Increased Daytime Somnolence despite Normal Sleep Patterns in Patients Treated for Nonfunctioning Pituitary Macroadenoma

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Objective: In patients treated for nonfunctioning pituitary macroadenoma (NFMA), increased fatigue scores on quality of life (QoL) have been reported. Because this may be related to altered sleep patterns, we evaluated daytime sleepiness and sleep patterns in patients successfully treated for NFMA in our center.

Design: This is a case-control study.

Patients and Methods: We assessed sleepiness and sleep patterns in 76 adult patients (41 men, mean age 63 yr, range 37–87) in remission of NFMA during long-term follow-up (10 yr, range 0.5–30) after surgical (n = 76) and additional radiotherapeutical (n = 28) treatment. We used two validated questionnaires for sleep parameters (Epworth Sleepiness Scale and Münchener Chronotype Questionnaire) and four validated questionnaires for QoL (Hospital Anxiety and Depression Scale, Multidimensional Fatigue Inventory-20, Nottingham Health Profile, and Short Form-36). Patient outcomes were compared with 76 healthy controls.

Results: Sleep duration and timing of sleep were not affected compared with healthy controls. However, sleepiness score was increased in patients compared with controls (7.6 ± 4.6 vs. 4.8 ± 3.1; P < 0.001), reflecting increased daytime sleepiness in patients. There were no correlations between any of the sleep pattern parameters (duration, onset, rise time, or midsleep) and sleepiness scores. Sleepiness scores were significantly correlated to 15 of the 21 QoL parameters, whereas sleep patterns were not. Sleep timing was influenced by previous radiotherapy, whereas sleep duration was negatively affected by panhypopituitarism.

Conclusion: Daytime sleepiness is increased despite normal sleep patterns in patients treated for NFMA. (J Clin Endocrinol Metab 92: 3898–3903, 2007)

NONFUNCTIONING PITUITARY macroadenomas (NFMAs) are the most prevalent pituitary macroadenomas (1, 2). The main symptoms are visual field defects and hypopituitarism, which are caused by mass effects of the tumor. Transsphenoidal surgery is considered the treatment of choice, leading to improvement of visual function in the majority of patients (3). However, in a substantial proportion of the patients, hypopituitarism persists after surgical treatment (4). In case of tumor recurrence, selected patients may be treated by postoperative radiotherapy or repeat surgery.

Previous studies have documented an impaired quality of life (QoL) in patients treated for NFMA compared with age-adjusted reference values (5, 6). In these patients increased general fatigue and physical fatigue were remarkable complaints (5). Sleep and sleep patterns can be impaired after surgical treatment for other pituitary/hypothalamic tumors than NFMA, resulting in increased daytime somnolence and longer sleep duration (7). In addition, cranial radiotherapy in brain tumors during childhood leads to increased sleep duration during adulthood, and radiation dose seemed to be a determinant of sleep changes (8). Therefore, we hypothesized that the increased fatigue scores in patients previously treated for NFMA could be related to disturbances in the sleep patterns.

Because it is unknown whether sleep and sleep patterns are affected after treatment for NFMA, the aim of this study was to assess sleep patterns and sleepiness in patients with NFMA in relation to QoL scores and clinical characteristics.

Patients and Methods

Patients

The present study was a cross-sectional study of consecutive patients with NFMA in our center. The study consisted of two parts: 1) QoL assessment, and 2) assessment of sleep and sleep patterns. First, 128 consecutive patients with NFMA, treated by transsphenoidal surgery in our center between 1985 and 2004, could be identified. Of these patients, 99 participated in the first part of the study, the QoL study (5). These patients were also asked to participate in the second part of the study by completing two additional questionnaires that assessed daytime sleepiness and sleep patterns. The questionnaires were sent to their home in prepaid envelopes. After 2 months, nonresponders were contacted by telephone to encourage completion and return of the questionnaires. Each patient was also asked to provide a healthy control person of comparable age and sex, who did not use any medication, to serve as a control group with a comparable socioeconomic status derived from the same geographical area. The control group was extended with controls derived from other studies in our center that were approached similarly.

