Sleep-Disordered Breathing Is Increased in Obese Adolescents with Craniopharyngioma Compared with Obese Controls

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Context: Retrospective studies suggest that adolescents with craniopharygnioma and hypothalamic obesity have increased sleep-disordered breathing (SDB).

Objectives: The objectives of this study were to compare the prevalence of SDB in adolescents with craniopharyngioma-related obesity compared with body mass index (BMI)-matched controls and to explore possible relationships between SDB, insulin resistance, and adipocytokines.

Design: This was a cross-sectional study of obese craniopharyngioma and obese control adolescents.

Setting: Subjects were evaluated in the clinical investigation unit at the Hospital for Sick Children, Toronto.

Patients: Fifteen patients with craniopharyngioma-related obesity and 15 BMI-matched controls were recruited and tested.

Interventions: Each subject underwent fasting blood work, frequent sampled iv glucose tolerance test, polysomnography, and abdominal magnetic resonance imaging with calculation of visceral and sc adipose tissue.

Main Outcome Measures: Main measures included insulin sensitivity, sleep efficiency, and fragmentation.

Results: Insulin sensitivity was lower in craniopharyngioma subjects compared with control subjects (0.96 ± 0.34 *vs.* 1.67 ± 0.7, $P = 0.01$). Sleep-onset latency (19.3 ± 27.8 *vs.* 31.9 ± 23.4, $P = 0.03$) and oxygen saturations (rapid eye movement sleep: 89.0 ± 5.1 *vs.* 94.2 ± 2.3, $P < 0.001$; non-rapid eye movement sleep: 88.4 ± 5.6 *vs.* 94.3 ± 1.5, $P < 0.001$) were lower in craniopharyngioma. Obstructive apnea-hypopnea index (OAHI) (7.5 ± 9.0 *vs.* 1.5 ± 1.5, $P = 0.03$) was higher in craniopharyngioma. Respiratory distress index and OAHI correlated negatively with adiponectin concentrations ($r = -0.61$, $P = 0.03$, $r = -0.71$, $P = 0.006$, respectively) in craniopharyngioma. On multiple regression, TNF-α and craniopharyngioma were independent positive predictors of sleep-onset latency and adiponectin and craniopharyngioma were significant predictors (negative and positive, respectively) of OAHI.

Conclusions: SDB is increased in adolescents with craniopharyngioma-related obesity compared with BMI-matched controls. Routine polysomnography should be considered in obese patients with craniopharyngioma and appropriate treatment initiated. **(*J Clin Endocrinol Metab* 95: 2211–2218, 2010)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2009-2003 Received September 18, 2009. Accepted February 26, 2010.
First Published Online March 23, 2010
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Abbreviations: BMI, Body mass index; CAI, central apnea index; CPAP, continuous positive airway pressure; CV, coefficient of variation; FSIGT, insulin-modified frequent sampling iv glucose tolerance test; MRI, magnetic resonance imaging; NREM, non-rapid eye movement; OAHI, obstructive apnea hypopnea index; OSA, obstructive sleep apnea; PSG, polysomnography; RDI, respiratory disturbance index; REM, rapid eye movement; SaO_2, oxygen saturations; SAT, sc adipose tissue volume; SDB, sleep-disordered breathing; SDS, SD score; Si, insulin sensitivity; SOL, sleep onset latency; TST, total sleep time; VAT, visceral adipose tissue volume; WC, waist circumference.

Sleep-disordered breathing (SDB), specifically obstructive sleep apnea (OSA) is common, occurring in 1–4% of healthy children (1). Estimates of the prevalence of OSA in obese children vary from 13 to 60%, depending on the definitions of OSA and obesity (2). Evidence suggests that insulin resistance is positively associated with SDB in adolescents (3). A pediatric study showed a positive correlation between fasting insulin and the respiratory disturbance index (RDI), a measure of sleep fragmentation (4). Furthermore, a retrospective review suggested an association between lower total sleep time (TST) and insulin resistance (5).

