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Pituitary diseases: long-term clinical consequences

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Chapter 17

Patients cured from craniopharyngioma or non-functioning pituitary macroadenoma suffer similarly from increased daytime somnolence despite normal sleep patterns compared to healthy controls

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ABSTRACT

Objective

Adults patients previously treated for craniopharyngioma have increased general and physical fatigue compared to healthy controls. This could be related to disturbed sleep patterns. The aim of this study was to compare sleepiness and sleep patterns in those patients to healthy controls and to patients treated for non-functioning macroadenomas (NFMA) of the pituitary.

Design

Case-control study.

Patients and methods

Sleepiness and sleep patterns were assessed in 27 adult patients (14 men, 8 patients diagnosed at childhood age, mean age of 53 years (range 27-80 yrs)) after long-term follow up and compared to 50 healthy controls and 38 age-, gender- and BMI matched patients with NFMA. We used two validated questionnaires for sleep parameters (Epworth sleepiness score and Münchener Chronotype Questionnaire).

Results

Sleep patterns (onset, sleep timing, duration, and rise time) were not statistically different between the three groups. However, daytime sleepiness scores were increased in patients treated for craniopharyngioma compared to healthy controls, but not different from patients with NFMA. Thirty-three percent of patients with craniopharyngiomas had ESS scores above 10 compared to 8% of healthy controls (p=0.005), indicating severe daytime hypersomnolence. Neither type of surgery, previous radiotherapy, or age at diagnosis influenced the sleepiness scores in patients with craniopharyngioma.

Conclusion

Patients treated for craniopharyngioma or NFMA have increased daytime somnolence despite normal sleep patterns, compared to healthy subjects. The results indicate that increased daytime somnolence is a general consequence of large tumors, and/or their treatment, in the hypothalamic/pituitary region, rather than a specific feature of craniopharyngiomas per se.

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INTRODUCTION

Craniopharyngiomas are rare benign tumors arising along the path of the craniopharyngeal duct. Most of these tumors are located in the sellar and parasellar region (1). The presenting symptoms are dependent on the proximity to, and pressure on, structures of the brain. Craniopharyngiomas most frequently present with headaches, nausea/vomiting, visual disturbances, and hypothalamo-pituitary hormone deficiencies (reviewed in (1)). Craniopharyngiomas are treated primarily by transsphenoidal and/or transcranial surgery, with success rates of radical surgery ranging from 18 to 84% (1). Therefore, adjuvant radiotherapy may be necessary in selected patients in whom surgery was not completely successful (1). Nonetheless, craniopharyngiomas and/or their treatment are associated with impaired quality of life (2;3), increased morbidity and mortality during long-term follow-up in adult patients (4).

These long-term sequelae in patients treated for craniopharyngioma have been attributed to damage by the craniopharyngioma and/or its treatment to surrounding tissues. For example, hypothalamic damage has been implicated in the development of hyperphagia and obesity, which is reported in 26-61% of the patients postoperatively (1). The decreased sympathetic tone found in patients with severe obesity after treatment for craniopharyngioma could possibly be due to damage to the ventromedial nucleus of the hypothalamus, that regulates sympathetic nervous activity (5).

Self-reported, general and physical fatigue is increased in adult patients treated for craniopharyngioma compared to healthy controls (2). We hypothesized that impaired quality of life may, at least in part, be related to alterations in sleep patterns. This hypothesis is supported by the observation that daytime sleepiness is increased in patients after successful treatment of craniopharyngioma in childhood (6). However, this has not been reported for patients treated for craniopharyngiomas in adulthood. Moreover, the alterations in sleep quality may be a consequence of large pituitary tumors and/or their treatment in general, rather than being a specific consequence of craniopharygeomas per se. Therefore, the aim of the present study was to compare daytime sleepiness and sleep patterns between adult patients previously treated for craniopharyngiomas and healthy controls, as well as with patients with non-functioning tumors in the sellar region: non-functioning pituitary macroadenomas (NFMA).

