Alterations in diurnal rhythmicity in patients treated for nonfunctioning pituitary macroadenoma: a controlled study and literature review

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Abstract

Objective: Patients treated for nonfunctioning pituitary macroadenomas (NFMA) have fatigue and alterations in sleep characteristics and sleep–wake rhythmicity frequently. As NFMA often compress the optic chiasm, these complaints might be related to dysfunction of the adjacent suprachiasmatic nucleus (SCN). We aimed to explore whether indirect indices of SCN functioning are altered in the long term after surgery for NFMA.

Methods: We studied 17 NFMA patients in long-term remission after transsphenoidal surgery, receiving adequate and stable hormone replacement for hypopituitarism, and 17 control subjects matched for age, gender, and BMI. Indirect indices of SCN function were assessed from 24-h ambulatory recordings of skin and core body temperatures, blood pressure, and salivary melatonin levels. Altered melatonin secretion was defined as an absence of evening rise, considerable irregularity, or daytime values > 3 pg/ml. We additionally studied eight patients treated for craniopharyngioma.

Results: Distal–proximal skin temperature gradient did not differ between NFMA and control subjects, but proximal skin temperature was decreased during daytime ($P=0.006$). Core body temperature and non-dipping of blood pressure did not differ, whereas melatonin secretion was often altered in NFMA (OR 5.3, 95% CI 0.9–30.6). One or more abnormal parameters (≥ 2.0 SDS of control subjects) were observed during nighttime in 12 NFMA patients and during daytime in seven NFMA patients. Similar patterns were observed in craniopharyngioma patients.

Conclusion: Heterogeneous patterns of altered diurnal rhythmicity in skin temperature and melatonin secretion parameters were observed in the majority of patients treated for NFMA. On a group level, both NFMA and craniopharyngioma patients showed a lower daytime proximal skin temperature than control subjects, but other group averages were not significantly different. The observations suggest altered function of central (or peripheral) clock machinery, possibly by disturbed entrainment or damage of the hypothalamic SCN by the suprasellar macroadenoma or its treatment.

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Introduction

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

We previously reported that patients treated for NFMAs by surgery suffer in the long term from impaired quality of life, increased daytime somnolence, fatigue, and sleeping difficulties (3). In addition, polysomnography showed a lower sleep efficiency and less rapid eye movement (REM) sleep, while actigraphy showed fragmentation of the sleep–wake rhythm and longer sleep duration (3).

It has been postulated that the complaints of fatigue and somnolence can, at least in part, be attributed to hypopituitarism, hormonal replacement therapy (4), and/or an apathy syndrome (5). An alternate hypothesis holds that these complaints result from dysfunction of the suprachiasmatic nucleus (SCN). The SCN consists of a small group of hypothalamic neurons located in direct proximity to the optic chiasm, controlling the sleep–wake cycle and coordinating this with circadian rhythms in other brain areas and other tissues (6). Indirect support for this line of thought has been provided by a recent study in which a history of a suprasellar tumor with permanent visual field defects (NFMA in one of five patients) was associated with a reduced arginine vasopressin immunoreactivity in post-mortem SCN tissue (7).

Our aim is to explore whether diurnal parameters reflecting SCN function are altered in the long term after surgery for NFMAs. We investigated a comprehensive set of indices of SCN function consisting of 24-h ambulatory recordings of blood pressure, skin and core body temperatures, and salivary melatonin levels. We compared the results with those of healthy control subjects matched for gender, age, and BMI. For illustrative purposes, we additionally examined a small number of patients treated for craniopharyngioma, as a model for usually more extensive damage, *inter alia* to the hypothalamus (8).

Subjects and methods

Subjects

Patients were selected from a database containing all patients consecutively treated by transsphenoidal surgery for NFMAs in our institution ($n=226$), between 1960

and 2008. Inclusion criteria were stable and adequate substitution of pituitary insufficiencies for at least 6 months (see [Supplementary Information File](#), see section on [supplementary data](#) given at the end of this article for definitions) and an age of 18–65 years. Patients using hypnotics or psychotropic medication were excluded, as were patients suffering from conditions that may alter circadian rhythmicity, i.e. sleep disorders, depression, hypertension, dyslipidemia, and diabetes mellitus. A total of 43 patients fulfilled the inclusion criteria, of whom 17 participated. The clinical characteristics (including age, gender, tumor extension, visual field defects, or adjuvant radiotherapy) of the participants did not differ from those who did not participate. Visual field defects were assessed by Goldmann perimetry and evaluated by an ophthalmologist, who was unaware of the outcomes of the study.

In this study 17 gender-, age-, and BMI-matched control subjects were recruited via advertisement in local newspapers, using the same inclusion and exclusion criteria except for pituitary pathology.

Additionally, we studied eight patients previously treated for craniopharyngioma by transsphenoidal surgery. Identical inclusion and exclusion criteria were used as for NFMAs, except that the presence of hypertension and dyslipidemia was allowed because these conditions are frequently present in craniopharyngioma patients. As the craniopharyngioma group size was small, unmatched to the control subjects, and with considerable comorbidity, these patients were studied for illustrative purposes, and the results will only be discussed concisely (for details, see [Supplementary File](#)).

Methods

Study design ► In this exploratory study, we assessed diurnal rhythmicity in 17 NFMA patients and 17 control subjects, using 24-h recordings of blood pressure, skin temperature, core body temperature, and 36-h profiles of salivary melatonin level. Measurements were obtained at home to facilitate normal sleep, simultaneous with previously reported polysomnographic and actigraphic measurements (see [Supplementary Fig. 1](#) for study schedule) (3).

In eight patients treated for craniopharyngioma, we studied skin and core body temperatures, subjective complaints by questionnaires, sleep characteristics by polysomnography, and sleep–wake rhythmicity by

actigraphy (see [Supplementary File](#) for methods and results from polysomnography, actigraphy, and questionnaires).

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

Recordings of 24-h skin and core body temperatures

► Core body temperature was monitored for ~24 h at 1 min intervals by an ingestible Capsule Sensor (Jonah, Mini Mitter Co, Bend, OR, USA), with an accuracy of ± 0.05 °C between 32 and 42 °C, and sent to the wearable Vitalsense monitor (Respironics, Bend, OR, USA). To minimize the influence of food and drinks, subjects were instructed to maintain an intake diary and consume only the products of 36–38 °C during the first 8 h.

Skin temperature was measured at 1 min intervals for 24 h using a wireless Thermochron iButton DS1921H (Maxim/Dallas Semiconductor Corp., San Jose, CA, USA), with a mean accuracy of -0.09 °C and precision of 0.05 °C (9) fixed to the skin using a Fixomul tape (Beiersdorf, Hamburg, Germany). An automated artifact rejection procedure as used by Lichtenbelt *et al.* (9) was applied to exclude extreme drops and rises in temperature. Distal skin temperature was defined as the average of the thenar eminence of both palms and the medial metatarsal area of the plantar side of both feet. Measurements at both infraclavicular areas, 1 cm supraumbilical, and the left mid-thigh on the rectus femoris muscle, were used to calculate the proximal skin temperature (10): $0.383 \times \text{mid-thigh} + 0.293 \times \text{infraclavicular} + 0.324 \times \text{supraumbilical}$. The distal–proximal gradient represents thermoregulatory skin blood flow of the extremities (11). Data were analyzed separately for the day and night periods (diary times of being in or out of bed).

