Sleep in Children With Neoplasms of the Central Nervous System: Case Review of 14 Children

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ABSTRACT. *Objective.* **Sleep is a complex neurologic process that is generated by and primarily benefits the brain. Sleep can be disrupted by a wide range of brain injuries, many of which may occur in children with neoplasms of the central nervous system (CNS). The specific sleep problems that have been associated with brain injuries include sleepiness, apnea, insomnia, and loss of circadian rhythmicity. The objective of this study was to characterize the sleep problems seen in children with neoplasms of the CNS through a comprehensive clinical and objective sleep evaluation.**

Methods. **A retrospective case series review was conducted of all children with neoplasms of the CNS referred to the sleep clinic for a clinical evaluation between 1994 and 2002. The sleep evaluation of the 14 children in this report included a sleep history, a sleep log, and a polysomnogram. In the 12 children with complaints of daytime sleepiness and/or fatigue, a multiple sleep latency test was performed the day after the polysomnogram. Three children also had a 2-week actigraphic study.**

Results. **The most common sleep complaint in this group of children was excessive daytime sleepiness (EDS), present in 9 of the 14 children. In these children, the sleepiness was manifest by 1 or more of the following symptoms: 1) an increase in total sleep time per 24 hours; 2) the resumption of daytime naps that had been previously discontinued at a younger age; 3) an inability to awaken in the morning to begin the days activities; or 4) the inability to remain awake during activities of daily living, such as school. Of the 9 children with daytime sleepiness, 8 had brain tumors requiring neurosurgical procedures at the time of their diagnosis, 6 of whom required ventricular shunting. The children with the most severe sleepiness had evidence of hypothalamic/pituitary injury with deficiencies in both anterior and posterior pituitary hormones. Five of the children with EDS had polysomnographic evidence of symptomatic narcolepsy with rapid eye movement sleep present on 2 or more of the daytime naps. The symptoms of EDS were effectively controlled with modest doses of daytime stimulant medication and/or scheduled naps. Central apnea leading to respiratory insufficiency and requiring mechanical ventilation to correct was present in 2 children with tumors involving the medulla. Although snoring with possible obstructive sleep apnea was the reason for referral to the sleep clinic in 5 children, none of the children in this series had polysomnographic evidence of significant obstructive sleep apnea. The other sleep problems seen in these children were hypoxia in 2 children, fatigue in 3 children, and seizures during sleep in 1 child. The interval between tumor diagnosis and sleep evaluation varied from 0 months to 9 years (mean: 42 months). The treatment of the sleep problems of this group of children took many forms, including stimulants, scheduled naps, mechanical ventilation, supplemental oxygen, and anticonvulsants.**

Conclusions. **Brain injuries, which invariably are present in children with neoplasms of the CNS, may result in a variety of diagnosable and treatable sleep disorders. The sleep symptoms did not appear to be directly related to the specific therapy the child received, nor the presence of residual tumor. Rather, the primary determinant of the sleep symptoms was the area of the brain that was damaged, regardless of how the damage occurred. Children who sustained damage to the hypothalamic/pituitary region developed EDS regardless of whether the damage was the result of the tumor, surgery, hydrocephalus, or radiation to the whole brain or localized to the suprasellar area. The only children who developed respiratory insufficiency had an injury to the medulla. This observation is consistent with the view that sleep is a specific, albeit complex, neurologic process that is controlled by specific brain regions. EDS and respiratory insufficiency were the most commonly diagnosed severe sleep disorders in these children. The sleep problems of children with brain tumors may develop before, but more often soon after, their tumor diagnosis and treatment. However, the sleep symptoms may not be appreciated by medical providers until years after their onset, which may delay the beginning of effective interventions.** *Pediatrics* **2003;112:e46–e54. URL: http://www.pediatrics.org/cgi/content/full/112/1/e46;** ***excessive daytime sleepiness, brain tumor, fatigue, multiple sleep latency test, polysomnography, actigraphy, symptomatic narcolepsy, respiratory insufficiency.***

ABBREVIATIONS. CNS, central nervous system; PSG, polysomnogram; MSLT, multiple sleep latency test; EDS, excessive daytime sleepiness; REM, rapid eye movement; EEG, electroencephalogram; OSA, obstructive sleep apnea; AHI, apnea hypopnea index; $ETCO_2$, end tidal CO_2; ESS, Epworth Sleepiness Scale; CRF, cancer-related fatigue; CFS, chronic fatigue syndrome.

Sleep is a complex neurologic process that is generated by and primarily benefits the brain. Patients who have sustained significant brain trauma commonly develop sleep symptoms. This asso-

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ciation has been demonstrated across a wide range of brain injuries caused by trauma,[1,2] tumors,[3–11] stroke,[12,13] ionizing radiation,[14–16] and infection.[17,18] The sleep diagnoses that have been associated with brain injury include sleepiness,[2–7,10,11,15,17,18] sleep apnea,[8] respiratory insufficiency,[19] insomnia,[9] and loss of circadian rhythmicity.[1] Aggressive treatment of children with neoplasms of the central nervous system (CNS) has led to improved survival[20]; however, some survivors develop residual neurologic deficits from the tumor itself, neurosurgery, hydrocephalus, radiation therapy, and/or chemotherapy. One group of such neurologic deficits are problems with sleep regulation, which often leads to specific sleep disorders. This report is the largest published case series of children with tumors involving the brain who have had a comprehensive clinical and objective sleep evaluation including polysomnography, the multiple sleep latency test (MSLT), and actigraphy.

