

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Severe Hypersomnolence After Pituitary/Hypothalamic Surgery in Adolescents: Clinical Characteristics and Potential Mechanisms

Ayelet Snow, Evelyne Gozal, Atul Malhotra, Dov Tiosano, Rina Perlman, Céline Vega, Eli Shahar, David Gozal, Ze'ev Hochberg and Giora Pillar

Pediatrics 2002;110:e74

DOI: 10.1542/peds.110.6.e74

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/110/6/e74>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2002 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



Severe Hypersomnolence After Pituitary/Hypothalamic Surgery in Adolescents: Clinical Characteristics and Potential Mechanisms

Ayelet Snow, MD*; Evelyne Gozal, PhD||; Atul Malhotra, MD¶; Dov Tiosano, MD‡; Rina Perlman, PhD‡; Céline Vega, PhD||; Eli Shahar, MDS; David Gozal, MD||; Ze'ev Hochberg, MD‡; and Giora Pillar, MD, PhD*

ABSTRACT. *Objectives.* After resection of hypothalamic/pituitary tumors, children are at risk for development of hormonal deficiencies, obesity, and hypersomnolence. However, the prevalence and pathophysiology of these complications are unclear. The purpose of this study was to assess the prevalence and severity of hypersomnolence in children after resection of pituitary tumors and to study the potential factors that contribute to this sleepiness if present. We further hypothesized that decrements in orexin levels may contribute to the sleepiness.

Methods. Six children who underwent hypothalamic/pituitary surgery were identified. Five of these patients and 5 matched control subjects underwent overnight polysomnography followed by a multiple sleep latency test. Children who had a primary sleep disorder (eg, obstructive sleep apnea) underwent treatment and were restudied subsequently ($n = 2$). Blood levels of pituitary hormones were measured. Blood and cerebrospinal fluid (CSF) were drawn from 4 patients and 3 control subjects to measure orexin levels.

Results. Endocrine control was appropriate in all children. Although patients had longer sleep duration but similar sleep efficiency than control subjects, relatively severe daytime somnolence was present (mean sleep latency: 10.3 ± 5.3 minutes vs 26.2 ± 1.1 minute in control subjects). Sleepiness did not correlate with body mass index or age. Furthermore, serum and CSF orexin levels did not differ between patients and control subjects.

Conclusions. Severe daytime sleepiness is frequent among children who undergo pituitary/hypothalamic surgery and does not seem to result from inappropriate cortisol or thyroxine replacement, disturbed nocturnal sleep, or low levels of orexin in the serum or CSF. We therefore speculate that other, unidentified neurohormonal mechanisms may mediate the excessive sleepiness of these patients. *Pediatrics* 2002;110(6). URL: <http://www.pediatrics.org/cgi/content/full/110/6/e74>; *sleep, excessive daytime sleepiness, adolescents, orexin (hypocretin), brain tumors, craniopharyngioma.*

ABBREVIATIONS. OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure; CSF, cerebrospinal fluid; ESS, Ep-

From the *Department of Pediatrics A and Sleep Laboratory, ‡Pediatric Endocrinology and §Pediatric Neurology Unit, Rambam Medical Center and Technion, Haifa, Israel; ||Kosair Children's Hospital Research Institute, University of Louisville, Louisville, Kentucky; and ¶Sleep Clinic, Harvard Medical School, Boston, Massachusetts.

Received for publication Apr 5, 2002; accepted Jul 31, 2002.

Reprint requests to (G.P.) Pediatrics Department A, Rambam Medical Center, Haifa 31096, Israel. E-mail: gpillar@tx.technion.ac.il

PEDIATRICS (ISSN 0031 4005). Copyright © 2002 by the American Academy of Pediatrics.

worth Sleepiness Scale; FT4, free thyroxine; MSLT, multiple sleep latency test; TIB, time in bed; SL, sleep latency; REM, rapid eye movement; RIA, radioimmunoassay; BMI, body mass index; TST, total sleep time; GH, growth hormone.

Intracranial space-occupying lesions such as craniopharyngiomas, germ cell tumors, and arachnoid cysts can expand into the hypothalamus, pituitary gland, third ventricle, and additional brain structures. The clinical outcome after surgical removal of the mass varies and has included neurologic and visual field abnormalities,^{1,2} endocrinologic disorders,³⁻⁵ weight gain and obesity,^{6,7} and excessive daytime somnolence.^{1,8,9} The endocrine management of these patients after surgery usually consists of replacement therapy of thyroid hormone, cortisol, and growth hormone as needed. Treatment for obesity is more complex and includes dietary restrictions, encouragement of physical activity, and occasional weight reduction surgery. However, the prevalence and pathophysiology of daytime hypersomnolence in these patients has not been frequently studied and is poorly understood.

Daytime somnolence could be the result of various hormonal deficits, such as found in hypothyroidism and hypoadrenalism.¹⁰ In contrast, the relationship between growth hormone or prolactin deficiency and excessive daytime sleepiness is not as clear.¹¹ Nevertheless, replacement therapy of cortisol and/or thyroxine deficiencies should reverse all of the clinical manifestations, including sleepiness, unless additional causes for sleepiness, such as sleep apnea, are present.¹²⁻¹⁵ Thus, well-treated patients would not be expected to display sleepiness, and if they do, other causes should be sought.

