interesting consideration requiring more research for clinicians treating glioma patients.

5. Parasomnias

Parasomnias are a set of sleep disorders that include night terrors, sleepwalking, or sleep paralysis and sleep-related eating disorders [33]. Various parasomnias have been reported in patients with gliomas of the brainstem, thalamus, or parietal lobe [15][20][21][22]. For example, a case reported by Gennaro et al. described a suspected glioma in the right thalamus of a 48-year-old woman [21]. She presented with night terrors in which she would sit up in bed, scream, and was agitated and unresponsive. While the patient refused biopsy and treatment for the glioma, medication for the night terrors successfully reduced her episodes. Treatment of parasomnias is unique to the type of disorder but generally includes medication or behavioral therapy. Medication can be ineffective for those experiencing parasomnias, so most often therapies are recommended in addition to medication. Psychotherapy, relaxation therapy, and autogenic training or hypnosis are recommended to treat parasomnias. These behavioral therapies are effective for the treatment of parasomnias with comorbid disorders, such as cancer, without impacting cancer treatments [34]. Behavioral therapy treatment for sleep disorder in glioma patients is more complicated because the location of the tumor can create cognitive, mood, or other psychiatric disorders that can complicate the therapy necessary to treat sleep disorders [35]. Parasomnias are unique to each patient in presentation and treatment, but if properly tracked can be a good indicator of dysfunction when they occur with sudden onset or with an increase in the number, duration, or severity of episodes.

6. Insomnia

Insomnia, common in the general population, has also been noted as a presenting symptom in patients with gliomas [23][36][37]. However, insomnia is difficult to correlate with tumor location alone since it is commonly associated with neuropsychiatric disorders and the general anxieties associated with cancer diagnosis [38]. It is also important to note that insomnia is often induced by the treatment of glioma and does not have to be a presenting symptom. One such case report of a 29-year-old female described by Reim et al. found that radiation therapy of a glioma in the basal ganglia caused severe insomnia that was not present before treatment [23]. The sleep medication Nitrapasepam did not improve the patient's insomnia, but melatonin supplements alone were able to reverse her symptoms. Insomnia is often a comorbidity seen in patients with cancer due to the anxiety and fear that accompanies diagnosis and does not necessarily indicate a brain tumor [39]. The key for understanding insomnia as a symptom of glioma is the onset, severity, and the number of episodes in correlation with other glioma symptoms. Treatment of insomnia in glioma patients includes medications, which can be ineffective, or cognitive behavioral therapy, which has shown promise in clinical trials for improving sleep in glioma patients [40].

7. Other Brain Disorders

Sleep disturbances are also correlated with other primary brain tumors, such as hemangioblastomas. Case reports have found sleep apnea in cases of hemangioblastomas located in the medulla and 4th ventricle as well as sleepwalking in dysembryoplastic neuroepithelial tumors and narcolepsy in a patient with a germinoma (**Table 1**) [24][25][26]. Additionally, evaluation of pediatric patients with uncharacterized brain tumors in the

hypothalamic/pituitary brain regions that underwent surgical resection reported severe hypersomnolence following surgery [41]. This indicates that iatrogenic disruption of the sleep centers during glioma removal is also an important and often under-considered consequence of treatment that should potentially be further discussed by surgeons and patients before intervention.

While there are relatively few care reports of patients with gliomas and sleep disturbance, TBI and stroke patients are known to have sleep disorders as a result of their injuries. For example, TBI patients where sleep disturbance has developed as a consequence of the injury are well-documented and more completely studied than tumor or stroke patients [42][43][44][45][46][47][48]. One study looking into sleep disturbances as a potential marker of brain injury in patients with mild TBI found that there were abnormalities in the polysomnography results [49]. The patients in this study suffered from OSA and/or restless leg syndrome, but no data indicating the location of injury were obtained. Patients that have had a stroke represent an interesting population to study sleep disturbance in because certain sleep disorders can be a risk factor for a stroke, or these disorders can result from the damage caused by the stroke itself [50]. Hypersomnolence secondary to a stroke has been studied clinically and found to be most closely associated in individuals with para median thalamic infarctions [51]. Cases of tumor growth, stroke, and TBI provide additional support for the idea that there is a potentially facile correlation of tumor growth and sleep disturbance that merits further exploration.

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