Patients Previously Treated for Nonfunctioning Pituitary Macroadenomas Have Disturbed Sleep Characteristics, Circadian Movement Rhythm, and Subjective Sleep Quality

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Context and Objective: Fatigue and excessive sleepiness have been reported after treatment of nonfunctioning pituitary macroadenomas (NFMA). Because these complaints may be caused by disturbed nocturnal sleep, we evaluated objective sleep characteristics in patients treated for NFMA.

Design: We conducted a controlled cross-sectional study.

Subjects and Methods: We studied 17 patients (8 women; mean age, 54 yr) in remission of NFMA during long-term follow-up (8 yr; range, 1–18 yr) after surgery (n = 17) and additional radiotherapy (n = 5) without comorbidity except for hypopituitarism and 17 controls matched for age, gender, and body mass index. Sleep was assessed by nocturnal polysomnography, sleep and diurnal movement patterns by actigraphy, and quality of life and subjective sleep characteristics by questionnaires.

Results: Compared to controls, patients had reduced sleep efficiency, less rapid eye movement sleep, more N1 sleep, and more awakenings in the absence of excessive apnea or periodic limb movements. Actigraphy revealed a longer sleep duration and profound disturbances in diurnal movement patterns, with more awakenings at night and less activity during the day. Patients scored higher on fatigue and reported impaired quality of life.

Conclusion: Patients previously treated for NFMA suffer from decreased subjective sleep quality, disturbed distribution of sleep stages, and disturbed circadian movement rhythm. These observations indicate that altered sleep characteristics may be a factor contributing to impaired quality of life and increased fatigue in patients treated for NFMA. (***J Clin Endocrinol Metab* 96: 1524–1532, 2011**)

Nonfunctioning pituitary macroadenomas (NFMA) can cause pituitary insufficiency and visual impairments due to compression of the optic chiasm. When visual field defects are present, transsphenoidal surgery is the treatment of choice, resulting in improvement of visual function in the majority of patients (1). Selected patients require treatment by postoperative radiotherapy (2).

Patients previously treated for NFMA report impaired quality of life (3, 4), with increased fatigue and increased daytime somnolence (5). To date, it is postulated that these

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Abbreviations: BMI, Body mass index; GHD, GH deficiency; IS, interdaily stability; IV, intradaily variability; L5, least active 5-h period; M10, most active 10-h period; NAP, near-zero activity period; NFMA, nonfunctioning pituitary macroadenomas; REM, rapid eye movement; SWS, slow-wave sleep; TST, total sleep time.

adverse effects, at least in part, can be attributed to the presence of hypopituitarism, replacement therapy, or apathy syndrome (6, 7). In addition, fatigue and daytime somnolence might be affected by direct effects on sleep via altered function of the suprachiasmatic nucleus. This hypothalamic nucleus is the major regulator of sleep-wake rhythmicity and is located close to the optic chiasm.

The current study, therefore, was designed to explore whether complaints of fatigue and daytime somnolence were accompanied by disturbed sleep in patients treated for NFMA. We compared characteristics of sleep and sleep-related functions between patients previously treated for NFMA with age-, gender-, and body mass index (BMI)-matched control subjects using polysomnography, actigraphy, and validated questionnaires.

Patients and Methods

Patients

We included 17 patients treated by transsphenoidal surgery for NFMA. They were selected from a database containing all patients previously treated for NFMA in our institution (n = 226) (3, 8). For the purpose of this study, the database was screened for the following inclusion and exclusion criteria. Inclusion criteria were previous transsphenoidal surgery for NFMA and age between 18–65 yr. This upper age limit was used to avoid age-related alterations in sleep characteristics (9). We excluded patients with any disorder that might affect sleep, including pregnancy, chronic use of sleep or psychotropic medication, previously diagnosed sleep disorders, hypertension, dyslipidemia, and diabetes mellitus. Pituitary insufficiency had to be adequately and stably substituted for at least 6 months. Fifty patients fulfilling these inclusion and exclusion criteria were invited for a screening visit. Of these, seven had comorbidity that was revealed at screening, and 26 chose not to participate, leaving 17 patients who consented. There were no differences in clinical characteristics, including age, gender, tumor size or extension, postoperative radiotherapy, or visual field defects between the 17 selected NFMA patients and the other 33 NFMA patients. All patients were evaluated at least yearly by an endocrinologist. GH deficiency (GHD) was defined as insufficient increase in GH levels (absolute value <3 μg/liter) after stimulation during an insulin tolerance test. When secondary amenorrhea was present for more than 1 yr, premenopausal women were defined as LH/FSH deficient. 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 low free T_4 level. ACTH deficiency was defined as an insufficient increase in cortisol levels (< 0.55 μmol/liter) after a CRH test or insulin tolerance test. If deficient, substitution with levothyroxine, 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. Recombinant human GH replacement was offered to GHD patients.