PATIENTS AND METHODS

Patients and controls

The present study was a case-control study of consecutive patients previously treated for craniopharyngioma in our center. Each patient was asked to provide a healthy control person of comparable age and sex. The control group was extended with controls derived from other studies in our center that were approached similarly. In addition, patients were compared to

38 patients previously treated for non-functioning macroadenomas (NFMA) matched for age, gender, and body mass index (BMI) derived from a previous study in our center (7). This number of patients was determined by choosing patients from the original NFMA cohort with the best match for age, gender and BMI and resulted in a case:control ratio of 1:1.4.

All patients were seen at least twice yearly by an endocrinologist, with appropriate evaluation and treatment of possible deficiencies of pituitary hormones. Growth hormone (GH) deficiency was defined as an IGF-I level below the reference range for age and sex and an insufficient rise in GH levels (absolute value <3 µg/l) after stimulation during an insulin tolerance test. Prior studies have demonstrated that patients with multiple pituitary hormone deficiencies, including two or more pituitary hormone deficiencies other than GH-deficiency, had a likelihood of approximately 95% of harboring GH-deficiency (8-10). Based on these data, we classified patients, in whom GH-stimulation test data were not obtained, but who were deficient in 3 other pituitary axes, as GH-deficient. When secondary amenorrhea was present for more than 1 year premenopausal women were defined as LH/FSH deficient. Post-menopausal women were defined as LH/FSH deficient when gonadotrophin levels were below the normal postmenopausal range (LH<10 U/l and FSH<30 U/l). In men, LH/FSH deficiency was defined as a testosterone level below the reference range (8.0 nmol/l). TSH deficiency was defined as a total or free T4 level below the reference range. ACTH deficiency was defined as an insufficient increase in cortisol levels (absolute value <0.55 µmol/l) after a corticotrophin releasing hormone test or insulin tolerance test. If results were below the lower limit of the respective reference ranges, substitution with growth hormone, thyroxine, hydrocortisone or testosterone was started. In the case of amenorrhea and low estradiol levels in premenopausal women, estrogen replacement was provided. Postmenopausal women were not treated with estrogen replacement therapy. None of the patients were using selective serotonin reuptake inhibitors, tricyclic antidepressants, or MAO inhibitors.

The Medical Ethics Committee of the Leiden University Medical Center approved the study protocol and all patients returning completed questionnaires gave written informed consent.

Study parameters

Primary study-parameters were the results of the two sleep questionnaires. The patients were asked to complete two questionnaires that assessed daytime sleepiness and sleep patterns. The questionnaires were sent to their home in prepaid envelopes. After two months non-responders were contacted by telephone to encourage completion and return of the questionnaires.

Patients with craniopharyngiomas were compared to controls and to patients with a NFMA. The results of the sleep questionnaires were linked to age and gender of the patients, body mass index, treatment characteristics (multiple surgical procedures, radiotherapy), visual field defects, and the presence of pituitary deficiencies.

Sleep questionnaires

Epworth sleepiness scale (ESS)

The ESS is a validated, eight-item questionnaire. The participants are asked to rate their likelihood of falling asleep in a variety of commonly encountered situations (11). Scores range from 0 (the least sleepy) to 24 (the most sleepy). Scores equal to or above 10 are interpreted as increased daytime sleepiness (6). An additional set of questions that evaluated the prevalence of snoring, observed apnoea's, and nocturnal restless legs was added (12) .

Münchener chronotype questionnaire (MCQ)

The MCQ is a validated questionnaire aimed at assessing chronotype and sleep patterns (13;14). Patients are explicitly asked to describe their sleep behavior under normal circumstances (without partying etc.). The temporal structure of sleep is assessed separately for workdays and free days. Parameters on free days are regarded to reflect individual sleep patterns without social obligations and are therefore reported in this paper (13).

Sleep duration on free days (SD_F), sleep onset on free days (SO_F) and rise time (RT_F) are calculated from questions concerning sleep onset and awakening on days on which there are no work or social obligations. The midsleep on free days (MS_F: clock time halfway during sleep duration) is calculated from SO_F and RT_F (14).

