CUSHING'S SYNDROME IS ASSOCIATED WITH SLEEP ALTERATIONS DETECTED BY WRIST ACTIGRAPHY

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Cushing's syndrome is associated with sleep alterations detected by wrist actigraphy

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Abstract

Background

The association between the hypothalamic–pituitary–adrenal (HPA) axis and sleep is well described. It is also known that HPA axis disturbances have an effect on sleep. In fact, patients affected by Cushing's syndrome (CS) often complain about poor sleep quality. Our aim was to evaluate objective sleep quality and duration in patients with Cushing's syndrome in active phase, using wrist actigraphy.

Patients and methods

In 12 patients with active CS without ongoing specific therapy (11 F, 1 M; age 40.0 ± 10.9 years; BMI 28.4 ± 6.7 kg/m^2) and 12 healthy control subjects (HS) (11 F, 1 M; age 44.0 ± 11.0 years; BMI 23.9 ± 4.2 kg/m^2) an actigraphic evaluation was performed on 3 consecutive days under free living conditions. Objective measurement of sleep duration and quality was estimated by an actiwatch, which is a wristwatch-like device used to detect motor activity.

Results

In CS patients, wrist actigraphy showed higher fragmented sleep (fragmentation index CS 16.2 ± 4.2, HS 13.0 ± 3.6; $p = 0.034$) and increased nocturnal motor activity (total activity score CS 8318 ± 4308, HS 4971 ± 2372; $p = 0.020$; mean activity score CS 8.7 ± 4.2, HS 5.4 ± 2.2; $p = 0.030$; mean score in active time CS 104.8 ± 39.2, HS 74.8 ± 23.1; $p = 0.030$). On the contrary, actual sleep time resulted similar in CS and HS. No correlation was found between sleep alterations and urinary free cortisol in patients.

Conclusions

The impaired actigraphic parameters described in our study suggest that hypercortisolism is associated with sleep alterations, which could contribute to the worsening of life quality and metabolic comorbidities associated with CS. These results have to be confirmed in a larger cohort of patients, using more accurate instruments for sleep assessment.

Introduction

Endogenous Cushing's syndrome (CS) is a relatively rare disease caused by chronic exposure to excess glucocorticoids produced by the adrenal glands. In Europe the annual incidence has been reported to range from 0.7 to 2.4 per million population [1]. CS is associated with an increased cardiovascular risk, showing a mortality rate four times higher than in the normal population [2, 3], due to glucocorticoid-induced metabolic impairments like central obesity, glucose intolerance, hyperlipidemia, and hypertension.

High corticosteroids levels induce detrimental effects also on brain, causing neurological and psychiatric symptoms, such as cognitive dysfunction, anxiety, irritability, and depression [4]. Moreover, patients with Cushing's syndrome, as well as those with exogenous glucocorticoid excess, often complain about sleep disruptions and daytime sleepiness. A tight bidirectional relationship between the hypothalamus–pituitary–adrenal (HPA) axis and sleep architecture is well documented; the nadir of both ACTH and cortisol secretion occurs during the first half of the night when the SWS phases prevail, whereas the ACTH and cortisol peaks are evident during the second half of the night when REM predominates on SWS [15]. Additionally, several

studies have demonstrated that neuropeptides and hormones controlling the HPA axis play a specific role in sleep regulation. For instance, early studies showed that corticotropin-releasing hormone (CRH), released from the hypothalamic paraventricular nucleus, increases vigilance and shallow sleep and decreases SWS [15].

However, the relationship between hypercortisolism and the variations in sleep quality and quantity has not been fully explored yet. Indeed, only few studies have evaluated sleep in CS using polysomnography (PSG), reporting reduced slow wave sleep (SWS), increased sleep latency, enhanced wake time, shortened rapid eye movement (REM) latency, and elevated REM density [5, 6]. Instead of PSG, which represents the gold standard for sleep assessment, it has been suggested that other cost-effective procedures might be used as screening tools for sleep disorders. For example, wrist actigraphy can usefully provide a good estimation of the sleep-wake cycle under ambulatory conditions for days, weeks, or even longer, objectively measuring sleep duration and fragmentation without differentiating REM sleep from non-REM sleep [7]. It is generally used for monitoring insomnia, circadian sleep-wake disturbances, and periodic limb movement disorder [7, 8]. Wrist actigraphy has been validated against PSG, demonstrating a correlation for sleep duration between 0.82 in insomniacs and 0.97 in healthy subjects [9]. As sleep disorders have been shown to increase the risk of developing cardiovascular diseases [10–12], it is conceivable that the cardiometabolic profile of patients with hypercortisolism may be worsened by impaired sleep.