In addition, we studied 17 healthy controls that were recruited by advertisement in local newspapers. The controls had a similar age, gender, and BMI distribution as the NFMA patients and fulfilled the same inclusion and exclusion criteria, except for the absence of pituitary pathology.

The study was approved by the Medical Ethical Committee of the Leiden University Medical Center, and all subjects gave written informed consent.

Methods

Study design

Objective sleep characteristics were assessed in the 17 patients and 17 age-matched controls during one night of polysomnography and 7 d of actigraphy. In addition, subjective sleep characteristics and quality of life were assessed by validated questionnaires.

Polysomnography

Polysomnography is considered the "gold standard" in objective assessment of sleep characteristics (10–12). The following overnight measurements where conducted by polysomnography (Titanium Embla; Embla, Broomfield, CO): electroencephalography, electrooculography, electromyography of the chin and anterior tibialis muscle, airflow, respiratory effort, lowest arterial oxygen saturation, heart rate, and body position. Sleep was recorded and scored by experienced technicians using the guidelines of the American Academy of Sleep Medicine (13). The following study parameters were assessed: duration of sleep periods; total sleep time (TST); sleep latency; sleep efficiency; the number of apneas and hypopneas per hour; total duration and percentage of sleep phases N1, N2, and N3; rapid eye movement (REM) sleep and awake state; the number of limb movements per hour; oxygen saturation; and average heart rate.

Actigraphy

Actigraphy is a noninvasive method to measure rest/activity cycles. Actigraphy has been validated to detect sleep in healthy adult subjects (14, 15) and can also be used to determine sleep patterns in sleep disorders, such as insomnia and periodic limb movement disorders (15–17). Furthermore, actigraphy can be applied in suspected circadian rhythm sleep disorders because actigraphy correlates well with sleep logs, polysomnography, and markers of the circadian phase in patients with these disorders (18, 19). A sleep diary was used in the assessment of subjective sleep latency, TST, awakenings at night, and naps during the day (20).

Using the Actiwatch Activity & Sleep Analysis version 7.31 software (CamNtech Ltd., Cambridge, UK), the following averages were calculated from the actigraphic measurements: total time in bed, actual sleep time, sleep efficiency, sleep latency, fragmentation index, and near-zero activity periods (NAPs). NAPs are periods during which there were less than 10 "activity counts" (*i.e.* the device recorded ~0.4 g of acceleration) per minute for at least 5 min. These periods can be naps or an indication of fatigue.

Three variables were computed using nonparametric calculations (21, 22): the interdaily stability (IS), the intradaily variability (IV), and the amplitude. The IS quantifies the strength of coupling of the rhythm to supposedly stable environmental Zeitgeber (German for "time givers"). In normal cases, the activity patterns of individual days resemble one another very much, whereas rhythm disturbances cause appreciable differences between days (indicated by a lower IS). The IS is composed of

the 24-h value from the χ^2 periodogram (23), normalized for the number of data, and was calculated as the ratio between the variance of the average 24-h pattern around the mean and the overall variance:

$$IS = \frac{n \sum_{h=1}^{p} (\bar{x}_h - \bar{x})^2}{p \sum_{i=1}^{n} (x_i - \bar{x})^2}$$

where n is the total number of data, p is the number of data per day, $\bar{x}_h$ are the hourly means, $\bar{x}$ is the mean of all data, and x_i represents the individual data points. The IS varies between zero for Gaussian noise and 1 for perfect IS. However, values around zero are reached only for lengthy data sets.