METHODS

A retrospective chart review was performed on all children with neoplasms involving the CNS referred to the Minnesota Regional Sleep Disorders Center in Minneapolis, Minnesota, or the Pediatric Sleep Clinic at Children's Hospital and Clinics in St. Paul, Minnesota, between October 1994 and October 2002. The institutional review board did not review this study.

All of the children had a complete sleep evaluation that included a comprehensive sleep history and an all-night polysomnogram (PSG). The PSG was performed as part of a clinical evaluation using standard recording techniques with a Compumedics system (Abbottsford, Victoria, Australia). During a PSG, physiologic data are collected which allows for the simultaneous determination of state (wake, rapid eye movement [REM] sleep, non-REM sleep) and the physiologic parameters of interest. The following signals were obtained: C_3/A_2, C_4/A_1, O_1/A_2, and O_2/A_1 electroencephalogram (EEG), right and left electro-oculogram, a bipolar submental electromyogram, right and left anterior tibialis electromyogram, thoracic impedance, thoracic and abdominal displacement (inductive plethysmography bands), airflow (nasal and oral thermocouple), end tidal CO_2 ($ETCO_2$), snoring (microphone), and oxygen saturation. This allows for assessment of the interplay between sleep state and the physiologic problems that occur during sleep (ie, obstructive apnea, central apnea, seizures, arousals, and leg movements). The PSG is the gold standard for the assessment of sleep quality, and is a necessary precursor for an MSLT.[21] In this case series, the MSLT was begun after the spontaneous morning awakening. The MSLT, performed the day after a PSG, is a series of 4 or 5 nap opportunities timed every 2 hours after awakening. The MSLT measures the latency between when individuals are put in bed and when they fall asleep, over the course of the day, and provides an objective measure of daytime sleepiness. PSGs were scored by polysomnographic technologists using standard criteria to stage sleep,[22] and following American Thoracic Society guidelines for defining obstructive and central apneas in children.[23] Obstructive apnea is defined as the absence of oral/nasal airflow in the presence of continued respiratory effort lasting longer than 2 respiratory cycles, associated with at least a 4% drop in oxygen saturation. Obstructive hypopnea is defined as a 50% or greater reduction in the amplitude of the oral/nasal airflow signal lasting longer than 2 respiratory cycles associated with at least a 4% drop in oxygen saturation. The apnea hypopnea index (AHI) is the sum of the number of obstructive apneas and obstructive hypopneas per hour. Central apneas are defined as the absence of oral/nasal airflow and the absence of respiratory effort lasting 20 seconds or longer. In the 12 children with a history of daytime sleepiness or fatigue, an MSLT was obtained the day after the all-night PSG using standard recording and scoring criteria. Excessive daytime sleepiness (EDS) is a specific sleep diagnosis that is based on the nighttime PSG and the sleep latencies on the MSLT the following day. In children, a mean sleep latency of <5 minutes indicates severe EDS; a mean latency between 5 and 10 minutes indicates moderate EDS; a mean latency between 10 and 14 minutes indicates moderate to mild EDS; and a mean sleep latency 15 minutes or greater is normal. Although the MSLT is designed to minimize many of the nonsleep variables, which may impact on sleep latency, there are times when a diagnosis of EDS is the correct one when the mean MSLT is in the normal range. However, there is no clearly accepted criteria for defining these exceptions. In 3 children, a 2-week actigraphic[24] (Actiwatch, Bend, OR) study was obtained to evaluate for a circadian rhythm disturbance, or because the PSG and MSLT did not confirm the parents' report of EDS. An actigraph is a small wristwatch-sized solid-state accelerometer with a scoring algorithm, which can store up to 2 weeks of data. The actigraph is used to differentiate between wake and sleep during prolonged monitoring at home. In this case series, a 2-week actigraphic evaluation was used to diagnose EDS in children with a long nightly sleep duration of >8 hours a night, consistent daytime napping, and weekend sleep extension when the mean MSLT was in the normal range. Symptomatic narcolepsy is a polysomnographic diagnosis that is based on the presence of moderate to severe EDS (mean sleep latencies <10 minutes) and 2 or more REM onset naps on the MSLT.[3,5] Nocturnal seizures were diagnosed if an epileptiform pattern was seen on EEG and there was a history of a clinical seizure occurring during sleep. Sleep efficiency is the percentage of total sleep time divided by the time in bed as recorded by PSG. Normal sleep efficiency in a child is generally >94%. Respiratory insufficiency was defined as present if during the PSG, the $ETCO_2$ rose above 75 torr and oxygen saturations dropped below 80%, and these gas exchange problems could only be corrected with mechanical ventilation.

