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CLINICAL STUDY

Sleep disturbances in patients with Addison's disease

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Abstract

Objective: The standard replacement therapy in Addison's disease does not restore normal nocturnal levels of the hormones of the hypothalamic–pituitary–adrenal axis. The aim of the study was to describe the prevalence and characteristics of sleep disturbances in patients with Addison's disease.
Methods: Sixty patients completed a self-administered sleep questionnaire and the Epworth Sleepiness Scale (ESS) questionnaire. Activity-based monitoring (actigraph recordings) and sleep diaries were obtained from eight patients.
Results: Thirty-four percent reported weekly sleep disturbances (difficulties falling asleep in 13%; repeated awakenings in 14%; early morning awakenings in 20%). The sleep need was 8.21 h (S.D. 1.34; range 6–14 h), and sleep onset latency was 29 min (S.D. 29, range 2–150 min). Forty percent of the patients were tired during daily activities more than once a week, but the scores of the ESS were 6.0 (S.D. 3.5), which is not higher than normal. The actigraph recordings showed higher sleep efficiency than the subjective recordings.
Conclusion: We did not identify specific sleep disturbances which were characteristic for patients with Addison's disease. Patients with Addison's disease have increased daytime fatigue, but no more daytime sleepiness than normal.

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Introduction

Patients with primary adrenal failure (Addison's disease) lack the normal diurnal variation in cortisol and dehydroepiandrosterone (DHEA) secretion. In a previous report on subjective health status in a large group of patients under standard replacement therapy we found significantly reduced general health perception and vitality, and increased daytime fatigue (1). Garcia-Borreguero and co-workers (2) recently postulated that reduced quality of sleep might explain some of the daytime fatigue experienced in the patients. With the available replacement therapy these patients have marked cortisol deficiency in the late night, which results in an inappropriate rise in adrenocorticotrophic hormone (ACTH), and presumably high corticotrophin-releasing hormone (CRH) levels during these hours of sleep. Some authors recommend replacement with small doses of synthetic glucocorticoids in the evening to mimic the normal nocturnal rise in serum cortisol (3), but the clinical effects are not well documented, and such treatment carries considerable risk of glucocorticoid-induced sleep disturbances (4, 5).

Most hormones show circadian variation that is regulated by hypothalamic pacemaker cells. Except for melatonin, however, a hormonal feedback mechanism on the timing of the sleep–wake cycle has not been described. Many associations have been described between the hypothalamic–pituitary–adrenal (HPA) axis and sleep architecture (6–8). The balance between growth hormone-releasing hormone (GHRH) and CRH appears to play a key role in sleep regulation (8). CRH inhibits slow-wave sleep (SWS), which is a major component of the restorative non-rapid eye movement (NREM) sleep (9, 10). ACTH primarily affects sleep through its effects on cortisol secretion (6, 8, 11). Cortisol enhances SWS probably by feedback inhibition of CRH (8). High levels of glucocorticoids inhibit rapid eye movement (REM) sleep (4, 12). However, Garcia-Borreguero and co-workers demonstrated that low cortisol levels also interfered with normal REM sleep in patients with adrenal insufficiency (2). Currently, the adrenal androgen precursor, DHEA, is under scrutiny for its effects on neurones (13, 14), and its possible influence on sleep has been discussed (15, 16).

So far no studies have described the prevalence of sleep problems in Addison's disease. High CRH levels, low cortisol levels and DHEA depletion during the night might interfere with physiological sleep, and perhaps cause subjective sleep disturbances. The aim of

this study, therefore, was to describe the prevalence and characteristics of perceived sleep disturbances in a large cohort of patients with Addison's disease on standard replacement therapy.

Subjects and methods

Patients

Eighty patients were invited to participate in the study, of whom 60 responded and gave informed consent (response rate 75%). For subgroup analysis the patient sample was divided into groups with isolated Addison's disease, autoimmune polyendocrine syndrome type I (APS I) and autoimmune polyendocrine syndrome type II (APS II), according to the classification by Neufeld and co-workers (17). The patients' characteristics are shown in Table 1. Data concerning glucocorticoid replacement therapy and shift work was obtained from 25 of the participants. None of these patients worked night shift. The mean daily dose of cortisone acetate was 37.6 mg (S.D. 10.9, range 25–75 mg). The last dose of cortisone acetate was taken between 1600 and 2300 h (mean 1854 h (S.D. 0200 h)). Three patients took prednisolone (2.5 mg, $n = 1$) or dexamethasone (0.025 mg, $n = 2$) in the evening. These 25 patients were categorised according to time of last dose (group 1: 1600–1800 h; group 2: after 1800 h or on prednisolone/dexamethasone).