The IV indicates fragmentation of the rhythm, *i.e.* the frequency and extent of transitions between rest and activity. Healthy subjects have a major activity period during the day and a major inactivity period during the night, whereas brief alternating bouts of rest and activity are characteristic of rhythm disturbances (indicated by a higher IV). The IV is calculated as the ratio of the mean squares of the difference between all successive hours (first derivative) and the mean squares around the grand mean (overall variance):

$$IV = \frac{n \sum_{i=2}^{n} (x_i - x_{i-1})^2}{(n-1) \sum_{i=1}^{n} (x_i - \bar{x})^2}$$

The IV values reach near zero for a perfect sinus wave; it is approximately 2 for Gaussian noise and may even be higher when a definite ultradian component with a period of 2 h is present.

The amplitude was calculated as follows. First, the average 24-h pattern was determined by averaging the values of the 7 registration days. From this pattern, the average hourly movement duration was calculated for the least active 5-h period (L5) and for the most active 10-h period (M10). The amplitude was calculated as the difference between M10 and L5.

Questionnaires assessing quality of life

Short Form-36 (SF-36). The SF-36 questionnaire reflects general well-being during the previous 30 d and consists of 36 items. It assesses eight health scales: 1) physical functioning; 2) social functioning; 3) role limitations due to physical health problems; 4) role limitations due to emotional health problems; 5) general mental health (psychological distress and well-being); 6) vitality (energy and fatigue); 7) pain; and 8) general health perceptions and change in health (24, 25). Because the HADS and the MFI-20 are more specific for mental health and fatigue, assessment of vitality and general mental health from the SF-36 were not used. Because the eight scales are scored separately from exclusive item-specific questions (26), the results of the scales presented in this study are not influenced by the two items that were left out in this evaluation. Scores are expressed on a 0–100 scale, higher scores being associated with better quality of life.

Hospital Anxiety and Depression Scale (HADS). The HADS consists of 14 statements scoring anxiety and depression. Each item is measured on a four-point scale. Scores for the anxiety and depression subscale range from 0 to 21, and for the total scale from 0 to 42. A high score points to more severe anxiety and depression (27). A total score of 13 or more was considered increased.

Multidimensional Fatigue Inventory (MFI-20). The MFI-20 assesses fatigue and contains 20 statements to be answered on a five-point scale (3). Five different dimensions of fatigue (four items each) are calculated from these statements: 1) general fatigue; 2) physical fitness; 3) reduction in activity; 4) reduction in motivation; and 5) mental fitness. Dimension scores vary from 0 to 20. Higher scores indicate more experienced fatigue.

Questionnaires assessing sleep quality

Epworth Sleepiness Scale (ESS). The ESS is an eight-item questionnaire. The subject is asked to rate the likelihood of falling asleep in a variety of commonly encountered situations (28). Scores range from 0 (the least sleepy) to 24 (the most sleepy). Scores equal to or above 10 are considered increased daytime sleepiness (29).

Clinical Symptom score for sleep disorders. This questionnaire is used in clinical practice by departments of pulmonology and sleep clinics to assess symptoms related to 1) chronic sleep-related complaints, and 2) sleep-disordered breathing and its consequences for daytime functioning (30). It consists of 12 questions to be answered with yes or no, and scores range from 0 to 12. A higher score indicates more sleeping difficulties.

Berlin Questionnaire (BQ). The BQ consists of 10 questions about risk factors for sleep apnea subdivided into three categories: 1) snoring behavior (6 points); 2) daytime sleepiness or fatigue (3 points); and 3) the presence of obesity or hypertension (2 points) (31). If there are two or more categories where the score is positive (categories 1 and 2, two or more points; category 3, one or more points), a person is at high risk of having sleep apnea (31).

Pittsburgh Sleep Quality Index (PSQI). The PSQI assesses sleep quality and disturbances over a 1-month time interval. Nineteen items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Each component has a range of 0–3 points, with higher points indicating more difficulty. The sum of scores for these seven components yields one global score with a range of 0–21 points (32).

Assays

Serum IGF-I concentration (nanograms per milliliter) was measured using an immunometric technique on an Immulite 2500 system (Diagnostic Products Corporation, Los Angeles, CA). The intraassay coefficients of variation were 5.0 and 7.5% at mean plasma levels of 8 and 75 nmol/liter, respectively. IGF-I levels were expressed as SD score based on measurements in 906 healthy individuals (5).