Since most chronotypes tend to accumulate a sleep debt on work days, which is compensated for on free days, midsleep on workdays (MS_C) was corrected for the confounder sleep debt as follows: $MS_C=MS_F-(0.5*SD_F-(5*SD_{working\ days}+2*\ SD_F)/7)$ (14). Since only 18 of our craniopharyngioma patients, 28 of our NFMA patients, and 41 of our controls had a daytime job, this correction was performed only for those subjects (14).

Statistics

SPSS for windows version 14.0 (SPSS Inc., Chicago, IL) was used for data analysis. Data are expressed as mean ± SD, unless otherwise mentioned. ANOVA analysis with post-hoc Tukey's HSD adjustment or chi-square test were performed to compare the three groups when appropriate. Variables influencing sleep parameters within the craniopharyngioma group were studied with independent samples T-test, Mann-Whitney tests or chi-square tests when appropriate. Differences were considered statistically significant at $P<0.05$.

RESULTS

Patients and controls

Twenty-nine of 34 (85%) patients returned the questionnaires on sleep characteristics (Table 1). Two of the patients preferred not to participate and 5 patients did not respond. Thus, 27

Table 17/1: Clinical characteristics of patients with craniopharyngioma compared to patients with non-functioning macroadenoma (NFMA).

	Cranio-pharyngeoma patients (n=27)	NFMA patients (n=38)	P-value
Age (mean, range (yrs))	53 (27-80)	55 (36-63)	0.599
Gender (F/M (%))	48/52	60/40	0.423
BMI (kg/m^2)	29.6 ± 7.5	27.8 ± 3.8	0.321
Radiotherapy (%)	26	37	0.354
GH deficiency (%)	91	78	0.191
IGF-I standard deviation score*	0.6 ± 2.1	1.1. ± 2.1	0.459
TSH deficiency (%)	96	66	0.003
Free T4**	18.5 ± 4.3	17.6 ± 3.0	0.438
ACTH deficiency (%)	78	63	0.208
LH/ FSH deficiency (%)	63	79	0.156

* in patients with substituted GH deficiency.

** in patients with substituted TSH deficiency.

completed questionnaires were received. The study-population (14 men) had a mean age of 53 years with a range of 27 to 80 years. All 27 patients were primarily treated by surgery. Eight of these patients had repeat surgery. Seven patients were also treated by radiotherapy, four for recurrent disease. The mean follow-up period after initial surgery and this study was 21.3 ± 14.3 years. All patients were considered cured from craniopharyngioma, because follow up MR imaging did not reveal the presence of recurrent disease. There were no significant differences in age, gender and clinical characteristics between the study-population and the patients who preferred not to participate or who did not return the questionnaires (n=7).

The patients were first compared to 50 controls (20 men) with mean age of 55 years (range of 45 to 63 years). There were no differences for age and gender between the patients and the control group (p=0.413 and p=0.318, respectively). Subsequently, patients were compared to 38 patients who had been previously cured by surgery from NFMA (20 men) with a mean age of 55 years (range 45 to 63 years) and a mean duration of follow-up of 9.4 ± 6.8 years. All 38 patients with NFMA had been operated previously, and 37 % had also been treated by postoperative radiotherapy.

In 16 patients with craniopharyngioma data of pre-operative Hardy classification were present. Seventy-five percent had Hardy B, compared to 19% C, and 1 patient presented with an intrasellar tumor (p=0.772). The other 11 patients with craniopharyngioma all had suprasellair disease without data on Hardy classification and all but two were operated transcranially. The other two patients were operated transsphenoidally in 1960 and 1967, respectively. The Hardy classification of suprasellar extension indicated stage B in 83% and stage C in 11% of NFMA patients (n=29 and n=11, resp., p=0.772 compared to craniopharyngioma patients (all except for 3 patients with NFMA could be classified according to Hardy)).

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Table 17/2: Sleepiness scores and subjective sleep patterns in patients with craniopharyngioma compared to controls.