The participants were recruited from a registry of patients with Addison's disease. The inclusion criteria in this registry is either a basal serum cortisol of less than 200 nmol/l in combination with an elevated plasma ACTH higher than 12 pmol/l, or failure of serum cortisol to rise above 500 nmol/l in a short ACTH test. Immunological and genetic features of the patients have been reported elsewhere (18, 19). The subjective health status in these patients as measured by the Short Form 36 (SF-36; higher scores indicate better health) and Fatigue (higher scores indicate more fatigue) questionnaires has been described in a recent publication (1). Thus the individual subjective health scores were available for correlation with sleep data.

Eight patients with Addison's disease were consecutively recruited from our endocrine outpatient clinic for objective measurement of sleep by activity-based monitoring with an actigraph (see below) for 14 days. During this period the patients also completed a sleep diary, as recommended by Kushida and co-workers (20). These patients were also assessed for depression by use of the Montgomery and Åsbergs Depression Rating Scale.

The investigation was approved by the Regional Committee for Ethics in Medical Research.

Self-reported sleep and sleepiness

The sleep questionnaire comprised 29 items concerning sleep and sleep behaviour during the last 3 months. The first part was a listing of 13 different sleep disturbances (as listed in Table 3), adapted from the Karolinska Sleep Questionnaire (21, 22). The responses were scored as: never [1], more than once per year [2], more than once per month [3], more than once per week [4] and every night or day [5]. Scores of 4 or 5 were considered clinically significant sleep disturbances. We also included questions concerning bedtime, perceived sleep onset latency, wake up time, assumed sleep need, daytime naps and some questions about sleep quality.

The Epworth Sleepiness Scale (ESS) measures sleepiness in the daytime as described and validated by Johns (23, 24). Eight items describe different activities and situations, in which the respondents score their liability to fall asleep (from: would never fall asleep [0] to high risk of falling asleep [3]). The average sleep propensity is the sum of these 8 scores, and a score above 10 points is considered as pathological sleepiness. Normative data from various populations were available for comparison (23, 25).

Objective sleep assessment

The actigraph (Actiwatch, Cambridge Neurotechnology Ltd, Cambridge, UK) records intensity and frequency of movement using a piezoelectric linear accelerometer. The orientation and sensitivity of the accelerometer are optimised for highly effective sleep–wake interference from wrist activity, which has been validated previously (20). Data from the actigraph, collected in 1-min epochs, were transferred via an interface to a computer and analysed (Actiwatch sleep analysis 98, version 4.13). We inserted the lights-off time and the get-up time from each respective day based on the

Table 1 Patients' characteristics.

	All ($n = 60$)	Isolated Addison's disease ($n = 26$)	APS I ($n = 7$)	APS II ($n = 27$)	Women ($n = 34$)	Men ($n = 26$)
Women/men	34/26	12/14	4/3	18/9		
Age (years)						
Mean (S.D.)	45.7 (16.0)	43.9 (19.5)	38.7 (9.5)	49.2 (12.9)	49.4 (16.2)	40.9 (14.7)
Range	17–85	17–85	21–52	20–74	21–85	17–84

sleep diary, and the software then calculated values for sleep onset latency (SOL), sleep efficiency, total sleep time and early morning awakening (interval between wake-up time and get-up time).

Statistics

The results are presented by descriptive statistics, as means with S.D. or ranges when appropriate. The sleep behaviour and sleep scores were analysed by multiple linear regression (backward stepwise). The proportions of the patients who reported sleep disturbances once a week or more were compared by multiple logistic regression analysis. The independent variables in the regression analyses were categorised, and dummy variables were introduced when necessary. Spearman's rank correlation coefficient (r_s) was calculated for certain sleep scales and for the SF-36 and Fatigue scales (1). The χ^2 test was employed for comparison with normative data. $P = 0.05$ was chosen as the level of significance.

Results

Self-reported sleep and sleepiness

Bedtime, get-up time, sleep need and SOL in the weekdays are shown in Table 2. The sleep need and SOL did not depend upon gender, age or disease category. The working disabled patients reported significantly higher sleep need (mean 8.88 h vs 7.82 h, $P = 0.04$) and SOL (mean 46.1 min vs 23.3 min, $P = 0.01$) than patients in work (not shown in table). Forty-two percent of the patients (36% of the men and 48% of the women, not shown in table) reported SOL $\geq$ 30 min. Mental health scores (SF-36) were non-significantly better in the patients with SOL $<$30 min compared with those with SOL $\geq$ 30 min (mental health scores 82 (S.D. 11) vs 75 (S.D. 16), $P = 0.08$).