Statistical analysis

SPSS for Windows version 17.0 (SPSS, Inc., Chicago, IL) was used for data analysis. Unpaired t tests, χ^2 tests, Pearson or Spearman's correlation, and ANOVA tests with least significance difference *post hoc* analysis were used when appropriate.

Differences were considered statistically significant at $P < 0.05$ and are marked in *bold*.

Results

Clinical characteristics (Table 1)

All 17 patients had been treated by transsphenoidal surgery for NFMA with suprasellar extension. Fourteen patients (82%) presented with visual field defects or decreased vision, which had resolved after surgery. Five patients received adjuvant radiotherapy for recurrent disease postoperatively. At the time of current evaluation, 29% of the patients had corticotrope deficiency, 65% somatotrope deficiency, 59% thyrotrope deficiency, and 35% gonadotrope deficiency (four of nine males and two of eight females; the other six females were postmenopausal). All patients were properly and stably treated for all pituitary deficiencies, except for GHD, which was untreated in three of 11 GHD patients. Free T_4 levels were in the normal range in all patients: mean (SE) values, 16.3 (0.4) pmol/liter (range, 11.8–19.0 pmol/liter). Mean (SE) IGF-I SD scores were 0.09 (0.4) (range, −2.9 to +2.2), including the three GHD patients without replacement therapy with IGF-I scores less than −2.0 SD. The patients and controls did not differ in gender, age, or BMI.

TABLE 1. Clinical characteristics of NFMA patients and controls

	Patients	Controls	*P* value
n	17	17	
No. of females	8 (47%)	6 (35%)	0.486
Age, median (range) (yr)	54 (26-65)	52 (30-63)	0.499
BMI (kg/m^2)	25.1 ± 2.5	27.1 ± 3.8	0.073
Years after surgery, median (range)	8 (1-18)		
Adjuvant radiotherapy	5 (29%)		
VFD at presentation	14 (82%)		
Pituitary insufficiency			
Any pituitary deficiency	15 (88%)		
ACTH deficiency	5 (29%)		
GHD	11 (65%)		
TSH deficiency	10 (59%)		
LH/FSH deficiency	4 (24%)		
Hardy tumor size			
II. >10 mm	12 (71%)		
III. Localized invasive	4 (24%)		
IV. Diffuse invasive	1 (6%)		
Hardy tumor extension			
A. Suprasellar cistern	1 (6%)		
B. Recesses of 3rd ventricle	16 (94%)		
D. Intracranial (intradural)	1 (6%)		
E. Into or beneath cavernous sinus	4 (24%)		

Data represent number (percentage) or number ± SD, unless described otherwise. VFD, Visual field defects.

TABLE 2. Polysomnography

	Patients	Controls	*P* value
n	17	17	
Sleep period	509 ± 97	487 ± 68	0.457
TST	433 ± 98	455 ± 66	0.441
Sleep latency	4.8 ± 4.1	5.1 ± 2.1	0.831
Sleep efficiency	86.1 ± 9.1	92.9 ± 3.1	**0.008**
AH per hour	5.7 ± 7.5	7.0 ± 6.0	0.607
AH per hour >15	3 (18)	1 (6)	0.287
Sleep phase N1	83.5 ± 45.7	45.7 ± 28.3	**0.007**
% N1 of TST	19.9 ± 10.2	9.5 ± 4.4	**0.001**
Sleep phase N2	183.2 ± 52.6	181.7 ± 30.3	0.923
% N2 of TST	42.3 ± 9.0	40.3 ± 7.0	0.478
Sleep phase N3	87.4 ± 54.3	112.9 ± 31.8	0.104
% N3 of TST	19.8 ± 9.3	24.6 ± 5.1	0.073
Sleep phase REM	77.0 ± 30.6	114.5 ± 20.2	**<0.001**
% REM of TST	17.1 ± 5.0	25.4 ± 4.4	**<0.001**
Awake	67.4 ± 47.1	31.8 ± 16.4	**0.008**
% awake of SP	13.7 ± 9.1	6.6 ± 3.1	**0.006**
PLM per hour	16.1 ± 18.8	17.0 ± 7.7	0.912
Lowest saturation (%)	85.5 ± 8.2	87.4 ± 5.3	0.431
Pulse frequency (bpm)	61.5 ± 7.3	59.1 ± 8.5	0.400

Data represent minutes ± SD or number (percent). AH, Apnea and hypopnea; PLM, periodic limb movements; SP, sleep period. *Bold* data indicate differences considered statistically significant at $P < 0.05$.