Sleep is complex and its physiological regulation is multifactorial. The cytokines, IL-6 and TNFα, are involved in physiological sleep regulation and correlate positively with the obstructive apnea-hypopnea index (OAHI; a measure of sleep fragmentation) in obese adults (6). Administration of exogenous IL-6 to adults results in increased sleepiness and fatigue (7). IL-6 and TNF-α are elevated in adults with either SDB or obesity (8). The adipocyte-derived proteins (adipokines) leptin and adiponectin play a role in energy homeostasis and insulin sensitivity (Si) (9). Leptin is secreted in proportion to adipose mass and is elevated in obesity. However, hyperleptinemia fails to suppress appetite or increase metabolic rates, presumably due to central nervous system leptin resistance (9). Leptin is increased in pediatric OSA, independent of the body mass index (BMI) (10). Adiponectin, an insulin sensitizer, is decreased in obesity (9). To date, adiponectin levels have not been correlated with SDB independently of obesity (10, 11). Furthermore, sleep abnormalities coexist frequently with cardiovascular disease, may activate pathways that cause or aggravate cardiovascular damage, or may cause resistance to conventional antiobesity therapies (12).

A primary hypothalamic function is to regulate the sleep-wake cycle. Hypothalamic damage, complicated by obesity, temperature, and sleep dysregulation and pituitary hormone deficiency, occurs commonly after treatment for pituitary or hypothalamic tumors, including craniopharyngioma (13). The literature evaluating SDB in this population is sparse. One questionnaire-based study reported frequent sleep abnormalities in craniopharyngioma (14). A prospective study in pediatric craniopharyngioma included three patients and identified increased SDB by questionnaire and polysomnography (PSG) (15). Our clinical experience is that patients with craniopharyngioma and hypothalamic obesity complain commonly of specific disturbed sleeping patterns, including difficulty falling asleep, nocturnal waking, and extreme sleepiness during the afternoon. Furthermore, adolescents with craniopharyngioma are at increased risk for metabolic abnormalities, including dyslipidemia, increased insulin resistance, and the metabolic syndrome (16, 17), which could exacerbate or contribute to SDB. Given the hypothalamic disturbances in craniopharyngioma patients, it is possible that they exhibit more SDB than otherwise healthy children of similar weight.

Aims

The aims of this study were to compare incidence of SDB and explore the relationships between SDB, Si, and inflammatory cytokines in adolescents with craniopharyngioma and hypothalamic obesity and age- and BMI-matched controls. We hypothesized that patients with craniopharyngioma would have more SDB than BMI-matched controls.

Methodology

Our institutional ethics review board approved this protocol. Inclusion criteria for craniopharyngioma subjects included craniopharyngioma diagnosed at least 1 yr before study participation and adequate replacement of all pituitary hormone deficiencies. Controls, recruited from a weight management clinic, were otherwise healthy and age, BMI, and gender matched to craniopharyngioma subjects. Exclusion criteria included: use of medications that might alter lipid levels, Si, or adiposity; respiratory abnormalities that might preclude interpretation of sleep studies; or known sleep abnormalities. Craniopharyngioma subjects took their usual hormone replacement medications before study participation.

At study initiation, each subject was admitted to the clinical research center for physical examination with anthropometrics, performed by a single examiner. Height and weight were measured using a wall-mounted stadiometer and a calibrated scale, respectively. BMI was calculated as weight (kilograms)/height^2 (square meters). BMI SD scores (SDS) were calculated using a program from the Centers for Disease Control and Prevention web site (18). Waist circumference SDS was calculated using published normal values (19).