RESULTS

Patient Characteristics

Table 1 describes the tumor type and location, treatment, and endocrine deficiencies of the 14 children with neoplasms of the CNS who were referred to the sleep center by their hematologist/oncologist. Table 2 describes the specific sleep complaints these children were experiencing that led to their referral, the results of their PSG and MSLT, and their sleep diagnosis and treatments. There were 5 males and 9 females. The median age of the children at the time of the tumor diagnosis was 11 years with a range of 5 months to 15 years of age. The time interval between tumor diagnosis and sleep evaluation ranged from 0 to 104 months with a median of 42 months. Twelve children had brain tumors including: 1 optic chiasm glioma, 1 brainstem glioma, 1 pineoblastoma, 1 craniopharyngioma, 3 medulloblastomas, 1 hypothalamic glioma, 2 cervical-medullary astrocytomas, and 2 atypical teratoid/rhabdoid tumors. One child had Langerhans cell histiocytosis infiltrating the hypothalamus and 1 child had a hypothalamic hamartoma. The children with Langerhans cell histiocytosis and hypothalamic hamartoma are included in this report because their sleep symptoms, brain injury, associated hormone deficiencies, clinical evaluation, and treatments were similar to that of the children with brain tumors. Neurologic deficits were present in several of the children including: visual impairment (No. 1), visual field cuts, ptosis, and third nerve palsy (No. 2), visual impairment with a pale optic disk (No. 4), ataxia (No. 6, No. 11), upper extremity tremor (No. 8), hypotonia (No. 12). Seven children in this case series had ventricular shunts (Nos. 1–4, 6, 9, and 11). At the time of the PSG and MSLT, several of the children were on psychotropic medications for treatment of complications of their brain tumors. These medications included carbamazepine (Nos. 1,

TABLE 1. Tumor Type, Location, Treatment, and Endocrine Deficiencies for Children With Neoplasms of the CNS

Patient/Age at Diagnosis	Tumor/Location	Treatment	Endocrine Deficiency
1/4 y	Glioma/optic chiasm	PR, RT, shunt	Thyroid*, growth, sex, cortisol
2/2 y	Glioma/brainstem Recurrence-hypothalamus/pituitary	NTR, shunt chemotherapy	Growth
3/13 y	Pineoblastoma/pineal	GTR, RT, shunt chemotherapy	Growth, sex
4/13 y	Craniopharyngioma/suprasellar and right frontal lobe	GTR, shunt	Thyroid*, growth, sex, cortisol, ADH
5/15 y	Astrocytoma/suprasellar	NTR, chemotherapy	Thyroid*, sex, cortisol, ADH
6/10 y	Meduloblastoma/posterior fossa	GTR, RT, shunt chemotherapy	Thyroid, growth, cortisol
7/2 y	Langerhans cell histiocytosis/hypothalamus	Chemotherapy	Growth, ADH
8/15 y	Hamartoma/hypothalamus	PR	Thyroid*, growth, sex, cortisol, ADH
9/10 y	Meduloblastoma/posterior fossa	GTR, RT, shunt chemotherapy	Thyroid*, growth, sex, cortisol
10/8 y	Astrocytoma/cervical-medullary	PR, RT, chemotherapy	None
11/5 y	Meduloblastoma/posterior fossa	GTR, RT, shunt chemotherapy	Thyroid
12/12 y	Astrocytoma/cervical-medullary	Chemotherapy	None
13/5 mo	Atypical teratoid rhabdoid tumor/ Posterior fossa	PR, chemotherapy	None
14/7 y	Atypical teratoid rhabdoid tumor/ left temporal	GTR, RT, chemotherapy	Thyroid, growth

PR, indicates partial resection; NTR, near total resection; GTR, gross total resection; RT, radiation therapy.
* Thyroid deficiency secondary to central cause.

4, 8), sertaline (No. 4), fluoxetine (No. 10), melatonin (No. 14), and thalidomide (No. 11).

Sleep Complaints and Associated Findings

The most common sleep complaint was daytime sleepiness seen in 9 children, 5 of whom also described an increase in their total daily sleep need. Three children complained of fatigue, but not daytime sleepiness. Two children had respiratory insufficiency, 1 during wake and sleep and 1 only during sleep. Two children had hypoxemia, 1 during sleep and 1 during wake and sleep. Snoring with possible sleep apnea was one of the reasons for the initial referral in 5 children. Some children had >1 sleep complaint (Table 2). In this report, the term sleepiness is used to describe a sleep complaint, and EDS is used to describe a sleep diagnosis. The diagnosis of EDS is based on either short sleep latencies on the MSLT, or a documented long sleep requirement and inappropriate daytime napping based on actigraphy. Fatigue is used to describe a feeling of tiredness that is not associated with changes in nighttime sleep or daytime sleepiness.