All patients had been treated by primary transsphenoidal surgery and...
were considered cured after surgery (sometimes in combination with postoperative radiotherapy). The mean follow-up period after initial surgery was 10 yr (range 0.5–30). All patients were seen at least twice yearly by an endocrinologist, with adequate evaluation and treatment of possible deficiencies of pituitary hormones. GH deficiency was defined as an IGF-I level below the reference range for age and sex and/or insufficient increase in GH levels (absolute value < 3 μg/liter) 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 (9–11). Based on these data, we classified patients, in whom GH-stimulation test data were not obtained, but who were deficient in three other pituitary axes, as GH deficient. When secondary amenorrhea was present for more than 1 yr, premenopausal women were defined as LH/FSH deficient. Postmenopausal women were defined as LH/FSH deficient when gonadotrophin levels were below the normal postmenopausal range (LH < 10 U/liter and FSH < 30 U/liter). In men, LH/FSH deficiency was defined as a testosterone level below the reference range (8.0 nmol/liter). 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/liter) after a corticotropin-releasing hormone test or insulin tolerance test. If results were below the lower limit of the respective reference ranges, substitution with GH, T4, hydrocortisone, or testosterone was started. In the case of amenorrhea and low estradiol levels in premenopausal women, estrogen replacement was provided. Postmenopausal women were treated with estrogen replacement therapy. At evaluation, the free T4 scores were 16.9 ± 3.5 pmol/liter in substituted patients (normal 10.0–24.0), indicating adequate thyroid hormone replacement. None of the patients were using selective serotonin reuptake inhibitors, tricyclic antidepressants, or monoamine oxidase 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 results were linked to age and gender of the patients, treatment characteristics (multiple surgical procedures, radiotherapy), visual field defects, the presence of pituitary deficiencies, and the QoL scores.

Sleep questionnaires

Epworth Sleepiness Scale (ESS). The ESS is a validated eight-item questionnaire. The subject is asked to rate his likelihood of falling asleep in a variety of commonly encountered situations (12). Scores range from 0 (the least sleepy) to 24 (the most sleepy). Scores equal to or above 10 are interpreted as increased daytime sleepiness (13). An additional set of questions that evaluated the prevalence of snoring, observed apneas, and nocturnal restless legs was added.

Münchener Chronotype Questionnaire (MCQ). The MCQ is a validated questionnaire aimed at assessing chronotype and sleep patterns (14, 15). Patients are explicitly asked to describe their sleep behavior under normal circumstances (without partying etc.). The temporal structure of sleep is assessed separately for weekdays and free days. Parameters on free days are regarded to reflect individual sleep patterns without social obligations and are, therefore, reported in this paper (14).

Sleep duration on free days (SDf), sleep onset on free days (SDO), and rise time (RTf) 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 (MSf) (clock time halfway during sleep duration) is calculated from SOf and RTf (15).

Because most chronotypes tend to accumulate a sleep debt on workdays, which is compensated for on free days, corrected midsleep on workdays (MSw) was corrected for the confounder sleep debt as follows: MSw = MSf − (0.5 × SDf + (5 × SDworking days) + 2 × SDf)/7 (15). Because only 32 of our patients and 27 of our controls had a daytime job, this correction was performed only for those subjects.

QoL questionnaires

The various QoL questionnaires have been described extensively in the previous paper (5). In short, the Short Form (SF)-36 questionnaire comprises 36 items and records general well-being during the previous 30 d. Scores are expressed on a 0–100 scale, and higher scores are associated with a better QoL. The Nottingham Health Profile (NHP) is frequently used in patients with pituitary disease to assess general well-being and consists of 38 yes/no questions, which are subdivided into six subscales. Scores are calculated as a weight mean of the subscales, and are expressed as a value between 0 and 100. A higher score is associated with a worse QoL. The Multidimensional Fatigue Inventory (MDI)-20 comprises 20 statements to assess fatigue, which are measured on a five-point scale. Scores vary from 0–20, and higher scores indicate greater experienced fatigue. The Hospital Anxiety and Depression Scale (HADS) consists of 14 items pertaining to anxiety and depression, which are measured on a four-point scale. Scores for the anxiety and depression subscale range from 0–21, and values for the total score range from 0–42. Higher scores indicate more severe anxiety or depression. A total score of 13 or more was considered increased.