Fasting blood samples were taken for baseline laboratory evaluation (including glucose, insulin, leptin, adiponectin, IL-6, TNFα). Insulin-modified frequent sam-

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pling iv glucose tolerance test (FSIGT) was performed after an overnight fast (20–22). Via an iv antecubital cannula, 0.3 g/kg of 25% dextrose, followed 20 min later by 0.03 U/kg of regular insulin (Humulin R; Eli Lilly, Indianapolis, IN), was injected. Thirty-four blood samples for glucose and insulin were taken over 3 h from the contralateral arm. The mathematical model of Bergman (minimal model) (23) using MINMOD computer software (MINMOD Millennium, Version 5.18, MINMOD, Inc., Pasadena, CA) and data from FSIGT was used to calculate Si (minutes^{-1} per milliunit^{-1} per milliliter^{-1}).

During a second admission, each subject had overnight PSG for evaluation of sleep abnormalities, supervised by trained pediatric sleep technologists in the sleep medicine laboratory. Every PSG was performed in a quiet, darkened room, without the use of sleep-inducing medications, with one parent present, and was interpreted by a single pediatric sleep medicine physician.

All PSGs were conducted and scored according to the American Academy of Sleep Medicine manual for scoring sleep and associated events (24) with a computerized system (XL-TEK, Oakville, Ontario, Canada). A standard overnight PSG included a 4-lead electroencephalogram (C3, C4, O1, and O2), two bilateral electrooculogram leads referenced to A1 or A2, and one submental and two tibial electromyograms. Respiratory measurements included chest wall and abdominal movement using inductance pneumography; airflow using a nasal cannula connected to a nasal pressure airflow; oxygen saturation (SaO_2); and transcutaneous carbon dioxide measurements. Video and audio recordings were obtained for each study. Sleep architecture was assessed by standard techniques (25). Information obtained from each PSG included sleep onset latency (SOL) and rapid eye movement sleep (REM)-onset latency, TST, sleep efficiency, time spent in each sleep stage (minutes and percentage), and the number of arousals. Recorded respiratory data included counts and indices of the following events: obstructive apneas and hypopneas (OAHI), central apneas [central apnea index (CAI)], and mixed apneas recorded in non-REM (NREM) sleep, REM sleep, and total sleep.

An obstructive apnea event was scored when airflow dropped at least 90% from baseline with chest and/or abdominal motion throughout the entire event, the duration of which was at least a minimum of two baseline breaths. An obstructive hypopnea event was scored when airflow dropped at least 50% from baseline, the duration of which was at least a minimum of two baseline breaths. The event must have been accompanied by one of the following: 1) 3% or greater drop in SaO_2; 2) an arousal; or 3) an awakening (24). A central apnea was defined as a cessation of airflow with an absence of respiratory and abdominal effort for 20 sec or longer or of the duration of two prior baseline breaths in which case the event must be accompanied by one of the following: 1) 3% or greater drop in oxygen saturation; 2) an arousal; or 3) an awakening.

Definitions

OSA severity was graded using current clinically accepted criteria according to the OAHI, the number of obstructive apneas, and obstructive hypopneas per hour during sleep. OAHI less than 1.5 was normal. OSA was defined as: mild, OAHI greater than 1.5–5; moderate, greater than 5–10; and severe, greater than 10. CAI was defined as the number of central apneas per hour during sleep; more than 1.0 per hour was abnormal. SOL was defined as the length of time in minutes from lights out to the first epoch of sleep. TST was defined as the sum of all the minutes spent in all stages of sleep or the total time in bed minus all time spent awake during the study. Sleep efficiency was defined as TST divided by the time in bed multiplied by 100. RDI was defined as the total number of apneas, hypopneas, and arousals per hour. The arousal index was defined as the number of arousals per hour. Sleep fragmentation is associated with a high arousal index, increase in wakefulness during the night, and an increase in stage 1 sleep (typically 5–10%).

Visceral and sc adipose tissue volumes (VAT and SAT) were measured in each subject using abdominal magnetic resonance imaging (MRI) (General Electric Twin Speed EXCITETM III 12.0 1.5 Tesla; GE Healthcare, Milwaukee WI), using previously published methodology (26).