Obesity has been implicated in daytime somnolence, either secondary to obstructive sleep apnea (OSA)¹⁴⁻¹⁹ or directly, possibly via a metabolic and/or circadian abnormalities.²⁰ When OSA exists, therapy with continuous positive airway pressure (CPAP) is effective and usually results in a substantial improvement of daytime vigilance.²¹⁻²³ Therefore, a patient who has OSA and is regularly treated with CPAP at an optimal pressure is not expected to be severely sleepy, although some residual sleepiness may remain.²¹

Some recently published reports have suggested a potential association between narcolepsy and hypothalamic-pituitary dysfunction.^{8,24-26} Hypocretin (orexin) is a peptide neurotransmitter produced by

group of neurons located in the posterior and lateral hypothalamus that have projections to the neocortex, limbic system, and brainstem. Recently, reduced orexin levels have been found in the cerebrospinal fluid (CSF) of narcoleptic patients,^{26–29} and a hypersomnolent girl with decreased CSF hypocretin levels was described after removal of a hypothalamic tumor.³⁰ These findings suggest the possibility that surgical removal of hypothalamic tumor can result in defective production of orexin and consequently induce daytime somnolence. We therefore hypothesized that after resection of hypothalamic/pituitary tumors, children will display daytime somnolence, which may result from decreased orexin levels. The purpose of our study was to assess the frequency and severity of hypersomnolence in children after surgical removal of pituitary/hypothalamic space-occupying lesions and to examine potential factors that contribute to such excessive somnolence.

METHODS

Subjects

All charts of children who underwent surgical resection of craniopharyngiomas, germ cell tumors, or arachnoid cysts during 1992 to 2000 at Rambam Medical Center were reviewed. Six such patients were identified, and 5 agreed to participate. Two children were prepubertal (ages 11 and 12, both Tanner stage 1), and the remaining 3 were 15 (Tanner stage 3), 17.5 (Tanner stage 4), and 19 (Tanner stage 5) years of age. Five age-matched healthy control subjects were recruited via family and friends of the university personnel. The study was approved by the hospital's committee for human subject studies, and parental informed consent and child assent, in the presence of a parent, were obtained.

All participants completed a sleep questionnaire that included questions regarding their appetite and symptoms related to narcolepsy, and the Epworth Sleepiness Scale (ESS) questionnaire, which we have adapted for children (the item "falling asleep while driving a car" was changed to "falling asleep at school"). In this questionnaire, the chances of falling asleep in 8 different conditions has to be estimated at a scale of 0 to 3 in each condition, and the total score is the summation of the scores for the 8 items. An ESS score >12 was considered pathologic sleepiness.

All patients underwent a thorough endocrinologic evaluation, including clinical evaluation and blood samples for thyroid hormone (free thyroxine [FT4]) and prolactin levels. FT4 blood levels of 0.8 to 2.3 ng/dL and prolactin blood levels of 3 to 8 ng/mL for boys and 3 to 24 ng/mL for girls were considered normal. All children received adequate replacement treatment with cortisol, Eltroxin, and antidiuretic hormone.

Protocol

All participants underwent a structured clinical interview and physical examination and underwent overnight polysomnography in the sleep laboratory, followed by a multiple sleep latency test (MSLT). Children who were found to have OSA ($n = 2$) underwent an additional night to titrate optimal CPAP pressure, were then given CPAP for regular home usage, and were restudied 3 months later. In these 2 patients, only the results of the polysomnography and MSLT while receiving CPAP were considered for this study.

Polysomnography

Children were studied for at least 8 hours in a quiet, darkened room with an ambient temperature of 24°C and in the company of 1 of their parents. No medications were used to induce sleep. The following parameters were measured: chest and abdominal wall movement using piezoelectric electrodes, heart rate by electrocardiogram, and air flow monitored with a thermistor. Arterial oxygen saturation was assessed by pulse oximetry, with simultaneous recording of the pulse wave form. The bilateral electro-oculogram, 2 channels of electroencephalogram, (C3-A2 and O2-A1), chin and anterior tibial electromyograms, and analog output from a body

position sensor were also monitored. All measures were digitized using a commercially available polysomnography system (EEG 4214; Nihon Kohden, Kogyo Co, Tokyo, Japan). Tracheal sound was monitored with a microphone sensor, and video recording was performed.

Sleep was staged according to standard criteria.^{31,32} The time in bed (TIB) was defined as the time between lights off and lights on. Sleep latency (SL) was defined as the time from lights off to the first 3 minutes of stage 1 sleep, and sleep period time was defined as the time from falling asleep to lights on in the morning. Sleep efficiency was calculated as the percentage of total minutes of actual sleep out of TIB. Arousals were scored as any electroencephalogram shift for >3 seconds in non-rapid eye movement (REM) stages and during REM sleep as 3 seconds of electroencephalogram shifts accompanied by either increases in electroencephalogram or body movement. The "arousal index" was calculated as the number of arousals divided by the number of hours of sleep. Respiratory events were scored according to the common practice for measurement in children.^{32,33} The respiratory disturbance index was calculated as the number of apneas plus hypopneas divided by the number of hours of sleep.