Based on this background, we hypothesized that excessive cortisol concentrations can alter sleep in treatment-naïve patients with active endogenous CS. To confirm our hypothesis, we used wrist actigraphy to objectively evaluate sleep duration and quality, for the first time in patients with hypercortisolism.

Subjects and methods

The study was approved by the Ethics Committee of the University of Turin, in agreement with the Declaration of Helsinki, and all participants gave written informed consent.

Twelve patients (11 women and 1 man) with endogenous CS were selected at diagnosis, before starting specific therapy: 8 with ACTH-secreting pituitary adenoma, 4 with cortisol-secreting adrenal adenoma. Out of the 12 patients, 8 had arterial hypertension, 5 dyslipidemia, 4 impaired glucose tolerance, and 1 diabetes mellitus. CS was diagnosed according to international criteria [13]: high 24-h urinary free cortisol (UFC), absent cortisol suppression after low-dose dexamethasone test (>1.8 μg/dl), and lack of the cortisol circadian rhythm (midnight cortisol >7.5 μg/dl). The diagnosis of ACTH-independent CS was based on low plasma ACTH levels and the presence of an adrenal lesion on CT or MRI. ACTH-dependent hypercortisolism (Cushing's disease) was defined as the presence of normal or high plasma ACTH levels, cortisol suppression after high-dose dexamethasone test, pituitary adenoma on MRI and was confirmed by bilateral inferior petrosal sinus sampling when necessary [14].

Twenty-four hour UFC was assayed on two different urine collections within 1 week before the wrist actigraphy monitoring.

Twelve age- and sex-matched subjects (11 women and 1 man) were enrolled as healthy controls (HS).

Neither the patients nor the healthy controls assumed any psychotropic medication in the month before the sleep evaluation. Other exclusion criteria included night shift workers and subjects having traveled across >2 time zones less than 1 month prior to the study.

In all subjects sleep recording was continuously assessed for 3 consecutive days and nights by an actigraph device (Actiwatch, Mini Mitter Co., Inc.; Bend, OR, USA) placed on the non-dominant wrist. The actigraph is an accelerometer that detects motion in all directions and converts it in a voltage depending on the frequency and intensity of the movement. The sampling epoch was set at 1 min and the "immobility"

threshold sensitivity at medium level (40), so that an epoch is scored as either “sleep” or “wake” if the number of activity counts is ≤40 or >40, respectively, based on the assumption that there is less movement during sleep and more during wake. Data collected were downloaded onto the computer and elaborated by the Actiwatch software producing several sleep parameters.

In our analyses the following actigraphic parameters were used:

- *Assumed sleep* the time difference between the sleep end and the sleep start;
- *Actual awake time* the time after the sleep start during which the activity counts exceed the threshold sensitivity value for wake set by the user;
- *Actual sleep time* calculated by subtracting the actual awake time from the assumed sleep;
- *Number of minutes immobile* the total number of minutes during the assumed sleep where the counts per minute are below the predetermined “immobility” threshold set by the user;
- *Number of minutes moving* the total number of minutes where scores greater than the “immobility” threshold were recorded during the assumed sleep;
- *Total activity score* a summation of all the activity counts during the assumed sleep;
- *Mean activity score* determined dividing the total activity score by the number of epochs during the assumed sleep period;
- *Mean score in active time* determined by dividing the total activity score by the number of epochs during which activity counts were scored;
- *Fragmentation index* a measure of the amount of interruption of sleep by physical movement; it is calculated as follows: 100× the number of groups of consecutive immobile epochs/by the total number of immobile epochs.