Biochemical analyses

Insulin was measured by chemiluminescence using the Immulite 2500 [Siemens, Melvern, PA; range of assay 15–2165 pmol/liter, intra- and interassay coefficient of variation (CV) $< 7.6\%$]. Leptin and adiponectin were measured by ELISA (Diagnostics Systems Laboratories Inc., Webster, TX; range 0.1–50.0 ng/ml; interassay CV 1.5–6.2%; and Linco Research Inc., St. Charles, MO; range 1–100 mg/liter; CV 2.4–8.4%, respectively). IL-6 and TNFα were measured using chemiluminescence (Siemens Immulite 1000; range: 2–1000 pg/ml; CV $< 7.5\%$; and range 1.7–1000 pg/ml; CV $< 6.5\%$, respectively).

Statistical analysis

Statistical analysis was performed using SAS software (SAS version 8.2, 1999; Cary, NC). Continuous variables were expressed as means $\pm$ SDs. Categorical variables were expressed as frequencies. Comparisons between groups were performed using the Fisher's exact test and χ^2 analysis for categorical parameters and Student's *t* test for con-

tinuous variables, with Bonferroni correction for multiple comparisons. Data distribution was first assessed using simple measures of central tendencies and completed by performing Shapiro-Wilk's test for normality. Log transformations were performed on nonnormative variables and then compared by Student's *t* test. Pearson correlation analyses were performed between measures of SDB and measures of Si and cytokines. Multiple regression analysis was performed using factors significant on univariate regression, with only three variables entered (due to the small number of subjects).

Results

Of 43 children who had surgery for craniopharyngioma and were followed up at our institution, 22 developed postoperative obesity, defined as BMI greater than the 95th percentile for age and gender (13). Sixteen (77.3%) consented to participate; one was subsequently excluded after starting metformin therapy. Therefore, we enrolled 15 children aged 10–21 yr. No subject had received radiotherapy. We also enrolled 15 age-, sex-, and BMI-matched children with exogenous obesity. However, craniopharyngioma children had higher waist circumference (WC) and WC-SDS than controls (Table 1).

Craniopharyngioma subjects had multiple pituitary hormonal insufficiencies but were receiving adequate replacement therapies including: 14 of 15 treated with desmopressin for diabetes insipidus; 14 of 15 treated with hydrocortisone (dose range 8–12 mg/m^2 · d); 14 of 15 treated with levothyroxine (free T_4 levels on treatment 14.5 ± 2.6 pmol/liter); and eight of 15 treated with sc GH (all for more than 12 months). Craniopharyngioma subjects were treated with GH if they were both GH deficient and had growth failure and with sex steroid replacement therapy if they had hypogonadism biochemically and clinically. Of seven of 15 patients GH untreated, five of seven had normal growth without GH, and two of seven had completed their growth and were postpubertal at the time of diagnosis with craniopharyngioma. Five patients received hormone replacement therapy for hypogonadotrophic hypogonadism. No control was receiving medication.

The duration of follow-up from diagnosis of craniopharyngioma to assessment was 4.9 ± 3.0 yr and correlated positively with both BMI (r = 0.58, $P = 0.02$) and BMI SDS (r = 0.64, $P < 0.01$). All craniopharyngioma subjects had evidence of hypothalamic damage on neuroimaging after tumor resection. Time between each of the two visits was 4.6 months (range 0–11) in the craniopharyngioma group and 3.0 months (range 0–8) in controls.

After their initial PSG, two craniopharyngioma subjects required initiation of nocturnal continuous positive airway pressure (CPAP) therapy. Their untreated PSG results are reported here. No control required CPAP initiation.