MSLT

Objective sleepiness was assessed by the MSLT, which we have modified for children. All participants underwent an MSLT during the day after the whole-night sleep study, during which subjects were given 5 opportunities to fall asleep every 2 hours (0800, 1000, 1200, 1400, and 1600 hours). Because children are generally "more alert" compared with adults, the traditional 20-minute nap opportunities were extended to 30 minutes to avoid a ceiling effect and reduce the likelihood of missing any differences between the groups.³⁴ For every nap, subjects were requested to lie in bed in a dark, quiet, and comfortable room with no external stimulation. The parents were allowed to stay in the room. SL for each trial was measured from the time of lights out to the first period of sleep. If subjects did not fall asleep after 30 minutes, then the nap was terminated and SL for that nap was assigned a value of 30 minutes. If subjects fell asleep during the nap, then they were allowed 15 minutes to examine whether REM sleep occurred, at which point 1 minute of REM was permitted or the test was terminated. Scoring was in 30-second epochs. Daytime sleepiness (MSLT) was determined from the average of the 5 sleep latencies. Additional variables included the number of naps in which the subject fell asleep and the number of REM sleep occurrences.

Orexin Levels

Orexin levels were determined in a blinded manner in plasma and CSF of 4 patients and 3 control subjects. Blood (7 mL) was drawn into a tube that contained ethylenediaminetetraacetic acid and aprotinin (0.8 TIU/mL blood) and centrifuged for 15 minutes at 16 000 g at 4°C for plasma collection. CSF (5 mL) was transferred to tubes that contained aprotinin (0.8 TIU/mL CSF). Samples were frozen at -20°C until assayed by radioimmunoassay (RIA) based on the competition of ¹²⁵I-Orexin with the orexin peptide in the samples (RIA; Phoenix Pharmaceutical, Mountain View, CA). Samples were acidified with an equal volume of 1% trifluoroacetic acid, centrifuged, and applied to a C-18 SEP-column (Phoenix Pharmaceutical). Columns were washed twice with 1% trifluoroacetic acid, and peptide was eluted with 3 mL of 60% acetonitrile in 1% trifluoroacetic acid. Samples were dried, frozen at -20°C, and lyophilized overnight. Lyophilized samples were resuspended in 250 μL of RIA buffer, and 100 μL/sample was assayed in duplicates. ¹²⁵I-Orexin was reconstituted, adjusted to a concentration of 10 000 cpm/100 μL, added to the samples and standards, and incubated for 16 hours at 4°C. Goat anti-rabbit immunoglobulin G and normal rabbit serum were added, and samples were incubated at room temperature for 90 minutes. Tubes were centrifuged at 1700 g for 20 minutes, and pellets were counted using a γ-counter (Packard, Meriden, CT). Total counts (only ¹²⁵I-Orexin), nonspecific binding (¹²⁵I-Orexin with RIA buffer), and total binding (¹²⁵I-Orexin with RIA buffer, and primary antibody) were determined, and sample concentrations were determined from the "best fit" curve of B/B₀ versus the log of standard concentrations (0–128 pg/mL) and adjusted for the initial dilution factor (2.5).

Statistical Analysis

Variables of patients and control subjects were compared using unpaired 2-tailed Student *t* tests. Because 2 of the patients were significantly overweight compared with all other participants, they were excluded for an additional set of comparisons between the patients (nonoverweight) and control subjects. In addition, correlation analysis was performed to assess the relationships between body mass index (BMI), age, thyroid levels, and daytime sleepiness (MSLT score). *P* < .05 was considered statistically significant.

RESULTS

Of the 5 patients, 3 underwent surgery for craniopharyngioma, 1 for germ cell tumor, and 1 for a thalamic arachnoid cyst. The craniopharyngiomas and germ cell tumor were located in the hypothalamus-hypophysis region, and the arachnoid cyst was in the thalamic region. In all cases, there was complete resection and resolution of their tumors. All patients underwent a relatively extensive surgery involving the hypophysis and hypothalamus, and they all required hormone replacement therapy. All patients had normal FT4 and prolactin blood levels. Patients also received adequate replacement therapy for adrenocortical insufficiency consisting of 6 to 8 mg/m²/d cortisol. Patients had significantly higher BMI (3.15 ± 2.2 vs 0.17 ± 0.6 standard deviations above mean BMI for age; *P* = .02; Table 1), and this was primarily attributable to 2 morbidly obese patients. These 2 patients received a diagnosis of OSA and underwent a subsequent sleep study 3 months after initiation of CPAP therapy. Although treatment with CPAP resulted in complete resolution of their sleep-disordered breathing, no changes in daytime somnolence occurred.

Patients reported on the average 13.6 ± 1.1 hours of sleep per day, with "good night's sleep" yet daytime sleepiness and frequent naps. None reported narcoleptic symptoms (sleep paralysis, hypnagogic hallucinations, or cataplexy), and 2 of them reported increased appetite after the surgery.

Subjective sleepiness was assessed by the modified ESS (Table 2). Significantly greater subjective sleepiness was present in patients compared with control subjects (15.2 ± 2.8 vs 5.0 ± 2.0 ; *P* < .001). These differences were prominent both during situations such as sitting quietly after lunch and during a car ride and during classes in school.