		Craniopharyngioma patients (n=27)	Controls (n=50)	P-value
ESS	Mean score (mean ± SD)	7.7 ± 4.1	4.8 ± 3.4	0.011
	>10 (%)	33	8	0.005
MCTQ	Sleep onset on free days (clock time h:min ± SD)	23:40 ± 1:20	23:48 ± 1:29	0.906
	Sleep latency (minutes ± SD)	30.6 ± 39.5	26.3 ± 24.2	0.860
	Rising time on free days (clock time h:min ± SD)	7:14 ± 1:00	7:05 ± 1:15	0.863
	Sleep duration on free days (duration h:min ± SD)	7:33 ± 1:11	7:17 ± 1:02	0.574
	Midsleep on free days (clock time h:min ± SD)	3:27 ± 1:01	3:27 ± 1:16	1.00
	Corrected midsleep (clock time h:min ± SD, n=25 vs. n=18/ n=41/ n=28)	3:54 ± 1:11	3:42 ± 0:45	0.673

Craniopharyngioma patients compared to healthy controls

Sleep duration on free days (SD_F) was not different between patients and controls. Sleep onset on free days, midsleep on free days, rising time on free days, and corrected midsleep (SO_F, MS_F, RT_F, and MS_C, respectively) were not different compared to controls (Table 2).

However, the Epworth Sleepiness Scale (ESS) score was increased in patients compared to controls (7.7 ± 4.1 vs. 4.8 ± 3.4, p=0.011) denoting increased daytime sleepiness in patients. Thirty-three percent patients had ESS scores above 10 compared to 8% in controls (p=0.005). The mean age and BMI in these patients (33% men) were 54.0 ± 16.2 yrs and 31.4 ± 4.1 kg/m^2, respectively, which was not different compared to the other patients with craniopharyngioma with ESS scores below 10. No differences in pituitary deficiencies were found between those two groups.

Seventy-two percent of patients reported snoring compared to 74% in controls, whereas 29% of patients reported observed apneas compared to 10% of controls (p=0.044). Restless legs were reported in 26% in patients compared to 24% in controls (p=0.852). Fifteen percent of patients reported feeling depressed compared to 5% in controls (p=0.199).

Craniopharyngioma patients compared to patients with non-functioning macroadenomas

Patients with craniopharyngioma were compared to age-, gender- and BMI-matched patients with NFMA (Table 1).

Sleep duration on free days (SD_F) was not different between patients with craniopharyngioma and patients with NFMA. Sleep onset on free days, midsleep on free days, rising time on free days, and corrected midsleep (SO_F, MS_F, RT_F, and MS_C, respectively) were not statistically different compared to patients with nonfunctioning macroadenomas (Table 3).

Table 17/3: Sleepiness scores and subjective sleep patterns in patients with craniopharyngioma compared to patients with non-functioning macroadenoma (NFMA).

		Craniopharyngioma patients (n=27)	NFMA patients (n=38)	P-value
ESS	Mean score (mean ± SD)	7.7 ± 4.1	7.5 ± 5.1	0.965
	>10 (%)	33	24	0.392
MCTQ	Sleep onset on free days (clock time h:min ± SD)	23:40 ± 1:20	23:43 ± 0:52	0.990
	Sleep latency (minutes ± SD)	30.6 ± 39.5	34.5 ± 36.8	0.887
	Rising time on free days (clock time h:min ± SD)	7:14 ± 1:00	6:49 ± 1:01	0.334
	Sleep duration on free days (duration h:min ± SD)	7:33 ± 1:11	7:05 ± 1:10	0.230
	Midsleep on free days (clock time h:min ± SD)	3:27 ± 1:01	3:15 ± 0:44	0.763
	Corrected midsleep (clock time h:min ± SD, n=25 vs. n=18/ n=41/ n=28)	3:54 ± 1:11	3:41 ± 0:35	0.654

ESS score was not different between the two groups. Thirty-three percent patients had ESS scores above 10 compared to 24% in patients with NFMA (p=0.392). The mean age and BMI in these patients with NFMA (44% men) were 52.0 ± 9.1 yrs and 27.5 ± 3.8 kg/m^2, respectively, which was not different compared to the other patients with NFMA with ESS scores below 10. No differences in pituitary deficiencies were found between those two latter groups.