Melatonin sampling ► Melatonin was measured in saliva, which is a reliable index of serum melatonin level (12). Saliva was collected using Salivettes (Sarstedt, Nümbrecht, Germany) on two subsequent evenings (at 3, 2, and 1 h before and at habitual bedtime, and upon waking up spontaneously at night) and on the day in between (at awakening, 1 and 2 h after awakening, noon, and 3 p.m.) (13).

Patients were instructed to remain seated for 10 min before sampling to minimize the influence of postural changes (14), avoid eating or drinking for 30 min before sampling and report mucosal wounds (15). From 4 h before bedtime, until habitual bedtime, subjects were

instructed to remain in dim light, e.g. by dimming light such that reading is just possible, closing the curtains, not sitting close to a lamp, not using a computer, and staying at least 3 m away from a television. During the entire collection period, subjects were not allowed to consume food dyes, chocolate, or banana (tryptophan increases melatonin production (16)), and alcohol, caffeine, or nonsteroidal anti-inflammatory drugs (which decrease melatonin levels (17, 18, 19)).

Samples were kept in the dark at 4 °C until the end of assessment, and then stored at -20 °C until analysis. Samples were centrifuged at 1800 *g* for 15 min and aliquots of 400 µl were added to RIA kit tubes (RK-DSM; Bühlmann Laboratories AG, Schönenbuch, Switzerland). The detection limit was 0.3 pg/ml and the intra-assay and inter-assay precisions were 7.9 and 11.7% respectively.

Melatonin data were fitted to a skewed baseline cosine function (SBCF, see ‘Statistical analysis’ section) (13). Altered melatonin secretion was defined as an absence of evening rise, daytime values >3 pg/ml, or severe irregularity in melatonin secretion, as indicated by non-fitting of the SBCF. Outliers were defined as values that severely deviated from the prior and following sample and that prevented adequate SBCF fitting.

Measurement of 24-h blood pressure ► During 24 h, using a Mobil-O-Graph v.12 (Industrielle Entwicklung Medizin (I.E.M.) technik GmbH, Stolberg, Germany) oscillometric blood pressure measurements were performed every 10 min (day) or 30 min (night) with an accuracy of ± 3 mmHg. Data were analyzed using Hypertension Management V6.02.040 (I.E.M. GmbH). Non-dipping of mean arterial pressure (MAP) in the evening was defined as $\text{MAP}_{\text{night/day}} < 10\%$ (20).

Patterns of alterations in diurnal parameters ► To evaluate the distribution of alterations in all diurnal parameters within the patient cohort, and to identify patterns of altered parameters, Z-scores were calculated for individual patients, based on the control subjects’ average and s.d. Altered diurnal parameters were defined as those deviating by more than 2.0 SDS and are separated for nighttime; i.e. low distal–proximal gradient, a delayed trough time or decreased trough depth in nighttime core body temperature, no melatonin rise, or non-dipping of blood pressure, and daytime, i.e. increased distal–proximal gradient, increased core body temperature, or increased melatonin values. Results were compared with the Z-scores from polysomnography and actigraphy, which were reported previously (3).

Statistical analysis

The skewed baseline cosine function (SBCF) (13) was used to fit the melatonin data too. This function parsimoniously quantifies the typical fixed low level during daytime and allows for skewness of the nocturnal peak, i.e. differences in the steepness of the rising and falling limb of the melatonin peak:

$$Y(x) = b + \frac{H}{2(1-c)} (\cos(x-\phi + v\cos(x-\phi)) - c + |\cos(x-\phi + v\cos(x-\phi)) - c|)$$

Y represents the predicted value of melatonin at time x (in radians, $0-2\times\pi$). The five parameters are directly proportional to the baseline level (b , average level during daytime), the relative peak height (H , peak level), the width (c , duration of peak), the phase (ϕ , in radians), and the skewness (v) of the peak. The best fit was calculated using the Levenberg–Marquardt algorithm for nonlinear curve fitting included in using SPSS for Windows, version 20.0 (SPSS, Inc.). The onset time of the rise from baseline was calculated as $(\phi-0.5c)/(2\pi)$, the peak time as the time of the highest SBCF value, the absolute peak as $b+H$, and the skewness of the evening upslope as $H/(\text{top time}-\text{starting time of rise})$. Patients were instructed to maintain their habitual bedtime, and melatonin samples were collected relative to that bedtime. To correct for the influence of differences in habitual bedtime on the individual timing of melatonin secretion, the data of all subjects were aligned at the individual bedtimes.

Unpaired Student's t -tests, Pearson's χ^2 -test or Fisher's exact test, and Pearson's or Spearman's correlation were used when appropriate. Differences were considered statistically significant at $P<0.05$.

Results

Clinical characteristics

All 17 NFMA patients (age 26–65 years, eight females) had been treated by transsphenoidal surgery for suprasellar extension and were in remission, considered as absence of or stable residual adenoma, for a median of 8 years (range 1–18 years) (Table 1). The tumor size according to Hardy's classification was invasive (III/IV) in six patients, extending into the suprasellar cistern in one, into the recesses of the third ventricle in 17 patients, and in the parasellar region in five patients; 14 patients (82%) presented with visual field defects that had resolved almost completely

postoperatively; and five patients received postoperative radiotherapy for remnants or postoperative tumor growth. At inclusion, 29% had adrenocorticotrophic hormone (ACTH) deficiency, 65% growth hormone (GH) deficiency (GHD), 59% thyroid-stimulating hormone deficiency, and 35% luteinizing hormone/follicle-stimulating hormone deficiency (four males and two females, the other females were postmenopausal). All patients received adequate stable replacement therapy for pituitary deficiencies except for GHD, which was untreated in three out of 11 GHD patients due to contraindications or patient's preference. As per inclusion criterion of the NFMA group, all patients were otherwise healthy. The 17 control subjects did not differ from the NFMA patients in gender, age, or BMI.

Diurnal variation in skin and core body temperatures

Distal–proximal gradient did not differ significantly between NFMA patients and control subjects, but the proximal skin temperature during daytime was decreased in NFMA patients (mean difference 0.49 °C, 95% CI 0.15–0.84 °C, $P=0.006$; Table 2). There were no significant group differences in the core body temperature or in any of the nighttime parameters. Within patients, lower proximal skin temperature during daytime correlated with more general fatigue (MFI-20 questionnaire; $r=-0.523$, $P=0.031$) and lower physical function (SF-36 questionnaire; $r=0.558$, $P=0.020$). In addition, a higher distal–proximal gradient during daytime correlated with less physical fitness (MFI-20; $r=0.479$, $P=0.052$ and SF-36; $r=-0.560$, $P=0.020$).

Melatonin curves in saliva

In three NFMA patients and eight control subjects, a distinct outlier was removed to fit the SBCF, and in seven NFMA patients (vs two control subjects), the two subsequent evening rises were so differently timed that only the first evening was used for fitting (Table 3).

Abnormal melatonin secretion was observed in seven NFMA patients vs two control subjects (OR 5.3, 95% CI 0.9–30.6, $P=0.12$). Of these seven NFMA patients, the SBCF curve could not be fitted in five NFMA patients due to either an absence of evening rise ($n=4$) or considerable irregularity ($n=1$). In one of the four patients with an absent evening rise, nighttime melatonin production was observed in a 0400 h sample. In the other three, no night samples were collected. In control subjects, only two curves could not be adequately fitted, both due to

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Table 1 Clinical characteristics of patients with NFMA or CR, and healthy control subjects. Data represent *n* (%) or average $\pm$ s.d., unless described otherwise.