Si from FSIGT data was significantly lower in craniopharyngioma subjects compared with controls (0.96 ± 0.34 *vs.* 1.67 ± 0.7, $P = 0.01$) (Table 1). TNFα was statistically higher in craniopharyngioma compared with controls, with no difference in IL-6 (Table 1). On abdominal MRI, there were no differences between groups in the volumes of SAT (craniopharyngioma 501.2 ± 155.4, controls 480.3 ± 185.5, $P = 0.77$), VAT (craniopharyngioma, 85.1 ± 40.5; controls, 67.5 ± 29.5, $P = 0.25$) or

TABLE 1. Comparison of patient demographics and biochemical measures between groups

Demographics	Craniopharyngioma	Control	*P* value
Age (yr)	15.5 ± 4.0	15.1 ± 2.3	0.77
Sex (females, males)	8, 7	10, 5	0.72
Height (cm)	159.5 ± 14.6	165.0 ± 8.8	0.22
Weight (kg)	91.2 ± 29.3	91.9 ± 18.0	0.94
BMI (kg/m^2)	35.2 ± 8.0	33.5 ± 4.9	0.49
BMI SDS	2.2 ± 14.6	2.1 ± 0.3	0.53
Tanner stage (I–V) (median)	3	4	0.07
SAT volume (cm^3)	501.2 ± 155.4	480.3 ± 185.5	0.77
VAT volume (cm^3)	85.1 ± 40.5	67.5 ± 29.5	0.25
VAT to SAT ratio	0.18 ± 0.08	0.16 ± 0.09	0.38
WC (cm)	122.1 ± 27.5	102.2 ± 11.5	0.02
WC SDS	7.3 ± 3.0	5.1 ± 1.8	0.04
Biochemical measures			
Adiponectin (mg/liter)	10.6 ± 5.4	8.4 ± 1.8	0.13
Leptin (ng/ml)	116.7 ± 93.9	99.6 ± 69.6	0.47
IL-6 (pg/ml)	3.0 ± 1.2	3.1 ± 3.1	0.86
TNFα (pg/ml)	5.8 ± 2.3	3.9 ± 1.4	0.01
Si (FSIGT) ($\times 10^{-4}$/min^{-1} · μIU · ml)	0.96 ± 0.34	1.67 ± 0.70	0.01

Data given are means ± SD, except where indicated.

TABLE 2. Sleep measures

	Craniopharyngioma	Control	*P* value
SOL (min)	19.3 ± 27.8	31.9 ± 23.4	0.03
TST (min)	392.6 ± 59.3	350.4 ± 54.1	0.08
Sleep efficiency (%)	82.7 ± 14.9	90.5 ± 11.1	0.83
REM latency (min)	164.3 ± 97.8	136.5 ± 47.1	0.37
Sleep stage 1 (% of TST)	4.6 ± 2.5	4.7 ± 3.3	1.00
Sleep stage 2 (% of TST)	48.7 ± 9.4	57.0 ± 9.7	0.04
Slow wave sleep (% of TST)	28.3 ± 11.0	23.9 ± 5.6	0.10
Sleep REM stage (% of TST)	17.6 ± 5.0	15.0 ± 5.0	0.20
Mean SaO_2 (% in REM)	89.0 ± 5.1	94.2 ± 2.3	<0.001
Mean SaO_2 (% in NREM)	88.4 ± 5.6	94.3 ± 1.5	<0.001
Minimum SaO_2 (%)	86.3 ± 5.9	93.6 ± 2.1	0.0005
Highest CO_2 (mm Hg)	50.8 ± 8.1	42.9 ± 13.5	0.10
RDI	18.1 ± 13.8	12.3 ± 7.1	0.38
OAHI	7.5 ± 9.0	1.5 ± 1.5	0.03
CAI	0.99 ± 1.5	0.22 ± 0.31	0.06

Data given are means ± SD.

VAT to SAT ratios (craniopharyngioma, 0.18 ± 0.08; controls, 0.16 ± 0.09, $P = 0.38$).