TABLE 1. Demographic Data in 5 Patients and Matched Control Subject

	Gender	Age (Years)	BMI (kg/m ²)
Patients	M	15	34.9
	F	11	20.7
	F	12	21.9
	M	19	33.3
	F	17.5	27.1
Mean ± SD		15 ± 3	28 ± 6*
Control subjects	M	15	19.6
	F	11	16.4
	M	12	20.0
	M	19.5	21.8
	F	15.1	18.5
Mean ± SD		15 ± 3	19 ± 2*

SD indicates standard deviation.

* *P* < .05.

TABLE 2. Subjective Sleepiness Evaluation (Modified ESS) in 5 Patients and Matched Control Subjects

Question	Patients	Controls	<i>P</i>
Sitting and reading	1.6 ± 0.9	0.6 ± 0.6	.07
Watching TV	2.8 ± 0.4	1.8 ± 0.4*	<.05
Sitting inactive in a public place	1.8 ± 1.3	0.0 ± 0.0*	<.05
As a passenger in a car	2.8 ± 0.4	1.2 ± 0.8*	<.05
Lying down to rest in the afternoon	3.0 ± 0.0	1.4 ± 1.1*	<.05
Sitting and talking to someone	0.4 ± 0.9	0.0 ± 0.0	.3
Sitting quietly after lunch	2.0 ± 0.7	0.0 ± 0.0*	<.05
During class at school	0.8 ± 0.4	0.0 ± 0.0*	<.05
Total score	15.2 ± 2.8	5.0 ± 2.0*	<.05

* In 6 of the 8 situations and in the total score, patients had significantly greater subjective sleepiness.

Polysomnographic results of the nocturnal sleep study are presented in Table 3. TIB was significantly longer in the patient group than in the control group, with similar sleep efficiencies. Total sleep time (TST) tended to be longer in patients (*P* = .07), and they also had significantly longer sleep in stages 3 and 4 (approximately 2.5 hours vs 1.5 hours; *P* < .05; Table 3). The arousal index was similar in the 2 groups (16.8 ± 6.4 in the control group vs 13.0 ± 5.3 arousals per hour of sleep in the patient group; not significant).

Mean MSLT in the patient group was 10.3 ± 5.3 minutes and 26.2 ± 1.1 minutes in the control group (*P* < .005). The differences were significant in all but the first nap (Fig 1). Patients had sleep epochs in 4.4 ± 0.6 of the naps, whereas the control subjects fell asleep in only 1.6 ± 0.6 of the naps (*P* < .005). REM sleep occurred in 1.0 ± 1.7 of the naps in the patients compared with 0.4 ± 0.5 of the naps among the control subjects (not significant). There was no significant correlation between MSLT and BMI or age (*R* = -0.21 and *R* = -0.34, respectively; not significant). Even when the 2 morbidly obese patients were excluded, leading to normalization of BMI, patients were significantly sleepier during the day (MSLT: 11.3 ± 5.6 vs 26.2 ± 1.1 minute; *P* < .001). As a group, significant correlations between subjective sleepiness as assessed by the ESS and MSLT were noted (*R* = -0.77; *P* < .01; Fig 2). Within each group, however, the results of the MSLT and ESS did not correlate.

Four patients and 3 control subjects underwent CSF and blood measurement for orexin levels (Table 4). There were no significant differences between the

TABLE 3. Polysomnographic and MSLT Measures in 5 Patients and Matched Control Subjects

	Patients	Controls
TIB (min)	503.4 ± 31.2	433 ± 23.1*
TST (min)	417.5 ± 86.2	350.2 ± 43.4
SL (min)	17.5 ± 10.8	36.4 ± 26.4
Sleep efficiency (%)	82.5 ± 13.8	80.8 ± 7.7
Sleep efficiency of TST (%)	85.6 ± 14.8	88.1 ± 3.7
Stage 3-4 (min)	143 ± 43.7	79.5 ± 30.7*
Stage 3-4 (% of TST)	34.2 ± 7.5	23.2 ± 9.1
REM sleep (% of TST)	15.2 ± 4.3	19.6 ± 3.7
MSLT average SL (min)	10.3 ± 5.3	26.2 ± 1.1†

* *P* < .05.

† *P* < .0005.

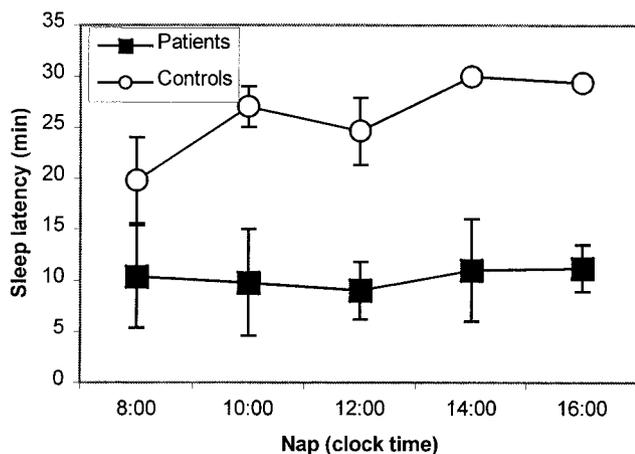


Fig 1. Average MSLT sleep latencies in 5 patients and matched control subjects. In all except the first nap (0800), patients had significantly shorter sleep latencies than control subjects ($P < .05$).