	NFMA (<i>n</i> = 17)	CR (<i>n</i> = 8)	Control subjects (<i>n</i> = 17)
No. of women	8 (47%)	1 (13%)	6 (35%)
Age (years), median (range)	54 (26–65)	50 (31–62)	52 (30–63)
BMI (kg/m ²)	25.1 $\pm$ 2.5	29.1 $\pm$ 2.7*	27.1 $\pm$ 3.8
Waist circumference (cm)	100.6 $\pm$ 12.9*	102.4 $\pm$ 9.1*	91.4 $\pm$ 10
Years after surgery, median (range)	8 (1–18)	21 (11–35)	
Adjuvant radiotherapy	5 (29%)	4 (50%)	
VFD at presentation	14 (82%)	7 (88%)	
Any pituitary insufficiency	15 (88%)	8 (100%)	
Sleep characteristics ^a			
Total sleep time (min)	433 $\pm$ 98	439 $\pm$ 67	455 $\pm$ 66
Sleep efficiency	86.1 $\pm$ 9.1*	87.7 $\pm$ 4.4*	92.9 $\pm$ 3.1
% NREM 1 of TST	19.9 $\pm$ 10.2*	7.9 $\pm$ 4.3	9.5 $\pm$ 4.4
% NREM 2 of TST	42.3 $\pm$ 9.0	38.1 $\pm$ 10.0	40.3 $\pm$ 7.0
% NREM 3 of TST	19.8 $\pm$ 9.3	24.0 $\pm$ 13.5	24.6 $\pm$ 5.1
% REM of TST	17.1 $\pm$ 5.0*	18.5 $\pm$ 4.7*	25.4 $\pm$ 4.4
% awake of sleep period	13.7 $\pm$ 9.1*	11.6 $\pm$ 4.4*	6.6 $\pm$ 3.1
Apnea or hypopnea per hour	5.7 $\pm$ 7.5	3.9 $\pm$ 3.4	7.0 $\pm$ 6.0
Sleep–wake rhythmicity ^b			
Average activity level	35.6 $\pm$ 4.3	38.4 $\pm$ 4.2	38.4 $\pm$ 4.3
Interdaily stability	0.75 $\pm$ 0.10	0.77 $\pm$ 0.11	0.78 $\pm$ 0.10
Intradaily variability	0.44 $\pm$ 0.10*	0.38 $\pm$ 0.07	0.34 $\pm$ 0.07
Subjective sleep quality ^c			
Berlin Questionnaire (high risk)	5 (29%)*	4 (50%)*	0 (0%)
Clinical symptom score	3.71 $\pm$ 2.0*	4.38 $\pm$ 1.85*	1.47 $\pm$ 1.4
Epworth Sleepiness Scale	6.53 $\pm$ 5.8	11.38 $\pm$ 4.31*	4.82 $\pm$ 3.2
Quality of life ^c			
HADS (total score)	7.74 $\pm$ 5.7	6.38 $\pm$ 4.6	4.59 $\pm$ 3.2
SF-36 (physical function)	85.58 $\pm$ 18.8*	75.63 $\pm$ 25.4*	97.06 $\pm$ 3.1

VFD, visual field defects; CR, craniopharyngioma; HADS, Hospital Anxiety and Depression Scale; SF-36, Short Form-36. *Significantly different from control subjects at $P < 0.05$.

^aAssessed with polysomnography.

^bAssessed with actigraphy.

^cSee reference (3) for NFMA details and Supplementary Information File for CR details.

irregularity of the evening rise. However, nighttime melatonin production was observed in both of them. Furthermore, in three NFMA patients (vs zero control subjects), increased mid-daytime melatonin values were observed (4.1, 4.3, and 67.7 pg/ml respectively), indicating incomplete suppression of melatonin production during daytime. Within patients, altered melatonin secretion correlated with more sleep disturbances (PSQI questionnaire; $r = 0.644$, $P < 0.01$) and lower physical function (SF-36 questionnaire; $r = -0.486$, $P = 0.048$). SBCF parameters of fitted curves did not differ significantly between patients and control subjects, nor did habitual bedtimes (2326 h $\pm$ 35 min vs 2340 h $\pm$ 39 min, $P = 0.279$).

Diurnal variation in blood pressure

No group differences in the physiological evening drop or morning rise in blood pressure were observed between

NFMA patients and control subjects (Table 4). Daytime systolic blood pressure was mildly increased in NFMA patients (mean difference 8.2 mmHg, 95% CI 0.3–16.2 mmHg, $P = 0.042$).

Patterns of alterations in diurnal parameters

Diurnal parameters during the night ► Out of 17 NFMA patients, 12 (71%) showed at least one of the five possible abnormal parameters during the night (Fig. 1), i.e. a low distal–proximal gradient ($n = 1$), a delayed trough time ($n = 2$), or decreased trough depth ($n = 3$) in nighttime core body temperature, no melatonin rise ($n = 4$), or non-dipping of blood pressure ($n = 2$).

The two most illustrative cases showed a nighttime distal–proximal gradient of -6.4 and -1.6 SDS. In these cases, polysomnography revealed an increased sleep period ($+2.4$ and $+1.4$ SDS), decreased percentages

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Table 2 Skin and core body temperatures in patients with NFMA or CR and healthy control subjects. Data represent average $\pm$ s.d. ($^{\circ}$ C).

	NFMA	CR ^a	Control subjects	P value ^b	
				NFMA	CR
Skin temperature (n)	17	7	17		
Distal skin temperature					
Daytime	33.3 $\pm$ 1.0	33.1 $\pm$ 0.94	33.4 $\pm$ 0.63	0.649	0.324
Nighttime	35.3 $\pm$ 0.73	34.7 $\pm$ 0.94	35.4 $\pm$ 0.50	0.553	0.071
Proximal skin temperature					
Daytime	33.5 $\pm$ 0.54	33.3 $\pm$ 0.87	34.0 $\pm$ 0.44	0.006	0.017
Nighttime	35.5 $\pm$ 0.47	34.7 $\pm$ 1.00	35.7 $\pm$ 0.34	0.232	0.032
Distal-proximal gradient					
Daytime	−0.24 $\pm$ 0.99	−0.24 $\pm$ 0.83	−0.62 $\pm$ 0.62	0.179	0.219
Nighttime	−0.22 $\pm$ 0.81	−0.02 $\pm$ 0.17	−0.40 $\pm$ 0.40	0.436	0.024
Core body temperature (n)	17	5	17		
Daytime	37.1 $\pm$ 0.24	36.7 $\pm$ 0.35	37.0 $\pm$ 0.18	0.115	0.197
Nighttime	36.6 $\pm$ 0.24	36.5 $\pm$ 0.40	36.5 $\pm$ 0.22	0.107	0.787
Lowest value at night	36.3 $\pm$ 0.26	36.2 $\pm$ 0.45	36.2 $\pm$ 0.22	0.116	0.843
Time of the lowest value	2:06 $\pm$ 2:02	0:53 $\pm$ 1:19	1:22 $\pm$ 0:59	0.329	0.915

CR, craniopharyngioma.

^aDistal skin temperature could not be assessed in one patient and core body temperature in three CR patients due to measurement errors.