Sleep indices (Table 2)

SOL was significantly lower in craniopharyngioma and TST trended toward longer, suggesting that craniopharyngioma subjects fall asleep quicker and remain asleep longer. OAHI was significantly higher in craniopharyngioma subjects. All 13 obese controls had either normal or mild OAHI (*i.e.* fewer than five episodes per hour) compared with seven of 13 craniopharyngioma subjects. Of the remaining six craniopharyngioma subjects, two had moderate and four had severe OAHI. There was no significant difference in RDI, percentage time in slow wave sleep, or sleep efficiency index between groups. Mean SaO_2 was lower in craniopharyngioma than control in both REM and NREM sleep. Minimum SaO_2 was lower in craniopharyngioma than controls. Craniopharyngioma and control subjects spent similar times in stage 1 sleep, but craniopharyngioma subjects had significantly shorter percentage of time in stage 2 sleep.

Whereas there were no differences found between subjects with craniopharyngioma who were GH treated or GH untreated, in OAHI (GH treated, 3.9 ± 5.6; GH untreated, 13.3 ± 11.0, $P = 0.17$) or RDI (GH treated, 14.0 ± 10.5; GH untreated, 24.8 ± 16.9, $P = 0.22$), with the relatively small number of subjects, it was unlikely such a difference could be identified.

SOL correlated positively with Si ($r = 0.79$, $P = 0.03$) and leptin ($r = 0.63$ $P = 0.02$) in the craniopharyngioma group. SOL showed no significant correlations in the control group. TST correlated positively with IL-6 ($r = 0.55$, $P < 0.01$) in the control group. OAHI correlated negatively with adiponectin and WC in craniopharyngioma subjects ($r = -0.7$, $P = 0.01$, and $r = 0.7$, $P = 0.03$, respectively) (Fig. 1) but showed no significant correlation in controls. RDI correlated negatively with adiponectin in craniopharyngioma subjects ($r = -0.61$, $P = 0.03$) (Fig. 1) but did not show significant correlations in controls. In craniopharyngioma subjects, after controlling for WC and WC-SDS, respectively, adiponectin correlated well with each of OAHI ($r = -0.70$, $P = 0.006$; $r = -0.71$, $P = 0.007$), CAI ($r = -0.92$, $P = 0.06$; $r = -0.85$, $P = 0.07$), and RDI ($r = -0.076$, $P = 0.008$; $r = -0.74$, $P = 0.009$).

TNFα predicted negatively and craniopharyngioma predicted positively SOL ($t = -0.32$, $P < 0.001$; $t = 1.0$, $P = 0.02$, respectively). Adiponectin predicted negatively and craniopharyngioma predicted positively OAHI ($t = -4.5$, $P < 0.001$; $t = 4.4$, $P < 0.001$, respectively). Si was not a significant predictor on multiple regression.

Discussion

Our data suggest that adolescents with craniopharyngioma-related obesity have more SDB than obese, otherwise healthy, BMI-matched adolescents. This is evidenced by increased OAHI and a trend toward increased CAI in the craniopharyngioma group, suggesting more sleep fragmentation and less sleep efficiency. They also exhibit decreased SOL and a trend toward increased TST, suggesting

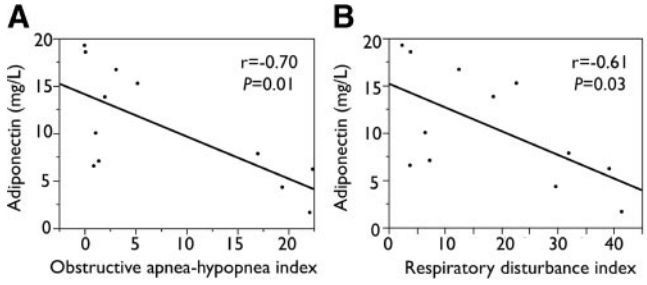

FIG. 1. A, Plot of adiponectin against OAHI. B, Plot of adiponectin against RDI.

more sleepiness in craniopharyngioma subjects. In particular, obese craniopharyngioma subjects exhibit more obstructive episodes and lower SaO_2 during both REM and NREM sleep than BMI-matched controls. These data suggest that the mechanism of obesity, not just the degree of obesity, may affect SDB. TNFα and diagnosis of craniopharyngioma are independent positive predictors of shorter SOL. Additionally, lower adiponectin and craniopharyngioma group predict higher OAHI.