The reported sleep disturbances are shown in Table 3. None of these scores depended significantly on age, gender or disease category. We found no correlation between the sleep disturbances and mental health status as measured by the SF-36.

The percentage of patients who reported clinically significant sleep disturbances (defined as once a week or more often) are shown in Table 4. None of these percentages varied significantly between age groups, gender, disease categories and dosage regimens. However, the percentage of patients who reported early morning awakenings increased with higher age groups. Patients in the age group 35–50 years reported less difficulty falling asleep and fewer awakenings than those in the younger and older age groups. A high percentage of the patients who took their last dose of cortisone acetate later than 1800 h reported weekly awakenings. Fifteen percent of the patients estimated a weekly or daily sleep deficit of 1 h or more, and 5% had taken sleep medication for a shorter or longer period (not shown in table). Thirty-two percent of the employed patients reported sleeplessness that had interfered with working abilities during the last year, and 25% of all the patients reported some kind of problems with sleep (not shown in table).

Average sleep propensity as measured by the Epworth Sleepiness Scale (ESS) was 6.0 (S.D. 3.5; median 6.0). Nine percent had an ESS score higher than 10. The ESS score did not correlate with the Vitality ($r_s = -0.11$, $P = 0.45$) or the mental health ($r_s = -0.24$, $P = 0.10$) scores of the SF-36, nor with the Fatigue scores ($r_s = -0.10$, $P = 0.49$). The ESS scores did not depend upon age, gender or disease category. The extent to which the patients reported that they were tired or sleepy during daily activities (Table 3) correlated weakly the ESS scores ($r_s = 0.39$, $P = 0.004$).

Objective sleep recordings

The results from eight patients are presented in Table 5. The actigraphy showed lower SOL and less awakenings (wake after sleep onset and early morning awakenings)

Table 2 Sleep behaviour in 60 patients with Addison's disease, presented as mean clock time (S.D.).

	Bed time (h)	Get-up time (h)	Sleep onset latency (h)	Sleep need (h)
Gender				
Women (n = 34)	2249 (0034)	0713 (0114)	0032 (0027)	0814 (0132)
Men (n = 26)	2301 (0038)	0651 (0102)	0027 (0031)	0802 (0131)
P-value[1]			$>$ 0.20	$>$ 0.20
Disease category				
Addison's disease (n = 26)	2251 (0044)	0656 (0101)	0025 (0021)	0812 (0157)
APS I (n = 7)	2251 (0033)	0654 (0101)	0029 (0026)	0800 (0033)
APS II (n = 27)	2300 (0027)	0721 (0110)	0035 (0035)	0809 (0114)
P-value[2]			$>$ 0.20	$>$ 0.20
All	2255 (0036)	0705 (0109)	0029 (0029)	0821 (0134)

[1,2]Comparison by multiple linear regression analysis: [1]between the genders and [2]between patients with isolated Addison's disease and patients with autoimmune polyglandular syndromes (APS I and APS II).

Table 3 Self-reported sleep disturbances and daytime sleepiness in 60 patients with Addison's disease as scored from items adapted from the Karolinska Sleep Questionnaire. The scores are presented as mean (S.D.), the scores representing: never [1], more than once per year [2], more than once per month [3], more than once per week [4] and every night or day [5].