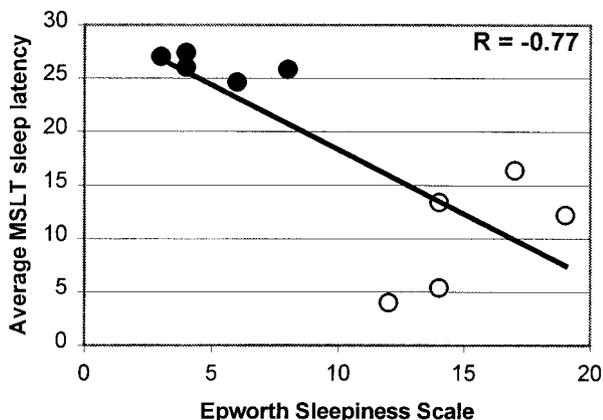


Fig 2. Correlation between ESS score (subjective sleepiness) and average SL on MSLT (objective sleepiness). ○, patients; ●, controls.

2 groups for either CSF or serum orexin levels. In addition, there were no correlations between the severities of daytime sleepiness and blood or CSF orexin levels ($R = -0.52$ and $R = 0.36$, respectively; not significant). Two of the patients complained of low back pain that lasted up to 1 month after the lumbar puncture.

DISCUSSION

In this study, we report that after surgical removal of a space-occupying lesion in the hypothalamic/pituitary region, children will commonly develop moderate to severe objective daytime sleepiness. However, the daytime sleepiness cannot be explained by sleep fragmentation or any other sleep disorders and is not accounted for by the presence of hormonal deficiencies or by decreased orexin levels.

One of the goals of our study was to assess the prevalence of sleepiness in children after hypothalamic/pituitary tumor removal. Because these tumors are relatively uncommon, we were able to identify only 6 candidates. Unfortunately, 1 of the patients refused to participate in the complete study. However, on the basis of her interview and ESS score (12), we can surmise that she was likely to have

TABLE 4. CSF and Blood Orexin Levels in 5 Patients and Matched Control Subjects

	CSF Orexin (pg/mL)	Blood Orexin (pg/mL)
Patients ($n = 4$)	127	15.6
	127	27.8
	154	6.2
	124	17.7
Mean \pm SD	133 ± 14	16.9 ± 8.9
Controls ($n = 3$)	147	2.6
	109	32.3
	79	32.3
Mean \pm SD	112 ± 34	22.4 ± 17.2

SD indicates standard deviation.

excessive daytime sleepiness. The remaining 5 patients all were hypersomnolent, both subjectively and objectively. Thus, daytime somnolence is extremely frequent in patients after this type of surgical intervention (100% in this study). In a retrospective clinical study, Duff et al¹ reported that 35 (29%) of 121 patients complained of lethargy, but in those who had poor outcome, 63% had a complaint of lethargy. On the basis of their criteria to assess outcome (ie, poor school achievements, disabilities, requirements for hormonal treatment, inability to find meaningful employment in the adult age), all of our participants had a poor outcome. Indeed, 1 patient died several months after the study, the 2 young adults are unemployed, and the 2 prepubertal children have poor school performance. In addition, all patients are on hormone replacement therapy. Thus, the extremely high frequency of daytime somnolence may account for these adverse outcomes in our cohort. However, that the number of participants in this study is small limits the ability to assess the true prevalence of sleepiness among individuals who undergo hypothalamic/pituitary surgery.

In this study, we used the ESS and MSLT to assess sleepiness. Patients' average ESS score was markedly higher than in control subjects, higher than that found in normal volunteers as reported in the literature (ESS score < 8), and compatible with those of sleepy populations.^{23,35-37} Although the ESS has not been validated in children, we believe that the significant differences between patients and control subjects indicate true subjective sleepiness. Before we discuss the MSLT findings, we must address a methodologic issue. Although the MSLT is currently considered the gold standard, it is infrequently used in children and will conventionally allow for a 20-minute nap opportunity.³⁸ However, preadolescent children are likely not to fall asleep within this time period, and therefore a 30-minute nap opportunity has been suggested.^{34,39,40} Because our patients' ages were heterogeneously distributed, we selected the 30-minute trials for all participants, thereby reducing the likelihood of missing a true difference between the index and control groups. In healthy prepubertal children, the average SL in the MSLT was reported at 23.7 minutes,³⁴ 23.5 minutes,⁴⁰ and 26.4 minutes,³⁹ and our control prepubertal subjects were no exception. Thus, the average SL of 5 and 16 minutes for the 2 prepubertal patients is clearly representative of

moderate to severe sleepiness in these children. Similarly, the 3 young adult patients had a mean SL of 9.9 minutes, compared with 25.5 minutes in the young adult control subjects, confirming their excessive sleepiness. Furthermore, there was a significant correlation between the subjective and objective sleepiness for the whole cohort (Fig 2), confirming some previous reports^{35,36} but not others.⁴¹ We should emphasize that the subjective and objective daytime somnolence of our patients was present despite similar nocturnal sleep (sleep architecture, sleep efficiency, and arousals from sleep) to that of control subjects and despite documented optimal treatment with thyroid and adrenal hormonal supplementation, suggesting that other mechanisms may underlie their excessive sleepiness.