EDS

The most common sleep complaint identified by the referring oncologists and parents was daytime sleepiness, present in 9 of the 14 children. In these children, the sleepiness was manifest by 1 or more of the following symptoms: 1) an increase in total sleep time per 24 hours, 2) the resumption of daytime naps that had been previously discontinued at a younger age, 3) an inability to awaken in the morning to begin the days activities, or 4) the inability to remain awake during activities of daily living, such as school. Of the 9 children with daytime sleepiness, 8 had brain tumors requiring neurosurgical procedures at the time of their diagnosis, 6 of whom required ventricular shunting (Nos. 1–4, 6, and 9). The children with brain tumors requiring neurosurgical procedures had a variety of neurologic symptoms that led to their diagnosis, but none had a history of sleepiness before surgery. The 1 child with daytime sleepiness who did not have a neurosurgical procedure had Langerhans cell histiocytosis, which was treated solely with chemotherapy. Of the 9 children with daytime sleepiness, 4 had tumors that involved the hypothalamus (Nos. 2, 3, 7, and 8), and 3 had tumors at the optic chiasm or in the suprasellar region (Nos. 1, 4, and 5). Some of these children also received chemotherapy and/or radiation therapy. The other 2 children with daytime sleepiness (Nos. 6 and 9) did not have tumor involvement of the hypothalamus, but they did both have a neurosurgical procedure, including ventricular shunting and both received chemotherapy and cranial radiation to the whole brain and posterior fossa.

The interval between the onset of the sleepiness and referral for a sleep evaluation varied from 2 months to 8 years. By this time the sleepiness was impacting the children's ability to function at home and in school. Before the sleep clinic evaluation, parents and schools had tried to adapt to the sleepiness by modifying the school start time, scheduling daytime naps, or home schooling.

In an attempt to distinguish between fatigue and sleepiness, all of the children with either of these complaints had a MSLT the morning after their PSG. Of the 9 children who described daytime sleepiness (Nos. 1–9), 7 (Nos. 1, 2, 4–7, and 9) had short mean sleep latencies on the MSLT (1–10 minutes), confirming EDS. Five of these children with EDS met the

TABLE 2. Sleep Complaints, PSG, and MSLT Data for Children With Neoplasms of the CNS

Patient/Age at Diagnosis	Sleep Complaint	Age at Sleep Study	PSG Findings	MSLT (Minutes) REM Naps	Sleep Diagnosis/Treatment
1/4 y	Sleepiness, snoring	12 y	Snoring, spike, and slow wave	Mean 10 REM 0/5	EDS/naps, anticonvulsant, stimulants (declined)
2/2 y	Sleepiness, ↑ TST	10 y	↓ Sleep efficiency	Mean 9 REM 1/4	EDS/stimulants
3/13 y	Sleepiness, ↑ TST	15 y	Snoring, AHI-4.9/h	Mean 18 REM 0/5	EDS/stimulants
4/13 y	Sleepiness, snoring, hypoxia	15 y	Snoring, AHI-1.2/h, hypoxia during REM sleep	Mean 2 REM 2/4**	EDS, REM, hypoxia/ stimulants, oxygen
5/15 y	Sleepiness, snoring	20 y	Snoring, AHI-6/h	Mean 1 REM 3/5**	EDS/stimulants
6/10 y	Sleepiness, ↑ TST, snoring	14 y	Snoring	Mean 10 REM 4/5**	EDS/stimulants (declined)
7/2 y	Sleepiness, ↑ TST, snoring	7 y	Snoring, AHI-0.3/h	Mean 6 REM 3/4**	EDS/stimulants
8/15 y	Sleepiness, ↑ TST	16 y	Long sleep duration	Mean 20 REM 0/4	EDS/stimulants
9/10 y	Sleepiness, respiratory insufficiency	14 y	Central apnea	Mean 10 REM 4/4**	EDS, respiratory insufficiency/nasal mask ventilation, stimulants
10/8 y	Fatigue	11 y	Snoring, AHI-0.7/h	Mean 20 REM 0/3	Fatigue/none
11/5 y	Fatigue	7 y	Snoring, AHI-2.5/h, movements during REM and NREM	Mean 15 REM 1/5	Fatigue/none
12/12 y	Respiratory insufficiency	12 y	Central apnea	—	Respiratory insufficiency/ trach and ventilator
13/5 mo	Hypoxia-wake and sleep	8 mo	Wake and sleep hypoxia	—	Hypoxia/oxygen
14/7 y	Fatigue	12 y	Snoring, AHI-0.5/h	Mean 20 REM 0/5	Fatigue/none

TST, indicates total sleep time.
** Symptomatic narcolepsy (2 REM onset naps).

diagnostic criteria for symptomatic narcolepsy with 2 or more REM-onset naps on the MSLT (Nos. 4–7 and 9). Three of these children (Nos. 4, 5, and 7) had evidence of both anterior and posterior pituitary hormone deficiency, requiring replacement therapy. None of the children with symptomatic narcolepsy described daytime cataplexy, sleep onset paralysis, or hypnogogic hallucinations. In all of the children with confirmed EDS, the PSG demonstrated some other abnormalities including: snoring, obstructive sleep apnea (OSA) with an AHI from 1.2 per hour to 6 per hour, central apnea, hypoxia, spike and slow wave on EEG, or a decreased sleep efficiency. However, these other findings did not appear to be the cause of the EDS. In some cases, the other PSG abnormalities were minor—snoring and infrequent obstructive apneas; in others, the problems noted on the PSG were already corrected before the MSLT was obtained—nocturnal seizures, respiratory insufficiency, and hypoxia.