Seventy-two percent of patients with craniopharyngioma reported snoring compared to 66% in patients with NFMA (p=0.604), whereas 29% of patients reported observed apneas compared to 17% of patients with NFMA (p=0.274). In addition, restless legs were reported in 26% in patients compared to 18% in patients with NFMA (p=0.468). Fourteen percent of patients reported feeling depressed compared to 5% in patients with NFMA (p=0.882).

In addition, patients with NFMA were compared to the healthy controls. ESS scores were higher in the patients with NFMA (7.5 ± 5.1 vs. 4.8 ± 3.4 in controls, p=0.010) without differences in sleep pattern parameters between the two groups (Figure 1).

Factors influencing sleepiness scores and sleep patterns in patients with craniopharyngioma

Surgery

There were no differences in sleepiness scores or sleep patterns between patients who had been treated by transsphenoidal surgery (37%) and patients treated by transcranial surgery (63%).

Radiotherapy

There were no differences in sleepiness scores or sleep patterns between patients who had been treated with radiotherapy (26%) and patients who were not (74%).

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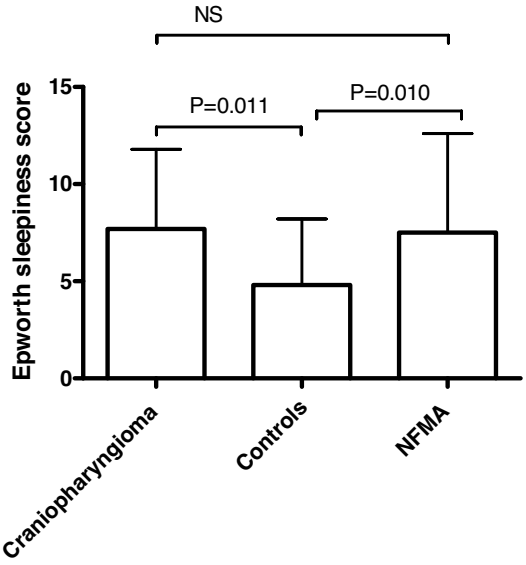

Figure 17/1: Epworth sleepiness scores are increased in patients with craniopharyngioma compared to healthy controls but do not differ from scores in age-, gender-, and BMI-matched patients with non-functioning macroadenoma (NFMA).

Age at onset

The diagnosis of craniopharyngioma was established in childhood in 8 patients (30%) and in adulthood in 19 patients (70%). No differences were found in sleepiness scores or sleep patterns between the two groups.

BMI

No correlations could be found in this limited number of patients sleepiness scores or sleep patterns on the one hand and BMI on the other hand.

DISCUSSION

We found increased daytime somnolence and increased prevalence of severe hypersomnolence despite normal sleep patterns in patients treated for craniopharyngioma compared to healthy controls. In addition, we observed an increased prevalence of self-reported apneas in these patients. However, daytime somnolence and sleep patterns in patients with craniopharyngioma did not statistically differ from age-, gender-, and BMI-matched patients with non-functioning macroadenoma. Therefore, these results indicate that increased daytime somnolence is a general consequence of large tumors, and/or their treatment, in the hypothalamic/pituitary region, rather than a specific feature of craniopharyngiomas per se.