We hypothesized that orexin deficiency, a wake-promoting neuropeptide, secondary to hypothalamic damage could mediate the excessive sleepiness of our patients. Indeed, narcolepsy has been associated with hypothalamic lesions,^{8,25} and low orexin levels were recently reported in narcolepsy.^{27,28} In addition, decreased CSF orexin levels were found after removal of a hypothalamic tumor from a hypersomnolent girl,³⁰ and a young man developed narcolepsy and low CSF orexin levels after an extensive hypothalamic stroke.²⁶ Finally, the number of orexin-expressing neurons is markedly reduced in human narcolepsy,⁴² and experimentally induced destruction of such neurons leads to a hypersomnolent state in rats.⁴³ Thus, on the basis of the aforementioned considerations, we anticipated that the excessive sleepiness in our patients after surgery in the hypothalamic region would be related to decreased orexin levels in their CSF. However, both serum and CSF orexin concentrations were similar in patients and control subjects. Furthermore, all individual orexin levels were within the same range, and none of the patients exhibited exceptionally low orexin levels in the CSF. This finding suggests that the posterolateral region of the hypothalamus was not functionally damaged. Also, none of our patients experienced cataplexy, which may be linked to low orexin levels more than sleepiness without cataplexy. Thus, it seems reasonable that the sleepiness of these patients is unlikely to be mediated by orexin deficiency. Nevertheless, caution should be taken in generalizing these findings because the sample size is relatively small. Several other potential mechanisms could also mediate excessive sleepiness in our patients. First, the radical neurosurgical procedure potentially could have damaged other wake-related regions such as the dorsal raphe, locus ceruleus, tuberomammillary nucleus, reticular formation, or basal forebrain. However, we are unable to assess this possibility objectively. Second, growth hormone (GH) deficiency may play a role in our patients' somnolence. Indeed, Astrom and Lindholm⁴⁴ have studied GH-deficient patients and found a greater need for extended TST compared with matched control subjects. Moreover, treatment with GH resulted in decreased TST and increased general "well-being."⁴⁵ In addition, Hayashi et al⁴⁶ reported that children with GH deficiency experience sleep disturbances and

speculated that nonrefreshing sleep may impinge on a favorable outcome. However, it should be mentioned that several other studies have reported contradicting results. For example, Tormey and Darragh⁴⁷ reported increased slow wave sleep, which further increased with GH administration in a dwarf. In addition, sleep-promoting effects have been ascribed to GH rather than promoting arousal.⁴⁸⁻⁵⁰ Thus, the role of GH in the excessive sleepiness of our children remains unclear. Only 1 of our patients received GH therapy. This patient reported on improved alertness and general "well being" on treatment but remained sleepy based on MSLT. Finally, obesity can play a substantial role in the sleepiness of patients after hypothalamic surgery. After resection of craniopharyngiomas, children will lose their ability to downregulate appetite, demonstrate abnormal food-seeking behavior, and rapidly gain weight.^{2,3,6,7,51,52} This can result in daytime somnolence either directly²⁰ or secondary to OSA.^{14,15,19} Our observation that in the 2 morbidly obese patients MSLT scores did not change significantly on documented optimal CPAP treatment suggests that their sleepiness was not caused by sleep-disordered breathing. Furthermore, the remaining 3 patients were average to mildly overweight, and sleepiness did not correlate with BMI, suggesting that obesity cannot solely explain their sleepiness. This is in agreement with other diseases of obesity such as the Prader-Willi syndrome, in which it has been shown that sleepiness remains primarily unaffected, even after weight reduction and improvement of sleep-disordered breathing.⁵³ However, because our control group consisted of primarily lean individuals, the differences in sleepiness may have been slightly enhanced. Thus, the lack of a control group consisting of obese individuals without brain surgery is a limitation of this study.

CONCLUSION

We demonstrate a high prevalence of daytime sleepiness in children after hypothalamic/pituitary resection of space-occupying lesions. This hypersomnolence does not seem to result from inappropriate cortisol or thyroxine hormonal balance and is not explained by disturbed nocturnal sleep, obesity, or low orexin levels in the serum or CSF. Future studies clearly are needed in these patients to elucidate potential mechanisms that mediate the regulation of sleep and wake in humans and their contribution to hypersomnolent states such as those induced by neurosurgical procedures.