The parents of 5 children (Nos. 2, 3, and 6–8) described an increase in their child's total nighttime sleep duration, in addition to the development of daytime sleepiness with a resumption of daytime napping, that had previously been discontinued at a younger age. Three of these children had EDS documented on the MSLT with latencies of 10 minutes or less. However, 2 children (Nos. 3 and 8) had a history of increased nighttime sleep duration and daytime sleepiness with normal sleep latencies on MSLT. In these 2 children, an actigraphic study and accompanying sleep log were collected in addition to the PSG and MSLT. Patients 3 and 8 wore an actigraph for 2 weeks while attempting to adhere to a school schedule that required them to awaken at 5:30 AM on school days. The actigraph showed that these children were getting 8 to 10 hours of sleep on school days, with naps occurring on most days. The spontaneous wake time for patient 3 on weekends was 2.5 hours later than her school day wake time, and for patient 8 spontaneous wake time was 7 hours later than her school day wake time. This finding suggests that the 8 to 10 hours of sleep these children were getting on schooldays was inadequate to meet their sleep needs, and as a consequence, both children were sleep-deprived during the week. They attempted to catch up on sleep on the weekends by substantially extending their sleep time. An actigraph and sleep logs were also collected on patient 1, whose parents reported their child developed an unusual sleep-wake pattern after her tumor treatment. This child had a regular sleep-onset time, short nighttime sleep duration with a spontaneous early-morning awakening, and irresistible daytime napping. The daytime napping made it impossible for her to attend school. The sleep pattern the parents described was confirmed with the PSG/MSLT and actigraphy.

All 9 children with sleepiness were offered treatment with daytime stimulants; 7 children were

treated and 2 parents declined treatment for their children. The stimulants used were methylphenidate, mixed amphetamine salts, and modafinil. All 7 of the treated children responded favorably to the stimulants, although several were changed from one to another because of side effects, dosing constraints, or lack of efficacy. In patient 8, the long sleeper, the primary clinical problem was an inability to awaken in the morning to get to school. She was successfully managed by being briefly awakened 1 hour before she needed to get up for school, given half of her morning dose of mixed amphetamine salts, and then allowed to return to sleep. An hour later she could be awakened without a great deal of difficulty. She took the other half of her morning dose with breakfast.

Fatigue

Three of the children (Nos. 10, 11, 14) presented with fatigue. The history in these children was different from that of children who described sleepiness. The parents of these children did not describe that their child was either falling asleep at inappropriate times or had an increase in total sleep time. Patient 10 developed an increase in nighttime sleep duration and daytime fatigue, but not daytime sleepiness during chemotherapy. Both symptoms resolved after chemotherapy was completed. Patient 11 developed daytime fatigue and continuous movements during sleep, but not changes in nighttime sleep duration or daytime sleepiness during a relapse of her tumor. She died soon after her sleep evaluation from progression of her tumor. Patient 14 developed fatigue, but not changes in nighttime sleep duration or daytime sleepiness, several years after she completed treatment for her tumor at a time when she was experiencing a great deal of academic difficulty because of an inappropriate school placement. The complaints of fatigue resolved after she was placed in a more appropriate school. These children did not have EDS as documented on the MSLT (mean sleep latencies 15–20 minutes), nor were they long sleepers. Two of the children complaining of fatigue had peripherally mediated hypothyroidism (Nos. 11 and 14), which was presumed to be secondary to craniospinal radiation therapy. At the time of their sleep evaluation, these children were on appropriate thyroid replacement and were felt to be euthyroid by the endocrinologist at the neuro-oncology clinic. Of the 3 children with fatigue, only patient 14 had a centrally mediated hormone deficiency (growth hormone). No specific sleep diagnosis was established in any of the children whose primary complaint was fatigue.

Respiratory Insufficiency

In 2 children (Nos. 9 and 12) the most significant manifestation of a sleep problem was an abnormality in the control of ventilation severe enough to require mechanical ventilation. Both of these children had tumors involving the medulla. One child (No. 12) presented to the sleep clinic 2 years before her diagnosis with a cervical-medullary astrocytoma, when she was referred for an evaluation of snoring and observed apnea, as part of an assessment for obesity/hypoventilation. An all-night PSG revealed central apnea, 5.5 per hour, and hypoventilation which caused oxygen desaturation to a nadir of 58% and rise in $ETCO_2$ to a peak of 50 torr. A computed axial tomographic scan of the brain at that time was normal. She was begun on a weight loss program. Two years later, she returned to the hospital in congestive heart failure, secondary to respiratory insufficiency. Magnetic resonance imaging of the brain at this time demonstrated a cervical-medullary astrocytoma. A repeat PSG revealed baseline awake oxygen saturation 56%, $ETCO_2$-65 torr; with sleep onset oxygen saturation dropped to 20%, $ETCO_2$ rose to 76 torr. The hypoventilation could not be corrected with noninvasive nasal mask ventilation, and soon after the study the child underwent a tracheotomy and was placed on a ventilator during wake and sleep. The child died soon thereafter from complications of her brain tumor and heart failure.