Statistics

SPSS for windows version 12.0 (SPSS, Inc., Chicago, IL) was used for data analysis. Data are expressed as mean ± SD, unless otherwise mentioned. We used unpaired t tests, χ² tests, and linear regression analysis, when appropriate. Differences were considered statistically significant at p < 0.05.

Results

Patients and controls (Table 1)

Of 99 patients, 85 (86%) returned the questionnaires on sleep characteristics. Nine of the patients preferred not to participate, 11 did not respond, two died since the previous study, and one moved without leaving a correct address. Thus, 76 completed questionnaires were received. The study population (41 men) had a mean age of 63 yr, with a range of 37–87 yr. No significant differences in age, gender, and tumor characteristics were found between the study population and the patients who preferred not to participate or who did not return the questionnaires.

The patients were compared with 76 controls (40 men),

| TABLE 1. Clinical characteristics of the NFMA patients and controls |
|----------------------|------------------|------------------|
|                      | Patients (n = 76) | Controls (n = 76) |
| Mean age (range) (yr) | 63 (37–87)       | 62 (31–81)       |
| Males                | 41 (54)          | 40 (53)          |
| Females              | 35 (46)          | 36 (47)          |
| Radiotherapy         | 28 (37)          |                  |
| Visual field defects | 16 (29)          |                  |
| Hardy classification |                  |                  |
| 2                    | 46 (61)          |                  |
| 3                    | 17 (22)          |                  |
| 4                    | 13 (17)          |                  |
| Suprasellar extension (Hardy classification) |                  |
| A                    | 3 (4)            |                  |
| B                    | 61 (85)          |                  |
| C                    | 8 (11)           |                  |
| GH deficiency        | 63 (84)          |                  |
| TSH deficiency       | 47 (64)          |                  |
| ACTH deficiency      | 49 (65)          |                  |
| LH/FSH deficiency    | 62 (82)          |                  |
| ADH deficiency       | 7 (9)            |                  |
| Panhypopituitarism   | 38 (50)          |                  |

Data represent number (percent). ADH, Antidiuretic hormone.
with a mean age of 62 yr (range 31–81). Age and gender from the control group were not different from the studied NFMA patients ($P = 0.417$ and $P = 0.871$, respectively). All 76 patients had been treated by transphenoidal surgery. The mean follow-up period after initial surgical treatment was 10 yr (range 0.5–30). There were 12 patients (17%) treated for tumor recurrence. A total of 28 patients (37%) received radiotherapy during the course of their disease, of whom 19 received prophylactic radiotherapy and nine patients to treat tumor recurrence. In 15 patients (26%), visual field defects were present at last follow-up.

At evaluation, panhypopituitarism of the anterior pituitary gland was present in 50%. A total of 63 patients (84%) had GH deficiency, of whom 32 (51%) received recombinant human GH replacement. There were 33 patients (81% of male patients) who had testosterone substitution. Of the 35 women, 14 were premenopausal, of whom 11 had LH/FSH deficiency and were substituted with estrogen substitution. A total of 47 patients (64%) needed thyroid hormone substitution, whereas 49 (65%) needed glucocorticoid substitution.

**Comparison with controls (Table 2)**

SD$_F$ was comparable in patients and controls (7:13 ± 1:09 vs. 7:18 ± 0:57 h; $P = 0.675$). SO$_F$, MS$_F$, RT$_F$, and MS$_C$ were not different compared with controls as well (Table 2).

However, the ESS score was increased in patients compared with controls (7.6 ± 4.6 vs. 4.8 ± 3.1; $P < 0.001$), denoting increased daytime sleepiness in patients. There were 19 patients who had ESS scores above 10 compared with seven controls (26 vs. 10%, respectively; $P = 0.001$).

Of patients, 67% reported snoring compared with 68% in controls ($P = 0.939$), whereas 20% of patients reported observed apneas compared with 13% of controls ($P = 0.219$). In addition, restless legs were reported in 20% in patients compared with 13% in controls ($P = 0.437$).