REFERENCES

1. Duff JM, Meye FB, Ilstrup DM, Laws ER, Schleck CD, Scheithauer BW. Long-term outcomes for surgically resected craniopharyngiomas. *Neurosurgery*. 2000;46:291-305
2. Villani RM, Tomei G, Bello L, et al. Long-term results of treatment for craniopharyngioma in children. *Childs Nerv Syst*. 1997;13:397-405
3. Curtis J, Daneman D, Hoffman HJ, Ehrlich RM. The endocrine outcome after surgical removal of craniopharyngiomas. *Pediatr Neurosurg*. 1994; 21(suppl 1):24-27
4. Newman CB, Levine LS, New MI. Endocrine function in children with intrasellar and suprasellar neoplasms: before and after therapy. *Am J Dis Child*. 1981;135:259-266
5. Paja M, Lucas T, Garcia-Uria J, Salame F, Barcelo B, Estrada J. Hypo-

- thalamic-pituitary dysfunction in patients with craniopharyngioma. *Clin Endocrinol (Oxf)*. 1995;42:467–473
6. de Vile CJ, Grant DB, Hayward RD, Kendall BE, Neville BG, Stanhope R. Obesity in childhood craniopharyngioma: relation to post-operative hypothalamic damage shown by magnetic resonance imaging. *J Clin Endocrinol Metab*. 1996;81:2734–2737
 7. Roth C, Wilken B, Hanefeld F, Schroter W, Leonhardt U. Hyperphagia in children with craniopharyngioma is associated with hyperleptinaemia and a failure in the downregulation of appetite. *Eur J Endocrinol*. 1998;138:89–91
 8. Aldrich MS, Naylor MW. Narcolepsy associated with lesions of the diencephalon. *Neurology*. 1989;39:1505–1508
 9. Palm L, Nordin V, Elmqvist D, Blennow G, Persson E, Westgren U. Sleep and wakefulness after treatment for craniopharyngioma in childhood: influence on the quality and maturation of sleep. *Neuropediatrics*. 1992;23:39–45
 10. Sridhar GR, Madhu K. Sleep in young untreated hypothyroid subjects. *J Sleep Res*. 1996;5:198–199
 11. Ho KY, Evans WS, Thorner MO. Disorders of prolactin and growth hormone secretion. *Clin Endocrinol Metab*. 1985;14:1–32
 12. Grunstein RR, Sullivan CE. Sleep apnea and hypothyroidism: mechanisms and management. *Am J Med*. 1988;85:775–779
 13. Lin CC, Tsan KW, Chen PJ. The relationship between sleep apnea syndrome and hypothyroidism. *Chest*. 1992;102:1663–1667
 14. Grunstein R, Wilcox I, Yang TS, Gould Y, Hedner J. Snoring and sleep apnoea in men: association with central obesity and hypertension. *Int J Obes Relat Metab Disord*. 1993;17:533–540
 15. Redline S, Tishler PV, Schluchter M, Aylor J, Clark K, Graham G. Risk factors for sleep-disordered breathing in children. Associations with obesity, race, and respiratory problems. *Am J Respir Crit Care Med*. 1999;159:1527–1532
 16. Pillar G, Peled R, Lavie P. Recurrence of sleep apnea without concomitant weight increase 7.5 years after weight reduction surgery. *Chest*. 1994;106:1702–1704
 17. Schwartz AR, Gold AR, Schubert N, et al. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis*. 1991;144:494–498
 18. Browman CP, Sampson MG, Yolles SF, et al. Obstructive sleep apnea and body weight. *Chest*. 1984;85:435–438
 19. Grunstein RR, Wilcox I. Sleep-disordered breathing and obesity. *Baillieres Clin Endocrinol Metab*. 1994;8:601–628
 20. Vgontzas AN, Bixler EO, Tan TL, Kantner D, Martin LF, Kales A. Obesity without sleep apnea is associated with daytime sleepiness. *Arch Intern Med*. 1998;158:1333–1337
 21. Kribbs NB, Pack AI, Kline LR, et al. Effects of one night without nasal CPAP treatment on sleep and sleepiness in patients with obstructive sleep apnea. *Am Rev Respir Dis*. 1993;147:1162–1168
 22. Engleman HM, Martin SE, Deary IJ, Douglas NJ. Effect of CPAP therapy on daytime function in patients with mild sleep apnoea/hypopnoea syndrome. *Thorax*. 1997;52:114–119
 23. Engleman HM, Martin SE, Kingshott RN, Mackay TW, Deary IJ, Douglas NJ. Randomised placebo controlled trial of daytime function after continuous positive airway pressure (CPAP) therapy for the sleep apnoea/hypopnoea syndrome. *Thorax*. 1998;53:341–345
 24. Bassetti C, Aldrich MS, Quint DJ. MRI findings in narcolepsy. *Sleep*. 1997;20:630–631
 25. Malik S, Boeve BF, Krahn LE, Silber MH. Narcolepsy associated with other central nervous system disorders. *Neurology*. 2001;57:539–541
 26. Scammell TE, Nishino S, Mignot E, Saper CB. Narcolepsy and low CSF orexin (hypocretin) concentration after a diencephalic stroke. *Neurology*. 2001;56:1751–1753
 27. Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficiency in human narcolepsy. *Lancet*. 2000;355:39–40
 28. Nishino S, Ripley B, Overeem S, et al. Low cerebrospinal fluid hypocretin (Orexin) and altered energy homeostasis in human narcolepsy. *Ann Neurol*. 2001;50:381–388
 29. Dalal MA, Schuld A, Haack M, et al. Normal plasma levels of orexin A (hypocretin-1) in narcoleptic patients. *Neurology*. 2001;56:1749–1751
