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Impact of growth hormone replacement therapy on sleep in adult patients with growth hormone deficiency of pituitary origin

Lisa L. Morselli[1,2], **Arlet Nedeltcheva**[1], **Rachel Leproult**[1], **Karine Spiegel**[3,6], **Enio Martino**[2], **Jean-Jacques Legros**[5], **Roy E. Weiss**[1], **Jean Mockel**[4], **Eve Van Cauter**[1], and **Georges Copinschi**[3,4]

[1]Department of Medicine, University of Chicago, Chicago, IL

[2]Department of Endocrinology, Università di Pisa, Pisa, Italy

[3]Laboratory of Physiology, Université Libre de Bruxelles, Brussels, Belgium

[4]Service of Endocrinology of Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

[5]Service of Endocrinology, CHR-Citadelle, Université de Liège, Liège, Belgium

[6]Centre de Recherche en Neurosciences de Lyon, Institut National de la Santé et de la Recherche Médicale U1028 – Centre National de la Recherche Scientifique UMR5292, Team "WAKING - Integrative Physiology of Brain Arousal Systems", Lyon, France

Abstract

Objectives—We previously reported that adult patients with GH deficiency (GHD) due to a confirmed or likely pituitary defect, as compared to healthy controls individually matched for age, gender and BMI, have more slow-wave sleep (SWS) and higher delta activity (a marker of SWS intensity). Here we examined the impact of recombinant human GH (rhGH) therapy, compared to placebo, on objective sleep quality in a subset of patients from the same cohort.

Design—Single-blind randomized cross-over design study.

Methods—Fourteen patients with untreated GHD of confirmed or likely pituitary origin**,** aged 22–74 yr, participated in the study. Patients with associated hormonal deficiencies were on appropriate replacement therapy. Polygraphic sleep recordings, with bedtimes individually tailored to habitual sleep times, were performed after 4 months on rhGH or placebo.

Results—Valid data were obtained in 13 patients. At the end of rhGH treatment period, patients had a shorter sleep period time than at the end of the placebo period (479±11 vs 431±19 min respectively; p=0.005), primarily due to an earlier wake up time, and a decrease in the intensity of SWS (delta activity) (559±125 vs 794±219 μV^2, respectively; p=0.048).

Conclusions—Four months of rhGH replacement therapy partly reversed sleep disturbances previously observed in untreated patients. The decrease in delta activity associated with rhGH treatment adds further evidence to the hypothesis that the excess of high intensity SWS observed

Corresponding Author: Lisa L. Morselli Sleep, Metabolism and Health Center (SMAHC), Department of Medicine, MC 1027, University of Chicago, Chicago, IL lmorsell@medicine.bsd.uchicago.edu.

DECLARATION OF INTEREST
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in untreated pituitary GHD patients is likely to result from overactivity of the hypothalamic GHRH system due to the lack of negative feedback inhibition by GH.

Keywords

growth hormone; sleep; slow-wave activity; hormonal replacement

INTRODUCTION

A large body of evidence has demonstrated bidirectional interactions between somatotropic activity and sleep regulation [1]. In particular, GHRH activity has been linked to the promotion of the deepest stages of non-rapid eye movement (NREM) sleep, i.e. slow-wave sleep (SWS) [2–5]. The absence of negative feedback regulation of GHRH, as occurs in untreated GH deficiency of pituitary origin, may result in a stimulation of the depth or intensity of NREM sleep, which can be estimated as EEG spectral power in the frequency band characteristic of slow-waves (delta band: 0.75 – 4 Hz; also referred to as slow-wave activity [SWA] or delta activity).

Very few studies have objectively compared sleep quality in GHD patients and in appropriately matched controls and the results have been inconclusive [6–9]. We recently reported that sleep is disturbed in patients with GHD due to pituitary damage compared to individually age-, gender- and BMI-matched controls. The disturbances involve excessive amounts of delta activity and an age-dependent increase in sleep fragmentation. Furthermore the patients reported poor subjective sleep quality and daytime sleepiness, as well as impaired quality of life (QoL) [10].