Multiple long-term sequelae of treatment of craniopharyngioma, such as hyperphagia, obesity and decreased sympathetic tone, have be attributed to damage to surrounding tissues including hypothalamic nuclei (1;5). The hypothalamus has also been identified as the main regulatory center of sleep: the suprachiasmatic nucleus (SCN) is considered to be the central circadian pacemaker of the body with one of the circadian outputs formed by the regulation of circadian variations in melatonin secretion by the pineal gland (15). In patients treated for craniopharyngioma in childhood, reduced nocturnal melatonin concentrations are associated with increased daytime somnolence (16). In addition, the multiple sleep latency test, a standardized test of daytime somnolence, showed severe daytime somnolence in 5 children who had been treated by hypothalamic/ pituitary surgery (17). In accordance, self-reported general and physical fatigue is increased in adult patients treated for craniopharyngioma compared to healthy controls (2). In the present study, the previous findings of increased daytime somnolence obtained in children treated for craniopharyngioma were extended to, and confirmed in, adult patients with craniopharyngioma. In addition, we found an increased prevalence of self-reported observed apneas, which could also contribute to the increased daytime somnolence.

Remarkably, daytime somnolence and sleep patterns in patients with craniopharyngioma did not differ from age-, gender-, and BMI-matched patients with non-functioning macroadenomas. The similar distortion of sleep patterns in patients with craniopharyngiomas and non-functioning macroadenomas points towards a shared origin of the increased daytime sleepiness possibly originating from damage to the suprachiasmatic nucleus.

Large tumors of the pituitary region are associated with deficient function of the anterior pituitary. In patients previously treated for non-functioning macroadenomas, the presence of anterior pituitary hormone deficiencies was associated with altered sleep patterns (7). Since almost all patients treated for craniopharyngioma in our cohort presented with multiple deficiencies of the anterior pituitary, we could not specifically evaluate the effects of anterior pituitary hormone deficiencies on sleep characteristics within this group. However, since both patients with craniopharyngiomas and NFMA presented with multiple anterior pituitary deficiencies, these abnormalities in pituitary function could also contribute to increased daytime sleepiness in both patient groups. Indeed, many interactions between nocturnal secretion of different hormones and the sleep electroencephalogram parameters have been described (18). Altered sleep patterns can induce changes in anterior pituitary hormone secretion (19). Conversely, endocrine deficiencies, like primary hypothyroidism, are associated with altered sleep patterns on polysomnographic recordings (20). However, it is maybe unlikely that these effects have played a major role in our study, since anterior pituitary hormone deficiencies were monitored regularly and appropriately replaced in our patients.

Some factors may have influenced our results. First, sleepiness and sleep patterns were evaluated by questionnaires. Although the MCQ assessed sleep during free days and working days on one occasion, data on sleep habits derived from the MCQ correlate highly with data obtained from sleep logs for 5 weeks (13). Moreover, in the present study patients with

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craniopharyngiomas were compared to healthy controls recruited by the patients. Although it is known that self-selected controls might be subject to selection bias, because patients might have chosen controls with a supposedly good health status (21), it is highly unlikely that sleeping pattern played any role in the choice for a specific control. Finally, the results in our study are supported by the fact that there was no difference between the results obtained in patients treated for craniopharyngiomas and NFMAs.

In conclusion, we report increased daytime somnolence and increased prevalence of severe hypersomnolence in patients treated for craniopharyngioma compared to healthy controls. In addition, there was no difference between patients treated for craniopharyngioma or non-functioning pituitary macroadenomas with respect to increased daytime sleepiness scores compared to healthy controls. Further detailed analyses are needed to elucidate the pathophysiology of the reported increased sleepiness seen in patients previously treated for large tumors in the (para)sellar region. These studies could provide further insight and treatment targets in the complex persisting morbidity in patients after successful treatment for craniopharyngiomas as well as non-functioning macroadenomas.