 30. Arii J, Kanbayashi T, Tanabe Y, Ono J, Nishino S, Kohno Y. A hyper-somnolent girl with decreased CSF hypocretin level after removal of a hypothalamic tumor. *Neurology*. 2001;56:1775–1776
 31. Rechtschaffen A, Kales A. *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. Los Angeles, CA: Brain Information Service/Brain Research Institute, UCLA; 1968
 32. American Thoracic Society. Standards and indications for cardiopulmonary sleep studies in children. *Am J Respir Crit Care Med*. 1996;153:866–878
 33. Kirk V, Kahn A, Brouillette R. Diagnostic approach to obstructive sleep apnea in children. *Sleep Med Rev*. 1998;2:255–269
 34. Gozal D, Wang M, Pope DW Jr. Objective sleepiness measures in pediatric obstructive sleep apnea. *Pediatrics*. 2001;108:693–697
 35. Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. *Sleep*. 1986;9:519–524
 36. Palm L, Persson E, Elmqvist D, Blennow G. Sleep and wakefulness in normal preadolescent children. *Sleep*. 1989;12:299–308
 37. Randazzo AC, Muehlbach MJ, Schweitzer PK, Walsh JK. Cognitive function following acute sleep restriction in children ages 10–14. *Sleep*. 1998;21:861–868
 38. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14:540–545
 39. Chervin RD, Aldrich MS, Pickett R, Guilleminault C. Comparison of the results of the Epworth Sleepiness Scale and the Multiple Sleep Latency Test. *J Psychosom Res*. 1997;42:145–155
 40. Guilleminault C, Yuen KM, Gulevich MG, Karadeniz D, Leger D, Philip P. Hypersomnia after head-neck trauma: a medicolegal dilemma. *Neurology*. 2000;54:653–659
 41. Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the Epworth sleepiness scale: failure of the MSLT as a gold standard. *J Sleep Res*. 2000;9:5–11
 42. Thannickal TC, Moore RY, Nienhuis R, et al. Reduced number of hypocretin neurons in human narcolepsy. *Neuron*. 2000;27:469–474
 43. Gerashchenko D, Kohls MD, Greco M, et al. Hypocretin-2-saporin lesions of the lateral hypothalamus produce narcoleptic-like sleep behavior in the rat. *J Neurosci*. 2001;21:7273–7283
 44. Astrom C, Lindholm J. Growth hormone-deficient young adults have decreased deep sleep. *Neuroendocrinology*. 1990;51:82–84
 45. Astrom C, Pedersen SA, Lindholm J. The influence of growth hormone on sleep in adults with growth hormone deficiency. *Clin Endocrinol (Oxf)*. 1990;33:495–500
 46. Hayashi M, Shimohira M, Saisho S, Shimozawa K, Iwakawa Y. Sleep disturbance in children with growth hormone deficiency. *Brain Dev*. 1992;14:170–174
 47. Tormey WP, Darragh AS. Increased slow wave sleep in a hypopituitary dwarf. *Postgrad Med J*. 1980;56:110–111
 48. Marshall L, Molle M, Boschen G, Steiger A, Fehm HL, Born J. Greater efficacy of episodic than continuous growth hormone-releasing hormone (GHRH) administration in promoting slow-wave sleep (SWS). *J Clin Endocrinol Metab*. 1996;81:1009–1013
 49. Kerkhofs M, Van Cauter E, Van Onderbergen A, Cautriez A, Thorner MO, Copinschi G. Sleep-promoting effects of growth hormone-releasing hormone in normal men. *Am J Physiol*. 1993;264:E594–E598
 50. Astrom C, Trojaborg W. Effect of growth hormone on human sleep energy. *Clin Endocrinol (Oxf)*. 1992;36:241–245
 51. Skorzewska A, Lal S, Waserman J, Guyda H. Abnormal food-seeking behavior after surgery for craniopharyngioma. *Neuropsychobiology*. 1989;21:17–20
 52. Sorva R. Children with craniopharyngioma. Early growth failure and rapid postoperative weight gain. *Acta Paediatr Scand*. 1988;77:587–592
 53. Harris JC, Allen RP. Is excessive daytime sleepiness characteristic of Prader-Willi syndrome? The effects of weight change. *Arch Pediatr Adolesc Med*. 1996;150:1288–1293

**Severe Hypersomnolence After Pituitary/Hypothalamic Surgery in Adolescents:
Clinical Characteristics and Potential Mechanisms**

Ayelet Snow, Evelyne Gozal, Atul Malhotra, Dov Tiosano, Rina Perlman, Céline Vega, Eli Shahar, David Gozal, Ze'ev Hochberg and Giora Pillar

Pediatrics 2002;110:e74

DOI: 10.1542/peds.110.6.e74

Updated Information & Services	including high-resolution figures, can be found at: http://www.pediatrics.org/cgi/content/full/110/6/e74
References	This article cites 49 articles, 22 of which you can access for free at: http://www.pediatrics.org/cgi/content/full/110/6/e74#BIBL
Citations	This article has been cited by 1 HighWire-hosted articles: http://www.pediatrics.org/cgi/content/full/110/6/e74#otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Neurology & Psychiatry http://www.pediatrics.org/cgi/collection/neurology_and_psychiatry
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.pediatrics.org/misc/Permissions.shtml
Reprints	Information about ordering reprints can be found online: http://www.pediatrics.org/misc/reprints.shtml

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