Treatment of adult GHD patients with recombinant human growth hormone (rhGH) is generally associated with a clear improvement in QoL [11–13]. However, as far as sleep is concerned, the few studies that evaluated the effect of GH therapy did not detect any consistent change [9, 14–17]. The purpose of the present study was therefore to assess the impact on sleep of 4 months of recombinant human GH (rhGH) treatment, as compared to placebo, in adult GHD patients, using a single-blind placebo-controlled randomized cross-over design. We hypothesized that rhGH replacement would restore the negative feedback regulation of central GHRH activity and therefore correct the excessive slow-wave activity that we had observed in patients with pituitary GHD in the absence of treatment.

SUBJECTS AND METHODS

Patients and experimental protocol

All 26 patients with GHD of confirmed or likely pituitary origin included in our study of sleep-wake regulation in untreated GH-deficient adults [10] were invited to participate in a single-blind randomized placebo-controlled cross-over design trial testing the impact of GH replacement therapy on sleep conducted at the Université Libre de Bruxelles (Belgium), the University of Pisa (Italy), the University of Liege (Belgium) and the University of Chicago (Illinois, USA). In each participating institution, the protocol was approved by the Institutional Review Board. Written informed consent was obtained from all participants.

Details of the inclusion criteria are given in our previous paper [10]. In summary, GHD was diagnosed based on an i.v. insulin tolerance test performed within the last 5 yrs, with a maximum GH response less than 3 μg/liter. Patients with evidence of substance abuse, liver disease, renal insufficiency, heart failure, malignant disease, chronic infectious disease, neurological or psychiatric disease, clinically significant hyperprolactinemia, or diabetes requiring administration of insulin or sulfonylureas, were excluded from the study.

Individuals employed as shift workers within the last 3 months and subjects having traveled across more than 2 time zones within 2 weeks prior to starting the study were not included. All subjects were off hypnotic drugs for at least 3 months. Additionally, patients were either rhGH-naïve or had been off treatment for at least 6 months prior to participation in the study. All patients with associated pituitary hormonal deficiencies received stable replacement therapy, as assessed by at least two clinical and biological evaluations performed at intervals of at least 3 months.

Of the 26 patients with pituitary GHD included in our baseline study, 6 patients declined participation. Thus, 20 adults with pituitary GHD were enrolled. The patients were studied in laboratories at the Universities of Chicago, Brussels (including 5 patients recruited at the University of Liège) and Pisa. The same procedures, equipment, instruments and recording techniques were used at each site.

Immediately after completing the baseline study of sleep-wake regulation [10], patients underwent a first intervention period during which either rhGH or placebo was administered daily for 4 months. The dose of rhGH (Genotropin, Pharmacia, Stockholm, Sweden) was sex- and age-specific, according to the Consensus guidelines for the diagnosis and treatment of adults with GH deficiency [18] (Table 1). Both Genotropin and placebo preparations were provided by Pharmacia. The dose of placebo was similarly titrated such that patients remained blind to the treatment condition. Patients were instructed to inject rhGH subcutaneously, approximately 30 minutes before bedtime. The participants returned for an outpatient visit at monthly intervals. Each visit included clinical examination, determination of IGF-I levels and assessment (whenever applicable) of the current replacement therapy for associated pituitary hormonal deficiencies. The rhGH dosage was titrated accordingly by one of the physician investigators (L.L.M., J.-J.L., R.E.W., J.M. or G.C.), who therefore did not remain blind to the nature of the injections. All other investigators and staff, including the sleep technologist who scored the recordings, were blind to the study condition.