Sleep characteristics

Polysomnography (Table 2)

Polysomnography was performed during one night in all subjects. Total sleep duration was not different between patients and controls. However, patients spent more time of their period in bed being awake than controls ($P = 0.006$) and, consequently, exhibited lower sleep efficiency ($P = 0.008$). Patients also spent approximately 10% more time in stage N1 of non-REM sleep ($P = 0.001$). The contribution of N2 sleep phase was not different. Patients spent a shorter percentage of sleep time in REM sleep (17.1 *vs.* 25.4%; $P < 0.001$). The different distribution of sleep stages was not explained by other sleep disorders such as sleep apnea or periodic limb movement disorder. Furthermore, patients and controls did not differ in sleep latency.

Actigraphy (Table 3)

Actigraphy was performed during 7 d and nights, including the night of polysomnography. Patients spent more time in bed than controls (8 h and 29 min *vs.* 7 h and 39 min; $P = 0.002$), and sleep duration was increased (7 h and 7 min *vs.* 6 h and 20 min; $P = 0.007$). Patients also showed more NAPs during the day ($P = 0.017$). Moreover, sleep diaries indicated more awakenings during the night in patients than in controls ($P = 0.019$). Consequently, IV, which indicates the disruption of a clear separation of high activity during the day and low activity during the night (as regulated by the circadian clock), was significantly increased in patients ($P = 0.004$).

TABLE 3. Actigraphy and sleep diary

	Patients	Controls	*P* value
n	17	17	
Actiwatch			
Time in bed	8 h 29 min ± 58 min	7 h 39 min ± 44 min	**0.002**
Actual sleep	7 h 7 min ± 1 h	6 h 20 min ± 53 min	**0.007**
Sleep efficiency	83.5 ± 5.9	81.6 ± 7.2	0.429
Sleep latency	21 ± 11 min	18 ± 19 min	0.562
Fragmentation	30.8 ± 11.3	31.3 ± 8.8	0.947
NAP (n)	8.1 ± 5.1	5.1 ± 2.9	**0.017**
Average activity level	35.6 ± 4.3	38.4 ± 4.3	0.068
L5	9.3 ± 4.4	8.8 ± 2.5	0.686
L5 onset	57 ± 57 min	48 min ± 1 h 1 min	0.657
M10	51.4 ± 4.8	54.0 ± 4.4	0.108
M10 onset	9 h 56 min ± 1 h 27 min	9 h 22 min ± 1 h 31 min	0.277
Amplitude	42.0 ± 5.5	45.1 ± 3.9	0.068
Interdaily stability	0.75 ± 0.10	0.78 ± 0.10	0.449
Intradaily variability	0.44 ± 0.10	0.34 ± 0.07	**0.004**
Diary			
Sleep latency	31 ± 23 min	25 ± 17 min	0.411
Awakenings (n)	1.8 ± 1.1	0.96 ± 0.95	**0.019**
Duration awakening	38 ± 24 min	25 ± 17 min	0.100
Actual sleep	7 h 1 min ± 52 min	6 h 30 min ± 57 min	0.113
Daytime naps (n)	0.16 ± 0.32	0.13 ± 0.48	0.803

Data represent average ± SD. *Bold* data indicate differences considered statistically significant at $P < 0.05$.

Figure 1 illustrates the differences in average activity levels between patients and controls, with the most distinct differences in the early morning activity levels.

There was a good correlation between the data obtained by actigraphy and polysomnography for time in bed and sleep period (r = 0.510; $P = 0.002$) and actual sleep and TST (r = 0.411; $P = 0.016$).