Patient 9 developed respiratory failure 4 years after his diagnosis and treatment for a medulloblastoma during sedation for a colonoscopy. He required intubation and mechanical ventilation at the time, but was successfully weaned to nighttime nasal mask ventilation with a backup rate, which he has continued to use successfully. Follow-up sleep studies have confirmed persistent sleep-related hypoventilation requiring ventilation, with adequate waking ventilation. An MSLT performed when the child was being adequately ventilated during sleep demonstrated short sleep latencies, confirming a diagnosis of EDS. Of note, this child's medulloblastoma was found to be intimately associated with the medulla at the time of his resection.

Hypoxemia

Two children were referred to the sleep clinic for evaluation of hypoxemia (Nos. 4 and 13). Patient 4 developed obesity, snoring, hypoxemia, and sleepiness after her surgery for a craniopharyngioma. The nighttime study revealed REM-related hypoxemia, snoring, and rare obstructive hypopneas (1.2 per hour). The sleep-related hypoxemia was thought to be caused by ventilation/perfusion mismatch and was easily corrected with supplemental oxygen during sleep. The EDS was improved with daytime stimulants. Patient 13 developed hypoxemia during wake and sleep after an episode of pneumonia. The PSG demonstrated a low baseline oxygen saturation during wake, which remained low during non-REM sleep and declined further during REM sleep. The wake and sleep hypoxemia was easily corrected using supplemental oxygen.

Snoring

Snoring and possible OSA was one of the reasons for referral to the sleep center for 5 children (Nos. 1, and 4–7). The PSG confirmed the presence of snoring, but did not demonstrate OSA severe enough to explain their clinical symptoms. AHI varied from 0.3 per hour to 6 per hour without concomitant oxygen desaturations, or rise in $ETCO_2$. Snoring without significant OSA was also noted as an incidental finding on the PSG of 4 other children (Nos. 3, 10, 11, 14).

Hormone Deficiencies

Eleven of the 14 children included in this case series had 1 or more hormone deficiencies. These are listed in Table 1 and include growth hormone, thyroid hormone, cortisol, estrogen, testosterone, and antidiuretic hormone. Three children (Nos. 6, 11, and 14) had evidence of a peripherally mediated thyroid deficiency. These children all received craniospinal radiation as part of their treatment, and all had elevated thyroid-stimulating hormone levels, suggesting an appropriately functioning hypothalamic pituitary control system, with low T4 levels. Two of the children with peripherally mediated thyroid deficiencies had other hormone deficiencies (growth hormone deficiency [Nos. 6 and 14], cortisol deficiency [No. 6]). With the exception of the peripherally mediated thyroid deficiencies, all of the other hormone deficiencies were centrally mediated. The presence of these centrally mediated hormone deficiencies were interpreted as evidence of a functional impairment of the hypothalamic/pituitary system, although the specific cause of the injury was not always clear. The children with the most severe EDS had evidence of both anterior and posterior pituitary hormone deficiencies (Nos. 4, 5, and 7). All of the hormone deficiencies in all of the children were corrected before the sleep evaluation, PSG, and MSLT.

DISCUSSION

Although the prevalence of sleep disorders in children with neoplasms involving the CNS is unknown, sleep complaints are not uncommon. Prospective studies with a greater number of patients are necessary to delineate the true scope of sleep problems in these individuals. The sleep complaints encountered in this referral population of children with tumors involving the brain were: daytime sleepiness, fatigue, respiratory insufficiency, hypoxia, nocturnal seizures, and snoring. These problems were successfully evaluated using the tools readily available in a sleep clinic: sleep history, sleep log, PSG, MSLT, and actigraphy. A specific sleep diagnosis was made in all of the children, except for those children who presented with fatigue. The sleep diagnosis led to an effective treatment, which improved the target symptoms and contributed to an improved quality of life for the children who followed the treatment recommendations.

All of the children in this case series have sustained numerous CNS traumas. They all have neoplasms of the CNS, which destroy and disrupt the CNS; all but 2 of the children had a neurosurgical procedure with a partial, near total, or gross total resection of their tumor; 7 of the children required ventricular shunting at the time of surgery, 7 of the children received radiation therapy; and 11 received chemotherapy. Most of the children had several of these treatments, all of which can damage the CNS. The sleep symptoms did not appear to be directly related to the specific therapy the child received, nor the presence of residual tumor. Rather, the primary determinant of the sleep symptoms was the area of the brain that was damaged, regardless of how the damage occurred. Children who sustained damage to the hypothalamic/pituitary region developed EDS regardless of whether the damage was the result of the tumor, surgery, hydrocephalus, or radiation to the whole brain or localized to the suprasellar area. Chemotherapy did not seen to be independently associated with EDS. The only children who developed respiratory insufficiency had an injury to the medulla. This observation is consistent with the view that sleep is a specific, albeit complex neurologic process that is controlled by specific brain regions.