To our knowledge, adiponectin levels have not previously been found to correlate with SDB independently of BMI or other measures of adiposity. Physiologically, adiponectin potentiates sensitivity to insulin peripherally. Recently adiponectin receptors have been identified in the periventricular nuclei and area postrema in mice models, in which their central effects include reduction of body fat, glucose, and lipids (27). Thus, adiponectin may play a role in SDB. IL-6 did not emerge as a significant predictor of SDB on multiple regression analyses. This is consistent with recent data suggesting that obesity, not SDB, is the major risk factor for insulin resistance (28), with a recent study that found no difference in IL-6 between groups with similar BMI but differed in the presence or absence of SDB (29). We found higher TNFα levels in patients with more SDB (as measured by lower sleep onset latency.) The interrelationship between TNFα and SDB is complex, and the cause and direction of the association are unclear (11). Sleep deprivation alone results in increased TNFα and IL-6, whereas TNFα is itself a hypnotic (30). Both SDB and obesity are inflammatory states associated with increased TNFα levels. One study suggests that TNFα levels are increased in SDB and that the level of TNFα correlates positively with both the degree of sleepiness and the severity of hypoxia (31). Our study supports these findings because we identified a significant positive relationship between TNFα and shorter SOL in this obese population.

Obesity contributes potentially to SDB via several potential mechanisms. First, both obesity and SDB are systemic inflammatory disorders. Second, impaired Si is associated with sleep disturbances (3). Third, increased sc tissue in the neck increases the risk of obstructive sleep apneas (32). Fourth, increased WC in the craniopharyngioma group, with implied increased intraabdominal fat accumulation, could also lead to SDB. However, adiponectin, when controlled for WC, still correlated significantly with measures of SDB, suggesting that factors other than visceral adiposity mediate alterations in SDB via Si. It is possible that in patients with craniopharyngioma, adiponectin is affected more by dysregulated insulin secretion through, for example, increased vagal tone, than it is affected by visceral adiposity. All four etiologies could contribute to SDB in patients with hypothalamic obesity.

An additional mechanism that may contribute to SDB in craniopharyngioma subjects is sleep disturbance and central apnea due to hypothalamic damage. Several hypothalamic nuclei, including the suprachiasmatic nuclei (which control the circadian drive to wakefulness) (33) and the ventrolateral preoptic nuclei (which control the homeostatic drive to sleep) (34), are responsible for regulation of sleep. The circadian rhythm is the result of a complex interaction between circadian and homeostatic processes (34). Specifically important in SDB and hypothalamic damage, three sets of hypothalamic nuclei are situated close to each other: those involved in sleep and wake regulation; those responsible for the release of pituitary-controlling releasing hormones; and those that produce and store hormones released by the posterior pituitary. Thus, damage to one of these nuclei groups may coexist with damage to neighboring nuclei.

Our study did not attempt to determine the physiological reasons for SDB in craniopharyngioma. Furthermore, the craniopharyngioma subjects in this study all had hypothalamic damage based on MRI. In subjects with craniopharyngioma but without hypothalamic obesity, the results of sleep studies may be different. Correlation of specific areas of hypothalamic damage to sleep parameters would be interesting, but the neuroimaging of our craniopharyngioma subjects are not sensitive enough to define which specific hypothalamic areas and nuclei are affected. This problem has been acknowledged previously (15). In the future, however, with advancing neuroimaging techniques, identification of these regions may be easier.