At the end of this first 4-month period, the participants had an outpatient admission that included clinical examination and routine laboratory blood tests. Following this outpatient admission, the patients underwent 6 days of ambulatory sleep monitoring by wrist actigraphy (Actiwatch, Philips Respironics, Bend, OR), a method providing accurate estimations of sleep onset and offset [19, 20]. The mean habitual bedtimes from these recordings were used to individually design the bedtime schedule during a 2-day inpatient study, which occurred within one week after the end of ambulatory monitoring. The subjects were admitted to the laboratory between 17h00 and 19h00 on day 1, and remained in the laboratory until discharge in the morning of day 3. Regular hospital meals were served at 08h00, 12h30 and 19h00. Lights were turned off 5 min before scheduled bedtime and turned on 5 min after scheduled wake time. During bedtimes, sleep was polygraphically recorded (DigiTrace Care Services, Boston, MA).

Upon awakening on day 2, a blood sample was taken for measurement of plasma IGF-I. Thereafter, patients were maintained under normal indoor light (± 300 lux) until bedtime. During waking hours, they had sedentary activities (reading, watching TV and simple neurobehavioral tests) and were free to ambulate around the unit. Naps were not allowed.

Immediately after this inpatient study, the participants entered a 3-month wash-out period, followed by a second 4-month period during which either placebo or rhGH was administered. Objective sleep quality was re-evaluated at the end of the second 4-month intervention period using the same procedures as during the first intervention period.

Throughout the study, patients who did not strictly conform to the instructions, who experienced side-effects or had to modify the replacement therapy for associated pituitary

hormonal deficiencies, were excluded from the study. At the end, valid sleep analyses in both placebo and rhGH conditions were obtained in 14 patients who completed the entire study. However, while reviewing the results of the spectral analysis of the sleep EEG, we noticed that one patient, a 29-year old man who suffered a transsection of the pituitary stalk (with associated hypoadrenalism, hypothyroidism and hypogonadism), had results at the end of the placebo period that were widely divergent from his own recordings obtained during the baseline study [10], i.e. also in the absence of active treatment. His delta activity levels were indeed approximately 7 times lower at the end of placebo treatment than at baseline. Delta activity is highly reproducible in a single individual [21–23], even in recordings separated by several months, with intra-subject correlation coefficients above 0.90. The most likely explanation for the large between-study difference observed in this patient is a technical artifact related to amplifier settings. The Grubbs test for detection of statistical outliers [24, 25] performed on differences of both delta power and theta power during NREM sleep between the two recordings indeed identified this patient as a significant outlier ($p<0.01$ for delta power; $p<0.05$ for theta power), and he was excluded from the analysis. Results are therefore presented for 13 patients.

Four of them had childhood-onset idiopathic GHD that persisted into adulthood (as assessed by the persistence of an abnormally low GH response to the i.v. insulin tolerance test). Nine patients had an adult-onset GHD: in 5 of them, the origin of GHD was had a primary pituitary defect without supra-pituitary involvement: surgical removal of a pituitary tumor without radiotherapy (n=4). None of them presented with diabetes insipidus. One patient was diagnosed with pituitary apoplexy in a non-functioning pituitary adenoma and had diabetes insipidus. In 2 patients with adult-onset GHD, the existence of primary pituitary lesions was confirmed but a supra-pituitary involvement could not be excluded (surgical removal of a craniopharyngioma, without any adherence to the hypothalamus or the optic chiasm with presence of diabetes insipidus (n=2)). Both pituitary and hypothalamic lesions were possible in one patient with histiocytosis and one patient with neurosarcoidosis. Individual patient descriptions are presented in Table 2.

Sleep analysis

All polygraphic recordings were visually scored at 30-sec intervals in stages wake, I, II, III, IV and REM using standardized criteria [26] by the same experienced scorer who was blind to the subject's condition. Sleep onset and morning awakening were defined as, respectively, the times of the first and last 30-sec intervals scored II, III, IV, or REM. The sleep period was defined as the time separating sleep onset from final morning awakening. Total sleep time was defined as the sleep period minus the total duration of wake after sleep onset (WASO). Sleep latency was defined as the time from lights off until sleep onset. Sleep efficiency was calculated as the total sleep time expressed as percentage of the time allocated to sleep (i.e. the interval between lights off and lights on). Periodic leg movements were identified only in one recording in one patient.