During the wrist actigraphy monitoring subjects were asked to fill out a sleep diary reporting bed time, sleep start, sleep end, and get up time. Moreover, all subjects and bed partners were asked about obstructive respiratory events during the assessment period. Data are expressed as mean ± standard deviation (SD). Differences in demographic and actigraphic data between patients and control subjects were tested using the Mann–Whitney nonparametric test. The Spearman rank correlation analysis was used to test for linear correlations. Threshold for statistical significance was set to $p = 0.05$. Statistical tests were performed using SPSS Statistics (v17 for Windows: SPSS Inc., 1989–2005, Chicago IL, USA).

Results

Demographic and actigraphic data are summarized in Table 1.

Table 1 Demographic and clinical features of Cushing’s syndrome patients (CS) and healthy controls (HS)

	CS (n = 12)	**HS (n = 12)**	***p***
Age (years)	40.0 ± 10.9	44.0 ± 11.0	NS
Gender (F; M)	11; 1	11; 1	NS
BMI (kg/m^2)	28.4 ± 6.7	23.9 ± 4.2	0.036
UFC (μg/24 h)	304 ± 185	–	–
Assumed sleep (hh:mm)	07:59 ± 00:55	07:22 ± 00:51	0.094
Actual awake time (hh:mm)	00:43 ± 00:10	00:33 ± 00:12	0.051
Actual sleep time (hh:mm)	07:08 ± 00:54	06:48 ± 00:44	0.177
Number of minutes immobile	434 ± 56	411 ± 44	0.137
Number of minutes moving	39 ± 10	32 ± 11	0.086
Total activity score	8318 ± 4308	4971 ± 2372	0.020
Mean activity score	8.7 ± 4.2	5.4 ± 2.2	0.030
Mean score in active time	104.8 ± 39.2	74.8 ± 23.1	0.030
Fragmentation index	16.2 ± 4.2	13.0 ± 3.6	0.034

Mean age (±SD) was 40.0 ± 10.9 years and 44.0 ± 11.0 years in CS patients and HS, respectively. There were no gender and age differences between CS patients and HS, as they were age- and sex-matched with HS. However, CS patients showed higher BMI (CS 28.4 ± 6.7 kg/m^2 vs. HS 23.9 ± 4.2 kg/m^2, $p = 0.036$).

In the CS group, mean UFC was 304 ± 185 μg/24 h (reference range values 20–90 μg/day), confirming the treatment-naïve active hypercortisolism.

Compared with HS, CS patients showed a higher fragmentation index (CS 16.2 ± 4.21 vs. HS 13.0 ± 3.6, $p = 0.034$), higher total activity score (CS 8318 ± 4308 vs. HS 4971 ± 2372, $p = 0.020$), higher mean activity score (CS 8.7 ± 4.2 vs. HS 5.4 ± 2.2, $p = 0.030$), and higher mean score in active time (CS 104.8 ± 39.2 vs. HS 74.8 ± 23.1, $p = 0.030$) measured by actigraphy. A trend for higher actual awake time was observed in the CS group (CS 43′ ± 10′ vs. HS 33′ ± 12′, $p = 0.051$).

No difference between the two groups was found in assumed sleep, actual sleep time, number of minutes immobile, and number of minutes moving.

No correlation between sleep variables and UFC levels was found in CS patients ($-0.6 < r < 0.6$, $p > 0.05$).

In both patients and healthy controls no significant correlation was found between any sleep variable and BMI or age ($-0.6 < r < 0.6$, $p > 0.05$), even when combining the two groups together.

Objective sleep data were consistent with self-reporting sleep logs. No perception of obstructive sleep apnea event was reported in both groups.

Discussion

Scientific knowledge about the effects of chronic hypercortisolism on sleep parameters in humans is scanty. Previous studies assessing sleep in patients with Cushing's disease demonstrated the detrimental effects of high glucocorticoid levels on sleep quality [5, 6] using EEG only or full polysomnography (PSG), which is the gold standard method for assessing sleep.