Pituitary hormone deficiencies also potentially increased SDB in craniopharyngioma in this study. Although all craniopharyngioma patients had adequate hormone replacement, there are possibly differences between prescribed hormone replacement therapies and hormone levels altered by autoregulation and feedback mechanisms. Also, the close proximity of sleep nuclei and pituitary hormone nuclei implies that damage to both nuclei groups might occur simultaneously. Further studies should evaluate this. We did not identify any association between GH deficiency and SDB. Previous studies have identified longer TST and less deep sleep in GH-deficient patients and decrease in TST after GH replacement (35). Furthermore, GH replacement in GH-deficient individuals has been associated with improved qualify of life (36). It is possible that we did not find any associations because GH was adequately replaced in many of the craniopharyngioma subjects. For those not receiving GH therapy but who may have been GH deficient, it may have been too early in their course to pick up major differences in sleep related to GH deficiency, although there were too few subjects in our study to realistically examine this question.

A study of sleep abnormalities in five pediatric patients with hypothalamic-pituitary obesity (three of five had craniopharyngioma) and five age- but not BMI-matched controls described more subjective sleepiness, more inefficient sleep (as measured by stage 3–4 sleep), and lower mean sleep length in patients with hypothalamic obesity (15). This study did not measure Si or adipokines (15). A retrospective case series, in which subjects were not matched with controls, identified increased TST and decreased SaO_2 in subjects with central nervous system tumors (37). The worst sleep abnormalities were identified in subjects with pituitary or hypothalamic abnormalities (37).

The type of central nervous system tumor might impact the severity of SDB. For example, a study using questionnaire assessments of sleep identified severe sleepiness in 35% of 79 children with craniopharyngioma and 15% of 19 children with pilocytic astrocytomas (14). No objective assessment of sleep abnormalities was performed, and there was no healthy control group. Another questionnaire study, in an adult population, identified increased subjective sleepiness and increased snoring in patients with either craniopharyngioma or nonfunctioning macroadenomas, compared with healthy controls (38). Sleep abnormalities were not assessed objectively.

To our knowledge, this is the largest study to date addressing SDB in a pediatric population with craniopharyngioma and hypothalamic dysregulation. Furthermore, our craniopharyngioma and control populations were age, gender, and BMI matched, suggesting that differences between the two groups are due to craniopharyngioma and hypothalamic damage. Additionally, we included craniopharyngioma and control subjects without prior screening with sleep questionnaires. Sleep questionnaires have not been found to accurately reflect SDB as detected by sleep studies assessments (39). However, measurements of neck circumference, which is a validated correlate of SDB in adult populations (32), might have helped to distinguish OSA related to oropharyngeal sc fat deposition from central sleep apneas. We acknowledge that our sample size was relatively small. However, craniopharyngioma with hypothalamic dysregulation is a rare disease, and this is one of the largest studies of this population to date.

Longitudinal sleep and metabolic studies will be required to establish the onset, etiology, and causation of SDB in craniopharyngioma. For example, sleep studies performed before surgery and the postoperative period of rapid weight gain (13) might identify the natural course of this disorder. Craniopharyngioma patients are at increased of cardiovascular disease (40), and the coexistence of SDB may further compound this risk. Common pathways of inflammation may increase endothelial dysfunction and cardiovascular risk as well as impact on SDB (12). Future studies to include evaluation of early endothelial dysfunction in relation to other metabolic and sleep parameters should address this question.

Conclusion

This study demonstrates that SDB is common among patients with hypothalamic dysregulation and obesity after craniopharyngioma treatment and that SDB in this group is more common than in an age-, gender-, and BMI-matched population. Two of 15 subjects required intervention with CPAP after the sleep assessment, indicating an unrecognized sleep disorder. We suggest that clinicians should consider performing routine PSGs in all patients with craniopharyngioma and hypothalamic dysregulation. Further multicenter studies will be required to evaluate longitudinally the potential effects of SDB treatment on weight gain, and metabolic parameters.

Acknowledgments

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This work was supported by a Hospital for Sick Children Research Institute seed grant. J.H. is supported through a Novo Nordisk Young Investigator Career Development award. J.S.-R. was supported by a fellowship from the Canadian Pediatric Endocrine Group.

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Disclosure Summary: The authors have no disclosures to make.

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