	Difficulties falling asleep	Repeated awakenings	Early morning awakenings	Too little sleep	Nightmares	Snoring	Breathing pauses during sleep	Vivid dreams when falling asleep	Tired or sleepy during daily activities	Unwanted sleep attacks at work or at school	Unwanted sleep attacks at home	Need to fight against sleep	Sudden loss of muscular strength (cataplexy)
Gender													
Women	2.5 (0.8)	2.6 (1.1)	2.3 (1.3)	3.0 (1.1)	1.6 (0.7)	2.5 (1.5)	1.2 (0.6)	1.7 (0.8)	3.4 (1.0)	1.4 (0.7)	1.9 (0.9)	2.5 (1.0)	1.7 (1.0)
Men	2.6 (1.2)	2.3 (1.0)	2.5 (1.0)	2.6 (1.2)	1.8 (0.7)	2.8 (1.4)	1.8 (1.3)	1.8 (0.8)	3.0 (1.2)	1.7 (1.0)	2.1 (1.1)	2.4 (1.0)	1.4 (0.7)
P-value[1]	> 0.20	> 0.20	> 0.20	> 0.20	0.18	0.16	0.04	> 0.20	0.11	> 0.20	> 0.20	> 0.20	> 0.20
Disease category													
Addison's disease	2.3 (0.9)	2.3 (1.2)	2.4 (1.1)	2.8 (1.4)	1.5 (0.6)	2.4 (1.3)	1.6 (0.1)	1.6 (0.7)	3.3 (1.2)	1.6 (0.7)	2.1 (0.9)	2.6 (0.9)	1.5 (0.8)
APS I	2.9 (1.3)	2.4 (1.1)	2.4 (1.3)	2.9 (0.7)	1.9 (0.9)	3.1 (1.6)	1.3 (0.8)	2.3 (1.0)	3.6 (0.8)	2.0 (1.0)	2.5 (1.0)	2.6 (1.3)	1.6 (1.1)
APS II	2.6 (0.9)	2.6 (0.9)	2.3 (1.2)	2.8 (1.1)	1.9 (0.8)	2.8 (1.6)	1.5 (1.1)	1.8 (0.8)	3.0 (1.1)	1.5 (0.9)	1.7 (0.9)	2.3 (1.1)	1.6 (0.9)
P-value[2]	0.14	> 0.20	> 0.20	> 0.20	0.05	> 0.20	> 0.20	0.13	> 0.20	> 0.20	> 0.20	> 0.20	> 0.20
All	2.5 (1.0)	2.4 (1.0)	2.4 (1.2)	2.8 (1.2)	1.7 (0.7)	2.7 (1.5)	1.5 (1.0)	1.8 (0.8)	3.2 (1.1)	1.6 (0.8)	2.0 (1.0)	2.4 (1.0)	1.6 (0.9)

[1,2]Comparison by multiple linear regression analysis: [1]between genders and [2]between patients with Addison's disease and patients with autoimmune polyglandular syndromes (APS I and APS II).

Table 4 Percentage of weekly sleep disturbances in 60 patients with Addison's disease as scored by items adapted from the Karolinska Sleep Questionnaire.

	Difficulties falling asleep	Repeated awakenings	Early morning awakenings	Tired or sleepy during daily activities
Gender				
Women (n = 34)	6	16	23	48
Men (n = 26)	23	12	17	31
P-value[1]	0.08	> 0.20	> 0.20	> 0.20
Age				
Age < 34 years (n = 15)	27	13	7	40
Age 35–50 years (n = 23)	8	9	14	35
Age > 50 years (n = 22)	14	18	39	47
P-value[2]	0.15	> 0.20	> 0.20	> 0.20
Disease category				
Addison's disease (n = 26)	12	13	17	46
APS I (n = 7)	29	0	29	43
APS II (n = 27)	11	11	22	35
P-value[3]	> 0.20	> 0.20	> 0.20	> 0.20
Doseage of cortisone acetate*				
Last dose at 1800 h or before (n = 14)	21	7	0	29
Last dose after 1800 h (n = 11)	18	30	40	50
P-value[4]	> 0.20	0.18	> 0.20	> 0.20
All (n = 60)	13	14	20	40

[1,2,3,4]Comparison by multiple logistic regression analysis: [1]between genders, [2]between patients aged 35–50 and the others, [3]between patients with Addison's disease and patients with autoimmune polyglandular syndromes (APS I and APS II) and [4]between patients taking the last dose of cortisone acetate before or after 1800 h. *Data from 25 of the patients.

than that recorded by the patients in the sleep diaries. Three of the patients (nos 4, 6 and 8) reported low sleep efficiency in the sleep diaries, but this was only verified by actigraphy in patient no. 6, who also displayed anxiety and mild depression.

Discussion

We have studied self-reported sleep disturbances in patients with Addison's disease and found that the majority of our patients did not have clinically important sleep disturbances. However, 33% of the patients experienced weekly sleep disturbances, characterised by difficulty falling asleep in 13%, repeated awakenings in 14% and early morning awakenings in 20% of the patients.

Forty-two percent of the patients in our study reported sleep onset latency of 30 min or more, but only 13% reported weekly or daily difficulties in falling asleep. This discrepancy between high SOL and perceived difficulty initiating sleep is also a finding in other populations (26, 27). In a large population-based survey in several European countries, Ohayon and co-workers found SOL of 30 min or more in as much as 37.6% of the general population (26). Ursin and co-workers (27) described shorter self-reported SOL in a Norwegian reference population of 40- to 45-year-old people. This age group possibly has less difficulty falling asleep than both younger and older people (27), and we, too, found this tendency. Furthermore, objective measurement by actigraphy in eight patients showed shorter SOL than that recorded by the patients in their sleep diaries. Taken together, difficulty in falling asleep does not appear to be a clinical problem that is associated with Addison's disease.