The most common complaint encountered in these children was daytime sleepiness, present in 9 of 14 of the children and fatigue present in 3 of 14. In the minds of the children, their parents and the referring oncologists, these 2 problems were one in the same. The blending of these 2 symptoms, sleepiness and fatigue, is also present in much of the oncology[25,26] and pediatric literature.[27] Cancer-related fatigue (CRF) has been the subject of research in both children and adults, but CRF and sleepiness have not been clearly differentiated. In a recent study of CRF[25] in adults, a classification schema was proposed for CRF that included 2 sleep symptoms-"insomnia/hypersomnia; and experience of sleep as unrefreshing or nonrestorative". In this study, 31% of the 179 cancer survivors surveyed endorsed both of these symptoms, more than any of the 8 other specific symptoms. Similarly, in a study of CRF in children,[26] sleepiness is included as a diagnostic criterion for fatigue. The inclusion of sleepiness as a symptom of fatigue is also present in the pediatric chronic fatigue syndrome (CFS) literature where sleepiness was present in 30% of children described as having CFS. The National Institutes of Health, Center for Disease Control, and the international CFS study group[28] avoided the confusion between sleepiness and fatigue by not including sleep symptoms as a major criterion in CFS but as only 1 of 8 minor criteria of CFS.

From the perspective of a sleep clinician, sleepiness and fatigue are very different symptoms. Sleepiness is understood as a narrowly defined, specific symptom that involves falling asleep at inappropriate times. The causes of sleepiness are: 1) inadequate sleep quantity (sleep deprivation), 2) poor sleep quality (sleep fragmentation), 3) attempting to remain awake during the circadian sleep phase (circadian), or as a 4) primary neurologic symptom. Sleepiness can be objectively quantified by the MSLT, which is an objective test of sleep tendency. Sleep propensity has also been subjectively quantified by self-report questionnaires, such as the Epworth Sleepiness Scale (ESS), which ask about the likelihood of falling asleep in a number of real-life situations.[11,29] The ESS has been well-validated in adults, but not in children; it has good face validity, and has been shown to discriminate between normal and pathologic levels of sleepiness in adults. Fatigue, on the other hand, is less well-defined and cannot be so easily quantified. It is largely a subjective symptom present in numerous conditions, including sleepiness, but fatigue is different from sleepiness. Sleepy individuals often describe fatigue, but most individ-

uals who are fatigued neither complain of sleepiness (ie, falling asleep at inappropriate times) nor are they objectively sleepy on MSLT.

It is well-recognized by clinicians that the MSLT is a good but not perfect test for defining EDS and for distinguishing EDS from fatigue. Two of the children in this case series had a convincing history of sleepiness, with a prolonged total sleep time and consistent daytime napping, but had normal sleep latencies on the MSLT. The fact that the MSLT was performed after allowing the children to awaken spontaneously from their nighttime study, thus allowing them to extend their sleep the night of the study, may have contributed to these normal results. In both cases, 2 weeks of actigraphy confirmed the child's description of a prolonged sleep requirement and daily napping. Carskadon[30] has described that adolescents normally demonstrate an increase in their daytime sleepiness, with a decrease in their mean MSLT's during Tanner 3 to 4, but there is not a change in their total sleep time. Thus, it is unlikely that the sleep complaints of these 2 children were the result of changes in sleep occurring as a result of normal adolescent development. In the context of this case series, these 2 children were considered to have EDS. Both of these children were treated with modest doses of stimulant medication, and the target symptom of daytime sleepiness improved in both.

In 5 of the 9 children who presented with the symptom of sleepiness, the parents described a net increase in the child's total sleep time per 24 hours in addition to an increase in their child's daytime sleepiness. Before becoming ill, all of these children had given up their daytime naps and had consolidated all of their sleep into 1 long nighttime sleep period. By the parents report, their child's sleep pattern changed after the child's surgery in the children with brain tumors, and at the time of disease progression in the child with Langerhans cell histiocytosis. The PSG in these children were often not entirely normal, but the abnormalities seen on the PSG were not felt to adequately explain the severity of their sleepiness. One way of understanding the sleepiness seen in these children with neoplasms involving the CNS is to view sleepiness as a primary neurologic symptom, not simply as a consequence of sleep fragmentation, sleep deprivation, or a circadian rhythm problem. The model of sleep-wake regulation described by Borbely and Achermann,[31] Edgar et al,[32] and Carskadon and Acebo[30] is helpful in understanding the sleepiness seen patients with tumors involving the brain. Borbely and Achermann[31] described 2 basic processes that underlie sleep regulation: 1) a homeostatic process, mediating the rise in sleep propensity during waking and its dissipation during sleep and, 2) a circadian process, a clock-like mechanism that is independent of prior sleep and waking and determines the alteration of periods of high and low sleep propensity. Edgar et al[32] elaborated on this model, with experimental evidence in supachiasmatic nucleus lesioned squirrel monkeys that demonstrated that the circadian process is alerting, and in opposition to the homeostatic process. Edgar et al[32] described the balance between the circadian and homeostatic processes as the "opponent process" model of sleep regulation. Carskadon and Acebo[30] demonstrated that this model was also useful in understanding the changes in sleep regulation that occurred during normal adolescent development. Viewed from this perspective, an increase in total sleep time, which is not secondary to poor sleep efficiency, or sleep fragmentation could occur from a change in the balance between the circadian and homeostatic processes: either a decrease in the circadian alerting process or an increase in the homeostatic drive to sleep. Both of these processes are controlled by a complex interaction among different hypothalamic nuclei.[33,34] The circadian process is controlled by the supachiasmatic nucleus.[30,31] The homeostatic process is less well understood, but the basal forebrain and the ventrolateral preoptic nuclei are thought to play a central role in its regulation.[33,34]