^bNFMA/craniopharyngioma vs control subjects.

of REM-sleep (−2.6 and −2.7 SDS), and NREM phase 3 (−2.5 and −3.1 SDS, deep slow-wave sleep), and increased percentages of NREM phase 1 (+3.7 and +7.1 SDS, drowsiness) and the awake period during the night (+8.4 and +0.6 SDS). Furthermore, actigraphy showed an increased variability of activity within days (+5.1 and +2.1 SDS) and more daytime periods of inactivity (+6.6 and +1.6 SDS), indicating fragmentation of the dichotomous activity pattern of day and night. Finally, their core temperature reached its lowest point during the night relatively late (+2.4 and +2.6 SDS). No alterations in blood pressure rhythmicity were observed.

Diurnal parameters during daytime ► Out of 17 NFMA patients, seven (41%) showed at least one of the three possible abnormal parameters during daytime, i.e. either an increased distal-proximal gradient ($n=4$), increased core body temperature ($n=2$), or increased melatonin values ($n=4$). Furthermore, lower daytime proximal skin temperatures in NFMA patients were associated with increased daytime melatonin values ($r=-0.527$, $P=0.036$), indicating that this feature may be linked to altered SCN function.

The four most illustrative patients showed high values of melatonin at 3 p.m. (+5.7, +6.7, +15.4, and +16.7 SDS)

Table 3 Melatonin SBCF in NFMA patients and healthy control subjects. Data are expressed as average $\pm$ s.d. or n (%).

	NFMA ($n=17$)	Control subjects ($n=17$)	P value
SBCF fitted	12 (71%)	15 (88%)	0.398
Baseline level (pg/ml)	0.49 $\pm$ 0.31	0.53 $\pm$ 0.28	0.796
Top height (pg/ml)	12.49 $\pm$ 7.22	12.43 $\pm$ 6.39	0.983
Acrophase (radian)	0.83 $\pm$ 0.29	0.65 $\pm$ 0.32	0.150
Width (radian)	−0.12 $\pm$ 0.16	−0.01 $\pm$ 0.20	0.148
Skewness (radian)	0.13 $\pm$ 0.28	0.02 $\pm$ 0.29	0.310
Strength of fit (R^2)	0.97 $\pm$ 0.03	0.96 $\pm$ 0.03	0.204
Time of start rise ^a	−2 h 19 min $\pm$ 1 h 13 min	−2 h 35 min $\pm$ 1 h 12 min	0.578
Slope (pg/ml per h)	2.18 $\pm$ 1.60	2.03 $\pm$ 1.05	0.773
Top time ^a	+3 h 41 min $\pm$ 1 h 33 min	+3 h 23 min $\pm$ 1 h 1 min	0.558
Abnormal profile ^b	7 (41%)	2 (12%)	0.118

SBCF, skewed baseline cosine function.

^aRelative to the person's habitual bedtime (mean bedtimes: 2326 h $\pm$ 35 min for NFMA and 2340 h $\pm$ 39 min for control subjects).

^bDefined as either non-fitting of the SBCF (five patients vs two control subjects) or daytime values >3 pg/ml (three patients vs zero control subjects).

Table 4 24-h Blood pressure in NFMA patients and healthy control subjects. Data are expressed as average $\pm$ s.d. (mmHg).

	NFMA (n=17)	Control subjects (n=17)	P value
Daytime			
Systolic	131.7 $\pm$ 10.6	123.5 $\pm$ 12.1	0.042
Diastolic	80.6 $\pm$ 9.6	78.9 $\pm$ 9.5	0.619
Nighttime			
Systolic	111.8 $\pm$ 10.9	106.1 $\pm$ 12.1	0.162
Diastolic	67.7 $\pm$ 8.5	65.6 $\pm$ 9.9	0.509
Dipping			
Δ MAP day–night	15.2 $\pm$ 5.7	14.7 $\pm$ 7.3	0.808
Non-dipping ^a	2 (13%)	1 (6%)	1.000
Morning rise			
Start time	4:58 $\pm$ 1:46	4:44 $\pm$ 1:47	0.718
End time	10:09 $\pm$ 1:27	10:11 $\pm$ 1:40	0.946
Time of max. rise	7:36 $\pm$ 1:16	7:28 $\pm$ 1:15	0.775
Maximum slope of rise (mmHg/h)	7.14 $\pm$ 2.80	7.71 $\pm$ 3.64	0.632

MAP, mean arterial pressure.

^aLess than 10% decrease in MAP, n (%).

and increased daytime distal–proximal skin temperature gradient (+1.6, +2.2, +2.8, and +1.9 SDS). A tendency toward a higher variability of activity within days (+0.9, +2.4, +0.4, and +3.9 SDS) and more daytime inactive periods (+1.4, −0.8, +2.4, and +2.7 SDS) was also observed by actigraphy. Blood pressure rhythmicity was not altered in any of them.

Inadequate diurnal parameters either during day- or nighttime did not correlate with clinical characteristics (including visual field defects) or treatment.

Craniopharyngioma patients

Skin and core body temperatures ► In accordance with the observations in NFMA patients, proximal skin temperature was decreased in craniopharyngioma patients when compared with control subjects ([Supplementary File](#)). In addition, the nighttime proximal skin temperature was also decreased, and the distal–proximal skin temperature gradient during the night was higher than control subjects.

Polysomnography and actigraphy ► As reported in NFMA patients (3), craniopharyngioma patients had increased percentages of awakening at night, lower sleep efficiency, and decreased percentages of REM sleep, when compared with control subjects. Furthermore, a slight trend toward increased fragmentation of day–night rhythmicity was observed by actigraphy.

Questionnaires ► Compared with control subjects, craniopharyngioma patients reported profoundly decreased quality of life, increased fatigue and sleepiness, and decreased sleep quality in questionnaires.

Discussion

The aim of this study was to explore whether indirect indices of diurnal SCN functioning were altered in the long term after surgery for NFMA. The main results were decreased proximal skin temperature during daytime, and altered patterns of melatonin secretion in 41% of patients. We did not observe significant group differences in core body temperature and blood pressure rhythmicity.

Although increasing attention has been focused on hypothalamic function in patients with pituitary disease ([Table 5](#)), research on diurnal rhythmic parameters is complex. The SCN rostrally projects into the adjacent preoptic area of the anterior hypothalamus that serves a central and direct role in the thermoregulation (21). The well-established 24-h pattern in both core and skin temperature, especially the relative warming of distal skin (expressed as the distal–proximal gradient), is closely related to sleep initiation (22). In addition to these direct effects of the SCN on thermoregulation, distal–proximal gradient is indirectly influenced via the effects of melatonin, secretion of which from the pineal gland is regulated by the SCN (23). In addition to the direct

Figure 1

Individual Z-scores of nonfunctioning pituitary macroadenomas (NFMA) and craniopharyngioma patients. BP MAP, mean arterial blood pressure; CBT, core body temperature; DPG, distal–proximal skin temperature gradient; PST, proximal skin temperature.

Table 5 Studies assessing temperature regulation, melatonin production, or blood pressure rhythms in adult patients with diseases in the suprasellar region.