Sleep diary (Table 3)

Subjective sleep was recorded by diaries during the 7 d of the actigraphy measurements. In control subjects, there was a fair and significant correlation between the number of hours slept at night according to actigraphy measurements and according to the sleep diaries (r = 0.619; $P = 0.008$). In contrast, there was no such correlation in the patient group (r = 0.396; $P = 0.115$). This may suggest that the patients are less able to make a fair estimation of the number of hours they actually slept.

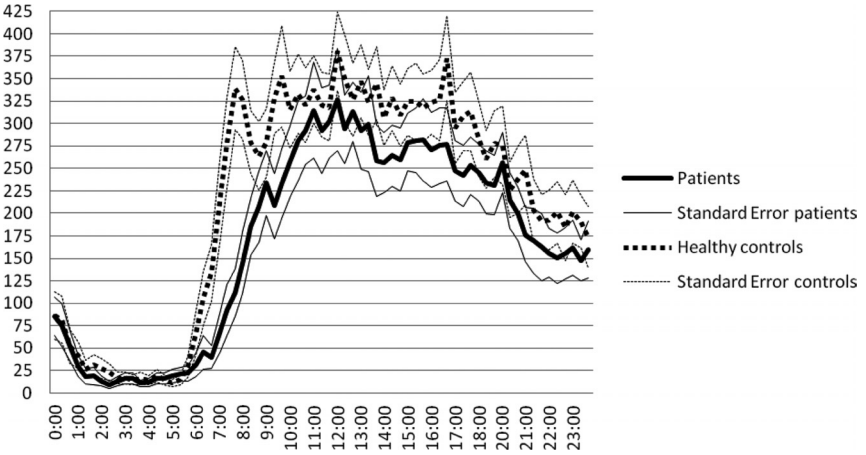

FIG. 1. Average actigraphic activity levels in patients with nonfunctioning macroadenoma and healthy controls. Average 20 min activity level, in counts (each count being ~0.4 g of wrist acceleration) against time in hours.

Questionnaires

Questionnaires assessing quality of life (Table 4)

Patients reported impaired quality of life compared with controls. Patients scored worse on all subscales of the MFI-20, indicating more fatigue. According to the HADS, patients tended to experience somewhat more anxiety and depressive symptoms ($P = 0.044$). However, a minority of patients had a HADS score of 13 or more (four patients *vs.* no controls; $P = 0.033$). According to the SF-36, patients suffered worse on physical function ($P = 0.024$), which played a large role in their daily activities ($P = 0.023$).

Actigraphy parameters correlated with scores of several questionnaires. Increased sleep latency correlated with worse scores of the SF-36 (r = −0.669; $P = 0.005$) and the HADS (r = 0.492; $P = 0.045$); a later M10 onset, reflecting a later start of the most active daytime period, correlated with the SF-36 (r = −0.535; $P = 0.030$), the HADS (r = 0.492; $P = 0.029$), and the MFI-20 (r = 0.483; $P = 0.050$); and a decreased IS correlated with the SF-36 (r = 0.531; $P = 0.005$).

TABLE 4. Questionnaires assessing quality of life

	Patients	Controls	*P* value
n	17	17	
SF-36			
Physical function	85.58 ± 18.8	97.06 ± 3.1	**0.024**
Social function	88.97 ± 16.5	97.06 ± 7.0	0.076
Role physical problem	76.47 ± 35.9	98.53 ± 6.1	**0.023**
Role emotional problem	90.20 ± 19.6	100.00 ± 0.0	0.056
Pain	87.76 ± 18.6	96.40 ± 6.2	0.084
General health perception	68.44 ± 22.6	80.29 ± 12.8	0.071
Change in health	57.81 ± 19.8	50.00 ± 8.8	0.163
HADS			
Anxiety	4.35 ± 3.7	3.12 ± 2.0	0.241
Depression	3.12 ± 2.8	1.47 ± 1.6	**0.044**
Total	7.47 ± 5.7	4.59 ± 3.2	0.079
Total score ≥13	4 (24)	0 (0)	**0.033**
MFI-20			
General fatigue	10.06 ± 4.7	5.82 ± 2.2	**0.003**
Physical fitness	9.17 ± 4.3	5.65 ± 1.8	**0.005**
Reduction in activity	9.29 ± 4.09	5.82 ± 2.0	**0.004**
Reduction in motivation	9.12 ± 3.4	5.12 ± 1.5	**<0.001**
Mental fitness	10.89 ± 5.3	7.12 ± 3.4	**0.020**

Data represent average ± SD or number (percent). *Bold* data indicate differences considered statistically significant at $P < 0.05$.