In our patients, no correlations could be found with linear regression analysis between any of the sleep pattern parameters (duration, onset, RT$_F$, or midsleep) and sleepiness scores on the ESS.

**Correlations with QoL (Table 3)**

There were no significant correlations between sleep pattern parameters and any of the QoL subscales of the four different QoL questionnaires, especially not for sleep duration and fatigue scores. Nonetheless, the ESS score was significantly correlated with 15 of 21 QoL subscales (Table 3).
treated with radiotherapy compared with patients who were not (0:00 ± 0:47 vs. 23:35 ± 1:04 h, P = 0.089, and 7:17 ± 0.43 vs. 6:48 ± 1:19 h, P = 0.051, respectively). ESS score and MSF did not differ between these two groups. No correlations were found between interval after radiotherapy and MSF.

Visual field defects. ESS scores tended to be higher in patients with present visual field defects compared with the other patients (9.6 ± 5.4 vs. 6.9 ± 4.1; P = 0.067), whereas sleep pattern parameters did not differ between these two groups.

Hypopituitarism. A total of 38 patients (50%) had panhypopituitarism at completion of the questionnaires. SDT was significantly shorter in those patients with panhypopituitarism (6:55 ± 1:22 vs. 7:32 ± 0:48 h; P = 0.028; Fig. 2) due to combined nonsignificant shifts in later sleep onset (SOF) and earlier RTF. Midsleep (MSF, MSF1) and ESS scores were unaffected by panhypopituitarism. ESS scores and sleep pattern parameters did not differ between patients with or without GH deficiency, or between patients with GH deficiency with and without GH substitution. Sleep duration was shorter in TSH deficient patients (n = 47, 64%) compared with those patients without secondary hypothyroidism (6:55 ± 1:19 vs. 7:45 ± 0:45 h; P = 0.006), whereas ESS scores, SOF, and MSF were unaffected. ACTH or LH/FSH deficiency did not influence sleepiness scores or sleep patterns.

Stepwise linear regression analysis

Stepwise linear regression was performed in a model including age, gender, radiotherapy, presence of visual field defects, panhypopituitarism, and TSH deficiency as independent variables, and ESS score, SDT, SOF, and MSF as dependent variables. Age, the presence of visual field defects, panhypopituitarism, and TSH deficiency did not influence any of the sleep pattern parameters or ESS scores. However, MSF was influenced by gender [male, 0; female, 1; β, −2179 sec (~36 min); P = 0.013] and radiotherapy [no, 0; yes, 1; β, 1731 sec (~29 min); P = 0.046]. SOF was also influenced by gender [β = −2417 (−40 min); P = 0.021].

Discussion

The data in this study indicate that patients successfully treated for NFMA experienced increased daytime sleepiness that was associated with a reduced QoL. However, sleep patterns such as sleep onset or sleep duration did not differ from healthy controls and were not correlated to increased daytime sleepiness scores or reduced QoL. Detailed analysis of the relationship between sleep patterns and clinical parameters in NFMA patients revealed gender and radiotherapy to influence sleep timing and panhypopituitarism to affect sleep duration.

Only a few studies have reported on QoL in patients with NFMA (5, 6), and to our knowledge no reports on sleep in NFMA patients have been published. We found increased daytime sleepiness in patients treated for NFMA in concordance with the reported increased fatigue in NFMA patients. Moreover, the daytime sleepiness scores in our patients treated for NFMA were comparable to scores found in patients with other pituitary tumors or cerebral diseases such as acromegaly (16), craniopharyngioma (17), hypothalamic tumors (17), subarachnoid hemorrhage (18), or traumatic brain injury (19), indicative for the relationship between ce-
rebral disease and increased daytime sleepiness. Severely increased daytime sleepiness (ESS scores above 10) was noted in almost one third of our patients with NFMA, in line with findings in patients with craniopharyngioma (20). Nonetheless, we did not find altered sleep patterns in our NFMA patients, suggesting that the increased experienced daytime sleepiness and reported fatigue scores of the QoL questionnaires are not due to major alterations in sleep duration or timing of sleep. However, this unaffected sleep duration was in contrast to findings in patients after pituitary/hypothalamic surgery or cranial radiotherapy for other tumors, in whom sleep duration was increased (7, 8).