References	Diurnal parameter	Subjects	Outcome
(46)	Melatonin plasma, 8×/24 h	Eight CD and four CS (untreated), and five control subjects	Decreased nighttime and increased daytime production in CS/CD
(47)	Melatonin, 24 h plasma	11 ACRO, 25 PRL, and 42 control subjects	Increased daytime and decreased nighttime production in both tumors
(48)	Melatonin, 24 h plasma every 4 h	11 CD/five CS, 19 ACRO, and 33 control subjects	Increased daytime secretion in acromegaly, no correlation with GH or IGF1. Normal secretion in Cushing's disease
(49)	Melatonin, 24 h plasma every 3 h	Eight acromegaly after radiotherapy	Decreased nocturnal secretion
(50)	Melatonin, 48 h plasma every 2 h	Ten active ACRO, before/after octreotide administration	Blunted nighttime secretion in ACRO, partial improvement by therapy
(51)	Melatonin, saliva 4×/24 h	79 CRANIO, 19 hypothalamic pilocytic astrocytoma, and 30 control subjects	Decreased nocturnal and morning melatonin levels in both patient groups
(52)	Melatonin, 9×/24 h plasma	11 GHD children with short stature and 11 idiopathic short stature (ISS)	Increased nighttime secretion in GHD compared with ISS
(53)	Melatonin, 24 h plasma	12 CD/CS and seven control subjects	Increased daytime and decreased nighttime values mostly in CS. Improvement by therapy
(40)	Melatonin, 48 h plasma every 20 min (dim light)	Three CRANIO with daytime hypersomnolence	Decreased nocturnal and mean 24-h plasma melatonin
Present study (2014)	Melatonin, saliva minimally 16×/36 h	17 NFMA and 17 control subjects	Decreased nocturnal and increased daytime values in subset
(54)	Skin temperature, 24 h	Hypothalamic compression in dog/rabbit and suprasellar lesions in men	(mostly reversible) Disturbed thermoregulation after compression. Relation with tumor extension in men
(55)	Skin and core body temperatures, 24 h	Seven suprasellar pituitary adenoma (six PRL and one NFMA) and five control subjects	Altered thermoregulation during active disease and normalization after surgery
(56)	Skin temperature during heat exposure/exercise	Six GHD (pituitary) and six control subjects	Decreased heat tolerance in GHD
(27)	Skin temperature, 24 h	15 narcolepsy (known to involve hypothalamic dysfunction)	Decreased daytime PST and increased daytime DST
(57)	Skin temperature, 24 h	33 hypopituitary with optic chiasm compression (16 NFMA) and 17 without (one NFMA)	Decreased daytime PST in optic chiasm compression. Absence of association between pre-sleep DPG and sleep onset latency
Present study (2014)	Skin and core body temperatures, 24 h	17 NFMA, eight CRANIO, and 17 control subjects	Decreased daytime PST in NFMA and CR, increased daytime DPG in subset
(58)	Blood pressure, 24 h	11 CD/five CS, 13 primary aldosterism, and 82 essential hypertension	Non-dipping of BP only in CD/CS
(59)	Blood pressure, 24 h	16 CS (eight pituitary) and 32 hypertensive/33 normotensive control subjects	Increased non-dipping in CS
(60)	Blood pressure, 24 h	Five ACTH deficiency, before/after hydrocortisone once or twice a day	Before: only dipping of diastolic BP. After: significant dipping only in once a day regime
(61)	Blood pressure, 24 h	Ten ACRO before and 6 months after octreotide treatment	Normal diurnal rhythm before treatment, deterioration of rhythm after treatment
(62)	Blood pressure, 24 h	16 ACRO and 16 control	Increased non-dipping in ACRO
(63)	Blood pressure, 24 h	22 patients with GHD	No altered diurnal rhythm in BP both in treated and untreated GHD
(64)	Blood pressure, 24 h	27 patients with GHD	More non-dipping
(65)	Blood pressure, 24 h	80 CD, 20 CS, and 40 essential hypertension control subjects	More non-dipping especially in CD and some improvement after therapy
(66)	Blood pressure, 24 h	61 pituitary macroadenoma (no CD/ACRO), 61 T2DM, and 20 control subjects	Increased non-dipping in both hypopituitarism and T2DM patients
(67)	Blood pressure, 24 h	Ten newly diagnosed CS and ten control subjects	Non-dipping of BP in eight Cushing vs four control subjects
Present study (2014)	Blood pressure, 24 h	17 NFMA and 17 control subjects	Non-dipping of BP in two NFMA vs one control

NFMA, non-functioning pituitary adenoma; ACRO, acromegaly; PRL, prolactinoma; CRANIO, craniopharyngioma; CD, Cushing's disease; CS, Cushing's syndrome; DPG, distal-proximal gradient; PST, proximal skin temperature; DST, distal skin temperature; BP, blood pressure; T2DM, type 2 diabetes mellitus.

soporific effect on the CNS (23), melatonin strongly promotes distal skin warming through selective opening of arteriovenous anastomoses in the skin (24). Although disruptions of temperature rhythmicity have been described in humans following a hypothalamic lesion (25, 26), diurnal regulation of skin temperature has never been studied in a cohort of patients with NFMA. However, our results are in general accordance with findings in other suprasellar or hypothalamic diseases (Table 5). The decrease in proximal skin temperature that we observed might explain the alterations in sleep quality and daytime wakefulness reported previously (3), as decreased proximal skin temperature is related to an increased sleep latency in both narcoleptics and healthy persons (27, 28), and to sleep depth (29).

In addition, altered melatonin secretion might explain the alterations, as 41% of NFMA patients either had high daytime values, no evening rise, or severe irregularity of melatonin secretion. By contrast, only two control subjects had irregularity of the evening rise. Melatonin has never been studied in NFMA patients, but the results are in general accordance with those in other pituitary tumors (Table 5).

Blood pressure follows a distinct diurnal pattern (30). Multisynaptic pathways connect the SCN to the heart (31) and the variations in blood pressure are abolished after a SCN lesion in rodents (32). In addition, both melatonin (33) and skin temperature (34) modulate blood pressure rhythmicity. On the other hand, some have proposed that the effects of sleep and activity patterns (35, 36), and sleep deprivation (37, 38), influence variability in blood pressure more than the direct effects of circadian pace-makers. This, in addition to the exclusion of patients with hypertension, might explain as to why we did not observe differences in the evening drop or morning rise. Although diurnal patterns of blood pressure have not been studied in NFMA patients before, non-dipping has been inconsistently observed in patients with Cushing's syndrome, acromegaly, and GHD (Table 5).

Parameters of hypothalamic diurnal rhythmicity were heterogeneously affected among NFMA patients. From a pathophysiological point of view, it is conceivable that variable damage of SCN and adjacent nuclei may be present in NFMA, regarding the highly variable clinical presentations and an unknown suprasellar growth velocity before presentation. The heterogeneous patterns of alterations might therefore be explained by the great variety of areas within the SCN and its efferent projections that can be damaged by a pituitary macroadenoma, as illustrated by studies attempting to specifically ablate SCN

in rodents (39). In our cohort of NFMA patients, various patterns of altered night parameters were observed in 71% and of daytime parameters in 41% of the patients. The results suggest irreversible damage to the SCN in patients in long-term remission after being treated successfully for NFMA. This suggestion is strengthened by a similar trend of an altered diurnal rhythmicity that we observed in craniopharyngioma patients, who are known to often exhibit hypothalamic dysfunction (8, 40). In addition, the hypothesis is supported by our previous observation of altered sleep characteristics and sleep-wake rhythmicity in long-term postoperative follow-up for NFMA (3). Other reports include decreased sleep duration after compression of the optic chiasm of miscellaneous origin (41) and increased adult sleep duration after cranial radiation therapy in childhood (42).