Questionnaires assessing sleep and sleep quality (Table 5)

Patients had higher scores on the Berlin Questionnaire, suggesting a higher risk for sleep apnea in comparison with controls ($P = 0.020$). The higher score was mainly due to positive answers on questions related to increased tiredness. Most differences in PSQI scores, assessing sleep quality, did not reach significance. However, NFMA patients reported a higher number of sleep disturbances ($P = 0.010$), reflected by questions about long sleep latency, early awakening, breathing difficulties, or uncomfortable temperatures. Furthermore, patients scored worse on the Clinical Symptom score for sleep disorders ($P = 0.001$), mainly due to more reports of drowsiness, fatigue, and trouble in concentrating. ESS scores did not differ significantly between patients and controls.

TABLE 5. Questionnaires assessing sleep quality

	Patients	Controls	*P* value
n	17	17	
BQ, high risk [no. (%)]	5 (29)	0 (0)	**0.020**
PSQI			
Subjective sleep quality	0.88 ± 0.60	0.71 ± 0.59	0.393
Sleep latency	1.35 ± 1.1	0.82 ± 1.0	0.157
Sleep duration	0.82 ± 0.96	1.12 ± 0.60	0.290
Habitual sleep efficiency	0.65 ± 1.2	0.35 ± 0.79	0.396
Sleep disturbances	1.18 ± 0.53	0.71 ± 0.47	**0.010**
Use of sleep medication	0.06 ± 0.24	0.00 ± 0.00	0.325
Daytime dysfunction	0.88 ± 0.86	0.47 ± 0.62	0.119
Total	5.82 ± 3.0	4.18 ± 2.5	0.095
Clinical symptom score	3.71 ± 2.0	1.47 ± 1.4	**0.001**
ESS	6.53 ± 5.8	4.82 ± 3.2	0.299
ESS ≥10 [no. (%)]	5 (29)	1 (6)	0.072

Data represent average ± SD, unless described otherwise. *Bold* data indicate differences considered statistically significant at $P < 0.05$.

Discussion

The aim of the current study was to evaluate whether sleep characteristics were disturbed in patients previously treated for NFMA. Polysomnographic analyses indicated that patients spent a greater part of their night awake than controls, resulting in reduced sleep efficiency compared with controls. When asleep, patients spent relatively more time in drowsiness (N1 stage) and less time in dream sleep. These findings were strengthened by actigraphic measurements during 1 wk, showing that patients spent more time in a nearly immobile state than controls, whereas they had more periods of activity during nights. The questionnaires strengthened the clinical relevance of these data because patients reported considerable fatigue, accompanied by impaired physical and mental fitness, depressive feelings, and limitations in daily life.

These observations indicate that increased fatigue and decreased quality of life in patients treated for NFMA is associated with, and most likely in part is caused by, disturbed sleep characteristics.

The present study confirms our previous study in which we documented increased daytime fatigue in NFMA patients (5). In addition, the presence of decreased quality of life and increased fatigue is in agreement with previous studies (3–5), even in a selection of otherwise healthy NFMA patients.

This study is the first to use polysomnography in a cohort of patients with NFMAs. Previous studies on sleep in pituitary diseases, excluding hormone excess syndromes, are summarized in Table 6. All previous studies were designed to study the effects of GHD or its treatment and included patients with GHD of heterogenous origin. For untreated GHD, the results of these studies vary greatly from an increased slow-wave sleep (SWS), decreased TST, and reduced sleep efficiency (33, 34), to an increased TST and a reduced SWS (35, 36), to even no differences in sleep characteristics (37). For treated GHD, all studies report normalization of sleep characteristics (35–37).