Pharmacological treatment with glucocorticoids is associated with problems maintaining sleep (4, 5). However, this was not particularly frequent in our patients, perhaps since most of the patients took their latest dose of cortisone acetate several hours before bedtime. Interestingly, we found problems with awakenings in a high proportion of the patients who took their last glucocorticoid dose after 1800 h. Among those who experienced sleeping problems, early morning awakening was the most frequent complaint. Since the early morning is the period of the largest hormonal disturbances in Addison's disease, disturbed early morning sleep is not unlikely. On the other hand, actigraphy showed generally high sleep efficiency, and the perceived early morning awakenings experienced by some of these patients could be attributed to clinical depression and higher age. The perception of sleep deficit was no higher among the patients than in the general population (27, 28). Thus, other than awakenings that could possibly be associated with late ingestion of glucocorticoids, we did not find particularly frequent awakenings among the patients. However, several studies have shown only a weak correlation between self-reported sleep and physiological sleep (20). Therefore, further studies of physiological sleep by use of sleep EEG are warranted.

Table 5 Sleep diary and actigraph recordings in 8 patients with Addison's disease.

				Sleep diary				Actigraph								
Patient no.	**Bed time** (h)	**Get-up time** (h)	**Time in bed** (h)	Sleep onset latency (h)	Wake after sleep onset (h)	Early morning awakening (h)	Sleep efficiency (%)	Sleep onset latency (h)	Wake after sleep onset (h)	Early morning awakening (h)	Sleep efficiency (%)	**Gender**	**Age** (years)	**Duration of Addison's disease** (years)	**MADRS**	**Other**
1	0039	0804	0725	0011	0006	0000	96	0000	0104	0000	86	Male	35	23	9	Olanzapine
2	2313	0759	0846	0019	0050	0036	80	0001	0056	0009	88	Female	45	20	8	
3	0016	0746	0730	0025	0014	0012	89	0001	0102	0000	86	Male	45	29	4	
4	2320	0810	0850	0004	0034	0353	49	0005	0024	0004	94	Male	45	38	18	
5	0002	0755	0753	0009	0029	0022	87	0005	0029	0001	92	Male	45	3	10	
6	0046	1005	0919	0024	0048	0103	76	0020	0128	0027	77	Male	55	7	11	APS II
7	2202	0810	1008	0015	0123	0010	82	0009	0055	0008	88	Female	35	1	18	
8	2308	0742	0834	0018	0009	0215	68	0003	0037	0008	89	Female	65	38	2	
Mean	2341	0813	0833	0015	0034	0103	78	0005	0051	0007	88		46	20	10	

MADRS = Montgomery and Åsberg's depression rating scale (range 0–60).

The patients went to bed slightly earlier, and rose slightly later than a Norwegian reference population of 40- to 45-year-old people (27). We did not identify specific sleep phase disorders associated with Addison's disease. This indicates that although the daily cortisol surge is delayed by approximately 4 h in these patients, the circadian pacemaker cells seem undisturbed. Working disability defined a group with significantly increased sleep need. This subgroup of patients had also previously reported reduced subjective health status as measured by the SF-36 (1). The perceived high sleep need in this group may, of course, be influenced by the opportunity to sleep longer than patients who are employed. On the other hand, these patients may be more vulnerable to the hormonal disturbances, or less well treated than the others, which could result in both reduced subjective health status and increased sleep need.

The sleep propensity of our patients, as measured by the ESS, was not different from that which has been described in control populations (23, 25). On the contrary, the proportion that reported that they were tired or sleepy in the daytime at least once a week (40%) was high compared with the corresponding figures in middle-aged Norwegians (17%) surveyed by the same questionnaire (27). Only some of this may be attributed to higher age in the patient group, since the scores in this scale only weakly correlated with age. It is noteworthy that the sleep propensity did not correlate with the Fatigue scale or the Vitality scores of the SF-36, which indicates that fatigue and sleepiness are distinctly different entities. We may, therefore, conclude that patients with Addison's disease are fatigued, but not sleepy.

In conclusion, we did not identify specific sleep disturbances which were characteristic for patients with Addison's disease on standard replacement therapy. Most of these patients do not experience clinically important sleep disturbances. Patients with Addison's disease have increased daytime fatigue, but no more daytime sleepiness than normal.

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