The children described in this paper who complained of daytime sleepiness all had evidence of a functional hypothalamic and/or pituitary injury, which was manifest by a centrally mediated hormone deficiency requiring hormone replacement therapy. One could postulate that these children sustained a hypothalamic injury that affected the hypothalamic nuclei important in regulating sleep, wake, or circadian rhythmicity, or possibly the interconnection between these nuclei and the reticular activating system. An injury in this area of the brain could lead to a change in the balance between sleep and wake that in turn could result in the symptom of increased sleepiness. The hypothalamic nuclei important in the regulation of sleep, wake, and circadian rhythms are all located in close physical proximity to many of the nuclei responsible for the synthesis of the releasing hormones, which control the pituitary gland, and to the nuclei, which synthesize the posterior pituitary hormones.[35] Damage to the hypothalamus in this area thus could impact on both control of hypothalamic pituitary hormones and sleep. Alternatively, injury to the lateral hypothalamic hypocretin-secreting cells could explain the increase in sleepiness in these children. Hypocretin is a recently discovered neuropeptide, synthesized by a small group of neurons in the lateral hypothalamus, and known to be important for the maintenance of normal wakefulness.[36,37] Damage to the hypocretin-producing neurons of the lateral hypothalamus, resulting in a deficiency of hypocretin in the CNS, has been shown to be the most common cause of idiopathic narcolepsy[37] and to be associated with some, but not all, cases of symptomatic narcolepsy.[7,29] Whatever the cause of sleepiness in the children described in this paper, the symptom was surprisingly easy to correct using modest doses of stimulants.

EDS has been previously described in association with hypothalamic tumors.[3–5,7] However, the prevalence of EDS in children with hypothalamic tumors varies with how the sleepiness is defined. In a study of 79 children with craniopharyngiomas and 19 children with pilocytic astrocytomas involving the hypothalamus, Muller et al[11] found 35% of the children with craniopharyngiomas, and 15% of the children with pilocytic astrocytomas had a score on the ESS

>10, suggestive of severe sleepiness, compared with 0% of normal controls.[11] Palm et al[4] evaluated 10 children with craniopharyngiomas using PSG and MSLT. He found that 2 were sleepy based on a mean MSLT <10 minutes and the remainder were not. Actigraphy was not used as a tool in the evaluation of the children in either Muller's or Palm's studies. The variability of the prevalence of EDS in children with hypothalamic tumors in these various reports is likely the result of differences in diagnostic criteria used to define EDS, differences in the tools used during the evaluation, as well as patient selection. In this case series, the patients were referred for sleep problems, and actigraphy was used as a tool to establish the diagnosis of EDS where the PSG and MSLT were normal; both of these factors would increase the frequency that EDS would be diagnosed. In 2 children in this case series, actigraphy proved to be a valuable tool, confirming that the children were long sleepers, and were sleeping at inappropriate times during the day. These findings were considered adequate to justify the diagnosis of EDS and to begin treatment with stimulant medication, in the absence of short sleep latencies on the MSLT. Neither of these children would have been diagnosed with EDS in the other studies mentioned. In each child with EDS in this case series, treatment of sleepiness was successful using modest doses of stimulant medication and was an important part in the reintegration of these children back into school and other activities.

The most serious, and the only potentially life-threatening sleep disorder seen in this group of children with tumors involving the brain, was respiratory insufficiency during wake and/or sleep. This problem was only seen in children whose tumors involved the medulla. The 2 children in this case series with respiratory insufficiency are illustrative of the temporal variability with which these respiratory symptoms can present, relative to the time of tumor diagnosis. In 1 child, the first symptom of her brain tumor was sleep-related hypoventilation associated with obesity, which was present 2 years before her diagnosis with a cervical-medullary astrocytoma. The absence of an abnormality on a head computed axial tomographic scan performed at the time of her initial presentation missed the true cause of her hypoventilation, a brain tumor that became apparent 2 years later on a brain magnetic resonance imaging. In the other child, respiratory insufficiency did not become apparent until 4 years after his tumor diagnosis with a meduloblastoma, when he developed respiratory insufficiency during sedation for a colonoscopy. This degree of variability in the presentation of the respiratory symptoms in children with brain tumors has not been previously described. One should keep this variability between the time of tumor diagnosis and the clinical presentation of respiratory insufficiency in mind when evaluating children with hypoventilation and when administering sedation to children with a history of tumors of the posterior fossa, particularly those tumors intricately associated with the medulla.

Although snoring and/or a modest degree of OSA was found on the PSG in 9 children in this case series, OSA did not appear to be the primary cause of EDS or other sleep problems in any of the children.

The purpose of a case review study is to highlight interesting and instructive associations in groups of clinically related problems. The associations do not prove causality, but can provide a focus for future clinical care and research. This study of sleep problems in children with tumors involving the brain does highlight some interesting associations, particularly that of daytime sleepiness and injury to the hypothalamus and pituitary, as well as respiratory insufficiency with injury to the medulla. Prospective, population-based studies are necessary to delineate the true nature and scope of this problem.

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