The increased daytime sleepiness and increased fatigue scores seen in our patients treated for NFMA could point toward possibly impaired sleep quality in patients with NFMA, despite normal sleep patterns. Indeed, sleep quality measured with polysomnography is altered in patients with Cushing’s disease (21), acromegaly (22), prolactinoma (23), and patients with craniopharyngioma (20). Nonetheless, it cannot be excluded that additional disturbances, e.g., in melatonin secretion, lead to increased daytime sleepiness in NFMA patients. In fact, it has been suggested that reduced nocturnal melatonin secretion may lead to increased daytime sleepiness in childhood craniopharyngioma patients (13, 17). Thus, in addition to direct measurement of melatonin secretion, future studies to elucidate the increased daytime sleepiness should include polysomnography and additional (objective) tests of increased daytime sleepiness, considering the ample aspects of increased daytime sleepiness that can be studied besides the ESS.

Detailed analysis of the relationship between sleep patterns and clinical parameters in NFMA patients revealed some factors to influence sleep patterns. First, radiotherapy was found to influence sleep timing. Midsleep timing, which is found to be significantly correlated to dim light melatonin onset [a marker of circadian phase (24)], was later in patients treated with radiotherapy. The hypothalamus has been identified as the main sleep regulatory center (25). Within the hypothalamus, the suprachiasmatic nucleus is thought to be the main circadian pacemaker, and one of its circadian outputs is formed by regulating melatonin secretion of the pineal gland. Indeed, the hypothalamus is thought to be more vulnerable to radiation-induced damage compared with the pituitary (26). Thus, damage to the hypothalamus due to radiotherapy could be involved in the delayed timing of sleep seen in our NFMA patients, which makes direct measurement of circadian melatonin secretion interesting. Second, the decreased duration of sleep in patients with panhypopituitarism suggests that intact anterior pituitary function, especially diurnal variations, is important for normal sleep. Alternatively, the diurnal variations in pituitary hormone secretion are the consequence of the same mechanisms involved in regulation of sleep-wake patterns. Indeed, many interactions between nocturnal secretion of different hormones and the sleep electromyelogram parameters have been described (27). Altered sleep patterns can induce changes in anterior pituitary hormone secretion (28). We found in NFMA patients that deficiencies in anterior pituitary hormones, especially secondary hypothyroidism, are associated with altered sleep patterns, which is in line with findings in patients with primary hypothyroidism (29). GH deficiency or ACTH deficiency did not specifically influence sleep patterns in our study patients, in line with reports on sleep in GH deficiency (30, 31) or Addison’s disease (32).

No relation between age and sleepiness scores was found. This is in contrast with findings in the general healthy population (33, 34). This discrepancy is likely due to the limited age range of the subjects included in our study due to the generally older age of patients with nonfunctioning macroadenomas.

Some factors may have influenced our results. First, sleepiness and sleep patterns were assessed using self-reported questionnaires. The MCQ assessed sleep during free days and working days, but only at one occasion. However, a comparison of the data on sleep habits from the MCQ and data from a sleep log for 5 wk by Roenneberg et al. (14) indicated that sleep times of both questionnaires on both workdays and free days correlated highly (P < 0.0001). Therefore, in addition to self-reported sleepiness and sleep patterns, the next step is to perform an objective test of sleepiness and polysomnography to assess sleep quality in patients treated for NFMA. Second, in the present study, NFMA patients were compared with healthy controls recruited by the patients. The advantage of using such controls is that they are from the same geographic area and socioeconomic class as the patients (35). 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 (36), it is not likely that sleeping pattern plays any role in the choice for a specific control.

In conclusion, we found self-reported increased daytime sleepiness despite normal sleep patterns in patients treated for NFMA, which was associated with an impaired QoL. Further detailed polysomnographic and circadian rhythm studies are needed to elucidate the pathophysiology of the reported increased sleepiness seen in our NFMA patients, which could produce further insight and treatment targets in the complex persisting morbidity in patients after treatment for NFMA.

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