REFERENCES

1. Karavitaki N, Cudlip S, Adams CB, Wass JA 2006 Craniopharyngiomas. Endocr Rev 27:371-397
2. Dekkers OM, Biermasz NR, Smit JW, Groot LE, Roelfsema F, Romijn JA, Pereira AM 2006 Quality of life in treated adult craniopharyngioma patients. Eur J Endocrinol 154:483-489
3. Muller HL, Bruhnken G, Emser A, Faldum A, Etavard-Gorris N, Gebhardt U, Kolb R, Sorensen N 2005 Longitudinal study on quality of life in 102 survivors of childhood craniopharyngioma. Childs Nerv Syst 21:975-980
4. Pereira AM, Schmid EM, Schutte PJ, Voormolen JH, Biermasz NR, van Thiel SW, Corssmit EP, Smit JW, Roelfsema F, Romijn JA 2005 High prevalence of long-term cardiovascular, neurological and psychosocial morbidity after treatment for craniopharyngioma. Clin Endocrinol (Oxf) 62:197-204
5. Roth CL, Hunneman DH, Gebhardt U, Stoffel-Wagner B, Reinehr T, Muller HL 2007 Reduced sympathetic metabolites in urine of obese patients with craniopharyngioma. Pediatr Res 61:496-501
6. Muller HL, Handwerker G, Wollny B, Faldum A, Sorensen N 2002 Melatonin secretion and increased daytime sleepiness in childhood craniopharyngioma patients. J Clin Endocrinol Metab 87:3993-3996
7. van der Klaauw AA, Dekkers OM, Pereira AM, van Kralingen KW, Romijn JA 2007 Increased daytime somnolence despite normal sleep patterns in patients treated for non-functioning pituitary macroadenoma. J Clin Endocrinol Metab 92:3898-3903
8. Bates AS, Evans AJ, Jones P, Clayton RN 1995 Assessment of GH status in adults with GH deficiency using serum growth hormone, serum insulin-like growth factor-I and urinary growth hormone excretion. Clin Endocrinol (Oxf) 42:425-430
9. Hartman ML, Crowe BJ, Biller BM, Ho KK, Clemmons DR, Chipman JJ 2002 Which patients do not require a GH stimulation test for the diagnosis of adult GH deficiency? J Clin Endocrinol Metab 87:477-485
10. Toogood AA, Beardwell CG, Shalet SM 1994 The severity of growth hormone deficiency in adults with pituitary disease is related to the degree of hypopituitarism. Clin Endocrinol (Oxf) 41:511-516
11. Johns MW 1991 A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 14:540-545
12. Venmans BJ, van Kralingen KW, Chandi DD, de Vries PM, ter Wee PM, Postmus PE 1999 Sleep complaints and sleep disordered breathing in hemodialysis patients. Neth J Med 54:207-212
13. Roenneberg T, Wirz-Justice A, Merrow M 2003 Life between clocks: daily temporal patterns of human chronotypes. J Biol Rhythms 18:80-90
14. Roenneberg T, Kuehnle T, Pramstaller PP, Ricken J, Havel M, Guth A, Merrow M 2004 A marker for the end of adolescence. Curr Biol 14:R1038-R1039
15. Mignot E, Taheri S, Nishino S 2002 Sleeping with the hypothalamus: emerging therapeutic targets for sleep disorders. Nat Neurosci 5 Suppl:1071-1075
16. Muller HL, Handwerker G, Gebhardt U, Faldum A, Emser A, Kolb R, Sorensen N 2006 Melatonin treatment in obese patients with childhood craniopharyngioma and increased daytime sleepiness. Cancer Causes Control 17:583-589
17. Snow A, Gozal E, Malhotra A, Tiosano D, Perlman R, Vega C, Shahar E, Gozal D, Hochberg Z, Pillar G 2002 Severe hypersomnolence after pituitary/hypothalamic surgery in adolescents: clinical characteristics and potential mechanisms. Pediatrics 110:e74
18. Van Cauter E, Leproult R, Plat L 2000 Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. JAMA 284:861-868
19. Spiegel K, Leproult R, Van Cauter E 1999 Impact of sleep debt on metabolic and endocrine function. Lancet 354:1435-1439
20. Ruiz-Primo E, Jurado JL, Solis H, Maisterrena JA, Fernandez-Guardiola A, Valverde C 1982 Polysomnographic effects of thyroid hormones primary myxedema. Electroencephalogr Clin Neurophysiol 53:559-564

Agatha BW.indd 268 10/29/08 3:19:27 PM

21. Wacholder S, McLaughlin JK, Silverman DT, Mandel JS 1992 Selection of controls in case-control studies. I. Principles. Am J Epidemiol 135:1019-1028