Alternatively, the decreased sleep efficiency and altered sleep stage distribution that we observed in our previous study (3), or intrinsic imperfections of hormone replacement therapy might cause or contribute to altered entrainment of central and peripheral clocks (43), which in turn could influence diurnal rhythms of melatonin and temperature. However, this does not explain as to why patients with a history of NFMA show disturbed sleep in the first place, even in the absence of hypopituitarism. Therefore, although the disturbed rhythmicity might also cause altered entrainment of clock genes, we believe that these macroadenoma cause damage in the hypothalamic region above the chiasm, resulting in the altered function of (and most importantly) the SCN *inter alia*.

If our hypothesis is correct, NFMA patients with complaints of insomnia, daytime fatigue, or daytime somnolence might benefit from treatment with melatonin, especially when the evening rise is absent. Additionally, behavioral therapy might improve daytime sleepiness, e.g. through regularization of sleep patterns by maintaining a regular schedule for going to bed and waking up, and engaging in stimulating activities and light exposure immediately after waking up (44).

Several limitations of this study need to be addressed. Data were collected at home, providing a patient-friendly assessment of natural sleep resulting in reliable polysomnographic results and an acceptable group size. However, the disadvantage of this method was that melatonin could only be measured at night if patients were awake and environmental temperatures could not be standardized. The latter might have affected the distal skin temperature. Although we assessed a group of patients without comorbidity other than pituitary disease, we cannot exclude that the (variable) degree of

hypopituitarism and its replacement influenced the results. However, this is an innate drawback of all human studies on pituitary disease. For example, oral contraceptives raise the core body temperature in young healthy women (45). In agreement, we found an increased core body temperature (+3.8 SDS at day and +2.9 SDS at night) in two premenopausal NFMA patients using estrogen/progesterone replacement. However, exclusion of these patients did not alter the results.

Finally, as a consequence of the strict exclusion of patients with comorbidity, our cohort represents the healthiest subgroup of patients. It is conceivable that in patients with more comorbidity, the macroadenoma was more damaging, possibly with a higher likelihood of hypothalamic damage. This selection bias, although providing us with the most reliable outcome measurements, might have limited our probability of observing hypothalamic dysfunction.

In conclusion, heterogeneous patterns of altered diurnal rhythmicity in skin temperature and melatonin secretion parameters were observed in the majority of patients treated for NFMA. At a group level, both NFMA and craniopharyngioma patients showed lower daytime proximal skin temperature than control subjects, but other group averages were not significantly different. The observed alterations might be caused by disturbed entrainment of central and peripheral clock machinery or damage of the hypothalamic SCN either caused by the suprasellar macroadenoma, or transsphenoidal surgery. Diurnal and autonomic parameters need to be further studied in larger cohorts of NFMA patients, under controlled and/or provoked circumstances.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-14-0172>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

- 1 Dekkers OM, de Keizer RJ, Roelfsema F, Vd Klaauw AA, Honkoop PJ, van Dulken H, Smit JW, Romijn JA & Pereira AM. Progressive improvement of impaired visual acuity during the first year after transsphenoidal surgery for non-functioning pituitary macroadenoma. *Pituitary* 2007 **10** 61–65. (doi:10.1007/s11102-007-0007-0)
- 2 Park P, Chandler WF, Barkan AL, Orrego JJ, Cowan JA, Griffith KA & Tsien C. The role of radiation therapy after surgical resection of nonfunctional pituitary macroadenomas. *Neurosurgery* 2004 **55** 100–106. (doi:10.1227/01.NEU.0000126885.71242.D7)
- 3 Biermasz NR, Joustra SD, Donga E, Pereira AM, van Duinen N, van Dijk M, van der Klaauw AA, Corssmit EP, Lammers GJ, van Kralingen KW *et al.* Patients previously treated for nonfunctioning pituitary macroadenomas have disturbed sleep characteristics, circadian movement rhythm, and subjective sleep quality. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 1524–1532. (doi:10.1210/jc.2010-2742)
- 4 Romijn JA, Smit JW & Lamberts SW. Intrinsic imperfections of endocrine replacement therapy. *European Journal of Endocrinology* 2003 **149** 91–97. (doi:10.1530/eje.0.1490091)
- 5 Weitzner MA, Kanfer S & Booth-Jones M. Apathy and pituitary disease: it has nothing to do with depression. *Journal of Neuropsychiatry and Clinical Neurosciences* 2005 **17** 159–166. (doi:10.1176/appi.neuropsych.17.2.159)
- 6 Moore RY. Suprachiasmatic nucleus in sleep–wake regulation. *Sleep Medicine* 2007 **8** (Suppl 3) 27–33. (doi:10.1016/j.sleep.2007.10.003)
- 7 Borgers AJ, Fliers E, Siljee JE, Swaab DF, Van Someren EJ, Bisschop PH & Alkemade A. Arginine vasopressin immunoreactivity is decreased in the hypothalamic suprachiasmatic nucleus of subjects with suprasellar tumors. *Brain Pathology* 2013 **23** 440–444. (doi:10.1111/bpa.12016)
- 8 Ullrich NJ, Scott RM & Pomeroy SL. Craniopharyngioma therapy: long-term effects on hypothalamic function. *Neurologist* 2005 **11** 55–60. (doi:10.1097/01.nrl.0000149971.27684.d4)
- 9 van Marken Lichtenbelt WD, Daanen HA, Wouters L, Fronczek R, Raymann RJ, Severens NM & Van Someren EJ. Evaluation of wireless determination of skin temperature using iButtons. *Physiology & Behavior* 2006 **88** 489–497. (doi:10.1016/j.physbeh.2006.04.026)
- 10 Krauchi K, Cajochen C, Mori D, Graw P & Wirz-Justice A. Early evening melatonin and S-20098 advance circadian phase and nocturnal regulation of core body temperature. *American Journal of Physiology* 1997 **272** R1178–R1188.
- 11 Rubinstein EH & Sessler DI. Skin-surface temperature gradients correlate with fingertip blood flow in humans. *Anesthesiology* 1990 **73** 541–545. (doi:10.1097/0000542-199009000-00027)
- 12 Voultsios A, Kennaway DJ & Dawson D. Salivary melatonin as a circadian phase marker: validation and comparison to plasma melatonin. *Journal of Biological Rhythms* 1997 **12** 457–466.
- 13 Van Someren EJ & Nagtegaal E. Improving melatonin circadian phase estimates. *Sleep Medicine* 2007 **8** 590–601. (doi:10.1016/j.sleep.2007.03.012)
- 14 Deacon S & Arendt J. Posture influences melatonin concentrations in plasma and saliva in humans. *Neuroscience Letters* 1994 **167** 191–194. (doi:10.1016/0304-3940(94)91059-6)
- 15 Benloucif S, Burgess HJ, Klerman EB, Lewy AJ, Middleton B, Murphy PJ, Parry BL & Revell VL. Measuring melatonin in humans. *Journal of Clinical Sleep Medicine* 2008 **4** 66–69.
- 16 Wurtman RJ, Larin F, Axelrod J, Shein HM & Rosasco K. Formation of melatonin and 5-hydroxyindole acetic acid from 14C-tryptophan by