Objective estimations of sleep duration and fragmentation may be also obtained by wrist actigraphy monitoring, which can be used under ambulatory conditions.

This is the first experimental study to evaluate sleep quality in CS patients by wrist actigraphy so far. Our results confirm that increased glucocorticoid levels are associated with sleep disruptions. Compared with sex- and age-matched healthy subjects, patients with active CS seemed to have alterations in sleep quality only, with apparently preserved sleep quantity. Indeed, patients and controls showed similar sleep periods whereas an increase in the fragmentation index and activity scores was observed in the CS group. This suggests that, even with no difference between groups in movement time recorded by actigraphy, active hypercortisolism was associated with more frequent nocturnal fragmentations and a higher frequency and/or intensity of wrist movements. These sleep patterns, as well as the trend toward a higher wake time in patients, may partially contribute to a less restorative sleep. In agreement with our results showing a higher fragmentation index, Shipley et al. [6] reported an increase in nocturnal awakenings in 11 non-apneic Cushing's disease patients evaluated with PSG, yet they found an increase in wake time and sleep latency.

Since actigraphy doesn't measure sleep stages, a specific analysis on SWS and REM alterations in CS, as previously described, could not be performed. Additionally, actigraphy doesn't assess the overnight distribution of awakenings, fragmentations, and movements and whether they are more prevalent in REM or non-REM sleep. In term of understanding the mechanism of higher fragmentation in CS, the lack of EEG to assess sleep architecture is a limitation of our study. The relevance of changes in fragmentation index,

with no changes in total sleep duration, without sleep architecture is problematic. However, even without assessment of EEG and breathing, actigraphy turns to be able to detect differences in sleep quality between CS and controls.

The alterations observed in our patients might be mainly explained by the high concentrations of cortisol, according to the several mechanisms postulated in the literature [15–17]. It is noteworthy that Cushing's syndrome is characterized not only by hypercortisolism but also the typical loss of circadian cortisol rhythm, which we hypothesize may play an additional role in sleep alterations found in our and other previous studies.

Moreover, metabolic impairments associated with chronic hypercortisolism could be also involved in the sleep derangement observed in our patients. In fact, it is known that overweight plays a crucial role in the pathogenesis of the sleep abnormalities, as it contributes to the occurrence of sleep apneas [18]. However, with the limitation of a small sample, our findings do not show a clear correlation with alterations in CS and increased BMI.

Actually, in our study no obstructive sleep apnea events were self-reported, but it has been demonstrated that self-reported measures poorly correlate with PSG measures, particularly apnea-hypoxia index [19]. We cannot exclude that sleep alterations in our CS group may be mediated by a higher BMI and consequentially a higher probability of having obstructive sleep apnea. With our critical, low sample size, a correlation between BMI and any sleep parameters was not observed, so we were not able to verify whether the degree of sleep disruption was independent of obesity.

Furthermore, actigraphic alterations observed in the patients group did not show an association with the glucocorticoid hypersecretion, expressed as urinary free cortisol, possibly due to the small cohort of patients enrolled in our study.

Among the effects of hypercortisolism on the neuromuscular system, it is known that glucocorticoid excess increases both cortico-spinal and spinal motor neurons excitability [20–23] on the one hand whilst decreases sarcolemmal excitability [24], muscle size and contractile properties [25] on the other hand. Although no direct recordings of central nervous system activity were obtained in this study, higher movement frequency/intensity assessed by actigraphy might be related to the well-known (although not completely understood) actions of glucocorticoids on the central motor control systems.

In conclusion, these results, though preliminary, indicate that hypercortisolism is associated with low sleep quality, showing increased fragmentation index and activity scores objectively measured by actigraphy. The occurrence of sleep impairment could contribute to the worsening of life quality and metabolic comorbidities inpatients affected by Cushing's syndrome. The clinical relevance of increased fragmentation index without a measurement of EEG and breathing remains unclear, however it opens a door to actigraphy for sleep screening in CS. Further studies in a larger cohort of patients and the use of polysomnography are needed to confirm our findings, validate the use of actigraphy as a screening tool, and explore more the effects of hypercortisolism on sleep.

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