A spectral analysis on the central EEG lead was performed (PRANA, PhiTools, Strasbourg, France). Muscular, ocular and movement artifacts were eliminated prior to spectral analysis. Delta, theta, and alpha activities were calculated as the absolute spectral power in the frequency bands 0.75–4 Hz, 4.5–8 Hz, and 8.5–12 Hz, respectively. Mean power per 30-sec epoch was calculated for each band. Mean delta power in non-REM sleep quantifies the intensity or "depth" of non-REM sleep. Alpha activity is an independent marker of the synchronization of high-frequency cortical oscillations that typically appear during quiet wake with eyes closed; it originates in neuronal networks distinct from those responsible for the generation of delta activity. Theta activity reflects spectral power in an intermediate frequency that is often contaminated by delta activity. For illustrative purposes, the

durations of NREM/REM cycles were also normalized to account for individual differences, as previously described [27].

All of the 56 nights recorded were scored; technical artifacts prevented spectral analysis for 4 of them. Comparisons between conditions used the second, rather than the first night of polysomnography, because patients were habituated to the experimental procedures and spent the preceding day in the same standardized and controlled environment, except in 4 cases due to highly artifactual recordings.

Quality of life (QoL) and subjective sleep quality

QoL was estimated by the global score of the QoL Assessment of Growth Hormone Deficiency in Adults questionnaire (QoL-AGHDA), which comprises 25 “yes or no” questions relative to specific complaints commonly reported by GHD patients [28]. A higher score corresponds to lower QoL. Subjective sleep quality was assessed using the Pittsburgh Sleep Quality Index questionnaire (PSQI) [29]. Additionally, the patients were asked to complete a Karolinska Sleep Log, a questionnaire used to assess subjective sleep duration and quality, for the 6 consecutive days preceding each inpatient session.

Statistical analysis

Comparisons between rhGH treatment and placebo were performed using the Wilcoxon signed rank test. All group values are expressed as means ± SEM. All statistical calculations were performed using JMP version 8.0.2 (S.A.S Institute Inc., Cary, NC, USA).

RESULTS

Six patients started the study with the placebo phase, and 7 started with the rhGH phase. The average dose of rhGH was 0.48 ± 0.03 mg/day; the “dose” of placebo averaged 0.50 ± 0.07 mg/day (p=1.000 *vs* GH). At the end of the rhGH period, plasma IGF-I levels averaged 231 ± 20 ng/ml, vs 97 ± 14 ng/ml at the end of the placebo period (p<0.001) (age-adjusted SD scores: −0.1 ± 0.3 SD, vs −2.1 ± 0.2 SD, respectively; p<0.001). Body mass index averaged 28.5 ± 2.1 kg/m^2 at the end of the rhGH period vs 27.8 ± 2.2 kg/m^2 at the end of the placebo period (p=0.266).

Objective sleep quality

Table 3 summarizes the findings. The sleep period time (from sleep onset to final morning awakening) was reduced by an average of 48 min under rhGH as compared to placebo (p=0.005), primarily reflecting a trend to an earlier wake up time. The relative distribution of the different sleep stages was not affected by treatment. The mean duration of SWS (stages III+IV) was reduced by 27%, but this reduction did not reach statistical significance (p=0.110). However, mean delta activity during NREM sleep in the first 6 hours of sleep was decreased by 30% at the end of the rhGH treatment period, compared to the placebo period (p=0.048) (Table 3). In contrast, theta and alpha activity levels were not affected by treatment. The average profiles of EEG delta, theta and alpha power during the first four sleep cycles in the two conditions are presented in Fig. 1.

Of note, 2 patients displayed low sleep duration (at least 1.5 h less sleep in the laboratory than assessed at home by wrist actigraphy) as well as low sleep quality (average number of awakenings 46; average duration of wake after sleep onset 2 h 40 min; average sleep efficiency 60%) in both study conditions. If those 2 patients were excluded from the analysis, the reduction in the sleep period time averaged 51 minutes (p=0.019), primarily reflecting earlier wake up time (p=0.027). The decrease in delta activity under rhGH treatment as compared to placebo averaged 32% (p=0.024). Results regarding sleep stages,

theta and alpha activity levels remained similar in both conditions when these 2 patients were excluded.