- rat pineal glands in organ culture. *Nature* 1968 **217** 953–954. (doi:10.1038/217953a0)
- 17 Wright KP Jr, Badia P, Myers BL, Plenzler SC & Hakel M. Caffeine and light effects on nighttime melatonin and temperature levels in sleep-deprived humans. *Brain Research* 1997 **747** 78–84. (doi:10.1016/S0006-8993(96)01268-1)
 - 18 Ekman AC, Leppaluoto J, Huttunen P, Aranko K & Vakkuri O. Ethanol inhibits melatonin secretion in healthy volunteers in a dose-dependent randomized double blind cross-over study. *Journal of Clinical Endocrinology and Metabolism* 1993 **77** 780–783.
 - 19 Murphy PJ, Myers BL & Badia P. Nonsteroidal anti-inflammatory drugs alter body temperature and suppress melatonin in humans. *Physiology & Behavior* 1996 **59** 133–139. (doi:10.1016/0031-9384(95)02036-5)
 - 20 Birkenhager AM & van den Meiracker AH. Causes and consequences of a non-dipping blood pressure profile. *Netherlands Journal of Medicine* 2007 **65** 127–131.
 - 21 Romanovsky AA. Thermoregulation: some concepts have changed. Functional architecture of the thermoregulatory system. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* 2007 **292** R37–R46. (doi:10.1152/ajpregu.00668.2006)
 - 22 Krauchi K. The thermophysiological cascade leading to sleep initiation in relation to phase of entrainment. *Sleep Medicine Reviews* 2007 **11** 439–451. (doi:10.1016/j.smrv.2007.07.001)
 - 23 Pevet P & Challet E. Melatonin: both master clock output and internal time-giver in the circadian clocks network. *Journal of Physiology* 2011 **105** 170–182.
 - 24 Krauchi K, Cajochen C, Pache M, Flammer J & Wirz-Justice A. Thermoregulatory effects of melatonin in relation to sleepiness. *Chronobiology International* 2006 **23** 475–484. (doi:10.1080/07420520500545854)
 - 25 Schwartz WJ, Busis NA & Hedley-Whyte ET. A discrete lesion of ventral hypothalamus and optic chiasm that disturbed the daily temperature rhythm. *Journal of Neurology* 1986 **233** 1–4. (doi:10.1007/BF00313981)
 - 26 Cohen RA & Albers HE. Disruption of human circadian and cognitive regulation following a discrete hypothalamic lesion: a case study. *Neurology* 1991 **41** 726–729. (doi:10.1212/WNL.41.5.726)
 - 27 Fronczek R, Overeem S, Lammers GJ, van Dijk JG & Van Someren EJ. Altered skin-temperature regulation in narcolepsy relates to sleep propensity. *Sleep* 2006 **29** 1444–1449.
 - 28 Raymann RJ, Swaab DF & Van Someren EJ. Cutaneous warming promotes sleep onset. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* 2005 **288** R1589–R1597. (doi:10.1152/ajpregu.00492.2004)
 - 29 Raymann RJ, Swaab DF & Van Someren EJ. Skin deep: enhanced sleep depth by cutaneous temperature manipulation. *Brain* 2008 **131** 500–513. (doi:10.1093/brain/awm315)
 - 30 Biaggioni I. Circadian clocks, autonomic rhythms, and blood pressure dipping. *Hypertension* 2008 **52** 797–798. (doi:10.1161/HYPERTENSIO-NAHA.108.117234)
 - 31 Scheer FA, Ter Horst GJ, Van der Vliet J & Buijs RM. Physiological and anatomic evidence for regulation of the heart by suprachiasmatic nucleus in rats. *American Journal of Physiology. Heart and Circulatory Physiology* 2001 **280** H1391–H1399.
 - 32 Witte K, Schnecko A, Buijs RM, Van der Vliet J, Scalbert E, Delagrè P, Guardiola-Lemaitre B & Lemmer B. Effects of SCN lesions on circadian blood pressure rhythm in normotensive and transgenic hypertensive rats. *Chronobiology International* 1998 **15** 135–145. (doi:10.3109/07420529808998678)
 - 33 Grossman E, Laudon M & Zisapel N. Effect of melatonin on nocturnal blood pressure: meta-analysis of randomized controlled trials. *Vascular Health and Risk Management* 2011 **7** 577–584.
 - 34 Krauchi K, Gompfer B, Hauenstein D, Flammer J, Pflüger M, Staderus E, Schotzau A & Orgul S. Diurnal blood pressure variations are associated with changes in distal-proximal skin temperature gradient. *Chronobiology International* 2012 **29** 1273–1283. (doi:10.3109/07420528.2012.719961)
 - 35 Smolensky MH, Hermida RC, Castriotta RJ & Portaluppi F. Role of sleep–wake cycle on blood pressure circadian rhythms and hypertension. *Sleep Medicine* 2007 **8** 668–680. (doi:10.1016/j.sleep.2006.11.011)
 - 36 Sheward WJ, Naylor E, Knowles-Barley S, Armstrong JD, Brooker GA, Seckl JR, Turek FW, Holmes MC, Zee PC & Harmar AJ. Circadian control of mouse heart rate and blood pressure by the suprachiasmatic nuclei: behavioral effects are more significant than direct outputs. *PLoS ONE* 2010 **5** e9783. (doi:10.1371/journal.pone.0009783)
 - 37 Stein PK & Pu Y. Heart rate variability, sleep and sleep disorders. *Sleep Medicine Reviews* 2012 **16** 47–66. (doi:10.1016/j.smrv.2011.02.005)
 - 38 Ewing DJ, Neilson JM, Shapiro CM, Stewart JA & Reid W. Twenty four hour heart rate variability: effects of posture, sleep, and time of day in healthy controls and comparison with bedside tests of autonomic function in diabetic patients. *British Heart Journal* 1991 **65** 239–244. (doi:10.1136/hrt.65.5.239)
 - 39 Coomans CP, van den Berg SA, Lucassen EA, Houben T, Pronk AC, van der Spek RD, Kalsbeek A, Biermasz NR, Willems van Dijk K, Romijn JA *et al.* The suprachiasmatic nucleus controls circadian energy metabolism and hepatic insulin sensitivity. *Diabetes* 2013 **62** 1102–1108. (doi:10.2337/db12-0507)
 - 40 Lipton J, Megerian JT, Kothare SV, Cho YJ, Shanahan T, Chart H, Ferber R, Adler-Golden L, Cohen LE, Czeisler CA *et al.* Melatonin deficiency and disrupted circadian rhythms in pediatric survivors of craniopharyngioma. *Neurology* 2009 **73** 323–325. (doi:10.1212/WNL.0b013e3181af78a5)
 - 41 Borgers AJ, Romeijn N, Van Someren EJ, Fliers E, Alkemade A & Bisschop PH. Compression of the optic chiasm is associated with permanent shorter sleep duration in patients with pituitary insufficiency. *Clinical Endocrinology* 2011 **75** 347–353. (doi:10.1111/j.1365-2265.2011.04053.x)
 - 42 Van Someren EJ, Swart-Heikens J, Ender E, Bisschop PH, Swaab DF, Bakker PJ, Romijn JA & Fliers E. Long-term effects of cranial irradiation for childhood malignancy on sleep in adulthood. *European Journal of Endocrinology* 2004 **150** 503–510. (doi:10.1530/eje.0.1500503)
 - 43 Moller-Levet CS, Archer SN, Bucca G, Laing EE, Slak A, Kabiljo R, Lo JC, Santhi N, von SM, Smith CP *et al.* Effects of insufficient sleep on circadian rhythmicity and expression amplitude of the human blood transcriptome. *PNAS* 2013 **110** E1132–E1141. (doi:10.1073/pnas.1217154110)
 - 44 Manber R, Bootzin RR, Acebo C & Carskadon MA. The effects of regularizing sleep–wake schedules on daytime sleepiness. *Sleep* 1996 **19** 432–441.
 - 45 Baker FC, Mitchell D & Driver HS. Oral contraceptives alter sleep and raise body temperature in young women. *Pflügers Archiv* 2001 **442** 729–737. (doi:10.1007/s004240100582)
 - 46 Soszynski P, Stowinska-Szrednicka J, Kasperlik-Zatuska A & Zgliczynski S. Decreased melatonin concentration in Cushing's syndrome. *Hormone and Metabolic Research* 1989 **21** 673–674. (doi:10.1055/s-2007-1009317)
 - 47 Lissoni P, Mainini E, Rovelli F, Mazzi C, Ardizzoia A, Gelosa M, Capra M & Rivolta MR. A clinical study of the pineal hormone melatonin in patients with growth hormone or prolactin secreting pituitary tumours. *European Journal of Medicine* 1992 **1** 407–410.
 - 48 Terzolo M, Piovesan A, Ali A, Codegone A, Pia A, Reimondo G, Torta M, Paccotti P, Borretta G & Angeli A. Circadian profile of serum melatonin in patients with Cushing's syndrome or acromegaly. *Journal of Endocrinological Investigation* 1995 **18** 17–24. (doi:10.1007/BF03349691)
 - 49 Zwirski-Korcza K, Ostrowska Z, Kos-Kudla B, Buntner B & Zych F. The lack of melatonin rhythm in active acromegaly after radiotherapy. *Endocrine Regulations* 1994 **28** 97–103.
 - 50 Sinisi AA, Pasquali D, D'Apuzzo A, Esposito D, Venditto T, Criscuolo T, De Bellis A & Bellastella A. Twenty-four hour melatonin pattern in acromegaly: effect of acute octreotide administration. *Journal of*