Our study was designed to examine the effect of a previous nonfunctioning adenoma with suprasellar extension on sleep characteristics. Therefore, we studied exclusively NFMA patients in whom hypopituitarism was adequately replaced, except for the three GHD patients without re-

TABLE 6. Studies assessing sleep parameters in patients with nonfunctioning pituitary diseases

First author, year (Ref.)	Design	Method	Subjects	Outcome
Present study, 2010	Cross-sectional	PSG and actigraph	17 NFMA (age, 25–65 yr)	PSG: reduced sleep efficiency, reduced REM sleep, increased sleep phase 1 and awake
			17 controls	Actigraph: longer sleep time, disruption of sleep-wake rhythms
Copinschi, 2010 (34)	Cross-sectional	PSG	33 untreated GHD (age 19-74) pituitary origin (n = 26)	More SWS and higher intensity of SWS. Older patients: less total sleep, fragmented
			Hypothalamic origin (n = 4)	Lower SWS intensity
Schneider, 2005 (37)	Longitudinal	PSG	17 untreated GHD patients	Sleep parameters comparable to healthy controls from literature
			6 months after start GH treatment	No effect of treatment on TST, sleep stages, REM density, daytime somnolence
van Cauter, 2004 (33)	Cross-sectional	PSG and actigraph	9 untreated GHD (pituitary/ hypothalamic), *vs.* 9 healthy controls	Decreased total sleep time, increased wake time, lower sleep efficiency and lower sleep maintenance in patients
Nolte, 2002 (36)	Longitudinal	PSG	5 treated GHD males	No PSG abnormalities, except for one obstructive apnea
			6 months after treatment cessation	Decreased SWS, one central apnea
Aström, 1995 (35)	Longitudinal	PSG	8 isolated GHD, before treatment	TST was increased and total Δ sleep time was reduced
			After treatment	TST normalized and total Δ sleep time was less reduced

PSG, Polysomnography.

combinant human GH substitution. We included predominantly middle-aged patients without comorbidity except for treatment of NFMA and hypopituitarism to exclude the possibility that sleep disorders were due to other medication or comorbidities. It is likely that the exclusion of these patients has underestimated the actual disturbances in sleep characteristics in NFMA patients in general. Therefore, we believe that our findings represent a rather conservative estimation of the magnitude of sleep disturbances in NFMA patients.

Using actigraphy in the evaluation of sleep-wake rhythms has not been previously done in NFMA patients. In a previous study focusing on GHD patients, decreased TST and increased wake time were reported (33), but this study did not assess circadian variation. The main result of our actigraphic measurements was that NFMA patients had more periods of near-zero activity during the day and more awakenings during the night. This increase in IV is associated with decreased functional status and well-being (38).

There are several possible explanations for our results. Damage to the retinohypothalamic tract, either by the tumor or by the treatment, may inhibit entrainment of the circadian clock. For instance, blindness is known to affect the regulation of circadian rhythms, and almost all our patients had had visual field defects preoperatively. However, the visual field defects had recovered completely shortly after surgery in all cases, so there were no major visual defects during the study. It remains unknown whether temporary visual defects might cause long-lasting impairments of diurnal rhythmicity, but this appears unlikely. Another possibility is that the initial tumor, surgery, or radiotherapy may have affected the function of the suprachiasmatic nucleus for a protracted period or affected melatonin secretion. The diurnal variation of melatonin is also controlled by the hypothalamus, but the intrinsic function of the pineal gland, which produces melatonin, is not affected by the pituitary tumor and/or its treatment, in contrast to pituitary functions. It would be interesting to assess the diurnal pattern of melatonin secretion in these patients and to relate this to the sleep patterns. Finally, we cannot exclude the possibility that intrinsic imperfections of long-lasting endocrine treatments alter the complex regulation of sleep (39). Depression *per se* was an unlikely explaining factor, at least in the majority of our cohort, for the observed sleep disturbances.

The results of this study are relevant for both doctors and patients. If patients are informed of these long-term

complications of NFMA in an early state, coping behavior and acceptance might be strengthened. In addition, because most disturbances documented in the present study reflected disturbed circadian regulation, treatment for these complaints should focus on enforcing circadian behavior such as regularization of sleep patterns, for example by maintaining a regular schedule for going to bed and waking up, and engaging in stimulating activities and light exposure immediately after waking up (40).

In conclusion, patients treated for NFMA suffer from decreased sleep quality, disturbed distribution of sleep stages, and disturbed circadian movement rhythm. These impairments are associated with disabling fatigue during the day and impaired quality of life. The observations add to the long-term sequelae of treated NFMA.

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