- Endocrinological Investigation* 1997 **20** 128–133. (doi:10.1007/BF03346890)
- 51 Muller HL, Handwerker G, Gebhardt U, Faldum A, Emser A, Kolb R & Sorensen N. Melatonin treatment in obese patients with childhood craniopharyngioma and increased daytime sleepiness. *Cancer Causes & Control* 2006 **17** 583–589. (doi:10.1007/s10552-005-9012-7)
 - 52 Karasek M, Stawerska R, Smyczynska J & Lewinski A. Increased melatonin concentrations in children with growth hormone deficiency. *Journal of Pineal Research* 2007 **42** 119–124. (doi:10.1111/j.1600-079X.2006.00388.x)
 - 53 Tomova A, Kumanov P, Robeva R, Manchev S & Konakchieva R. Melatonin secretion and non-specific immune responses are differentially expressed in corticotropin-dependent and corticotropin-independent Cushing's syndrome. *Medical Science Monitor* 2008 **14** CR327–CR332.
 - 54 Clar HE. Disturbances of the hypothalamic thermoregulation. *Acta Neurochirurgica* 1985 **75** 106–112. (doi:10.1007/BF01406330)
 - 55 Behr R, Hildebrandt G, Koca M & Bruck K. Modifications of thermoregulation in patients with suprasellar pituitary adenomas. *Brain* 1991 **114** 697–708. (doi:10.1093/brain/114.2.697)
 - 56 Juul A, Behrenscheer A, Tims T, Nielsen B, Halkjaer-Kristensen J & Skakkebaek NE. Impaired thermoregulation in adults with growth hormone deficiency during heat exposure and exercise. *Clinical Endocrinology* 1993 **38** 237–244. (doi:10.1111/j.1365-2265.1993.tb01001.x)
 - 57 Romeijn N, Borgers AJ, Fliers E, Alkemade A, Bisschop PH & Van Someren EJ. Medical history of optic chiasm compression in patients with pituitary insufficiency affects skin temperature and its relation to sleep. *Chronobiology International* 2012 **29** 1098–1108. (doi:10.3109/07420528.2012.708000)
 - 58 Imai Y, Abe K, Sasaki S, Minami N, Nihei M, Munakata M, Murakami O, Matsue K, Sekino H, Miura Y *et al.* Altered circadian blood pressure rhythm in patients with Cushing's syndrome. *Hypertension* 1988 **12** 11–19. (doi:10.1161/01.HYP.12.1.11)
 - 59 Piovesan A, Panarelli M, Terzolo M, Osella G, Matrella C, Paccotti P & Angeli A. 24-hour profiles of blood pressure and heart rate in Cushing's syndrome: relationship between cortisol and cardiovascular rhythmicities. *Chronobiology International* 1990 **7** 263–265. (doi:10.3109/07420529009056985)
 - 60 Matsumura K, Abe I, Fukuhara M, Fujii K, Ohya Y, Okamura K & Fujishima M. Modulation of circadian rhythm of blood pressure by cortisol in patients with hypopituitarism. *Clinical and Experimental Hypertension* 1994 **16** 55–66. (doi:10.3109/10641969409068584)
 - 61 Fallo F, Barzon L, Boscaro M, Casiglia E & Sonino N. Effect of octreotide on 24-h blood pressure profile in acromegaly. *American Journal of Hypertension* 1998 **11** 591–596. (doi:10.1016/S0895-7061(98)00029-6)
 - 62 Terzolo M, Matrella C, Boccuzzi A, Luceri S, Borriero M, Reimondo G, Pia A, Rovero E, Paccotti P & Angeli A. Twenty-four hour profile of blood pressure in patients with acromegaly. Correlation with demographic, clinical and hormonal features. *Journal of Endocrinological Investigation* 1999 **22** 48–54. (doi:10.1007/BF03345478)
 - 63 Ahmad AM, Hopkins MT, Weston PJ, Fraser WD & Vora JP. Effects of GH replacement on 24-h ambulatory blood pressure and its circadian rhythm in adult GH deficiency. *Clinical Endocrinology* 2002 **56** 431–437. (doi:10.1046/j.1365-2265.2002.01491.x)
 - 64 Conceicao FL, de Rooij Mansur VA, Brasil RR & Vaisman M. Ambulatory monitoring of blood pressure in growth hormone-deficient adults. *Blood Pressure Monitoring* 2002 **7** 89–94. (doi:10.1097/00126097-200204000-00001)
 - 65 Zacharieva S, Orbetzova M, Stoynev A, Shigarminova R, Yaneva M, Kalinov K, Nachev E & Elenkova A. Circadian blood pressure profile in patients with Cushing's syndrome before and after treatment. *Journal of Endocrinological Investigation* 2004 **27** 924–930. (doi:10.1007/BF03347534)
 - 66 Krzyzanowska K, Schnack C, Mittermayer F, Kopp HP, Hofer M, Kann T & Scherthaner G. High prevalence of abnormal circadian blood pressure regulation and impaired glucose tolerance in adults with hypopituitarism. *Experimental and Clinical Endocrinology & Diabetes* 2005 **113** 430–434. (doi:10.1055/s-2005-865772)
 - 67 Fallo F, Maffei P, Dalla PA, Carli M, Della MP, Lupia M, Rabbia F & Sonino N. Cardiovascular autonomic function in Cushing's syndrome. *Journal of Endocrinological Investigation* 2009 **32** 41–45. (doi:10.1007/BF03345677)

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