Quality of life (QoL) and subjective sleep quality

The global score of the QoL-AGHDA scale was decreased under GH as compared to placebo (4.75 ± 0.57 vs 8.75 ± 0.89, p=0.023), indicating an improvement in QoL ratings. The PSQI averaged 4.1 ± 0.7 under rhGH vs 5.8 ± 1.1 under placebo, but this difference did not reach statistical significance (p=0.102). Consistent with the polysomnographic findings, at the end of the GH treatment period, patients reported an earlier wake up time (difference about 24 min, p=0.002), and a shorter sleep time (difference about 46 min, p=0.007) compared to the end of the placebo period.

DISCUSSION

The present study examined sleep duration, sleep architecture and EEG power in the delta, theta and alpha ranges in adult GHD patients of confirmed or likely pituitary origin**,** after 4 months of rhGH versus placebo administration. In light of the results of our previous study on adult patients with pituitary GHD [10], we hypothesized that the peculiar sleep disturbance observed in this cohort, i.e. an increase in NREM sleep intensity, would be reversed as the physiology of the somatotropic axis was restored by rhGH replacement. As compared to placebo, rhGH treatment in patients with pituitary GHD resulted in shorter sleep period time by almost one hour, and decreased intensity of NREM sleep as quantified by EEG delta activity. Additionally, in keeping with previous reports [11–13], patients experienced an improvement in their QoL under rhGH.

A unique aspect of our study is that, in each treatment condition, the time allotted for sleep during the inpatient study was based on habitual sleep time derived from one week of ambulatory wrist actigraphy immediately preceding the inpatient study. Following rhGH treatment, the patients had shorter habitual time in bed than under placebo, primarily because they got out of bed earlier. Accordingly, sleep period time was nearly one hour shorter under rhGH than under placebo. The shorter sleep period time could be explained by the lower levels of delta activity. Delta activity is a measure of sleep pressure and decreases exponentially throughout the night to reach minimal levels at the end of the night. This is thought to reflect the completion of the recovery process during sleep [30, 31]. When delta activity is lower, the minimum is reached sooner and therefore the sleep episode is shorter. Vice versa, after a night of total sleep deprivation, a rebound of delta activity is typically observed during the following period of recovery sleep, which is typically longer than a regular night [32].

Sleep architecture (the proportions of the various sleep stages) was similar under both treatment conditions. The maintenance of a normal sleep architecture under rhGH treatment is in accordance with previous reports, as several authors observed no impact of replacement therapy administered for 6 months on sleep stages, compared to placebo [9] or to a baseline evaluation before treatment [14, 16, 17] (Table 4). The only exception is a very small study (n=5) that found a decrease in SWS duration in middle-aged patients with GHD of variable etiology after 6 months of rhGH withdrawal, compared to results obtained after 1 to 2 years of high dose rhGH replacement [15].

Quantitative EEG analysis of our results revealed a decrease in delta activity after rhGH replacement. In our previous study comparing sleep in patients with GHD of pituitary origin versus controls individually matched for age, gender and BMI, we had observed excessive amounts of delta activity, associated with poor subjective sleep quality [10]. We indicated that this combination of objective and subjective symptoms represents an unusual form of sleep

disturbance as the most prevalent sleep disorders, such as obstructive sleep apnea, are characterized by the combination of reduced delta activity in association with increased daytime sleepiness [33, 34]. While limited by the small sample size, the present findings nonetheless suggest that rhGH therapy corrects this peculiar sleep disturbance. Our results are consistent with the hypothesis of an enhanced GHRH drive in patients with GHD of pituitary origin, which could be reversed by rhGH treatment. Indeed, a large body of literature supports a role of GHRH in the modulation of sleep and in particular the generation of SWS/delta activity [2, 4, 5]. The only previous study [16] that had performed quantitative EEG analysis before and after rhGH treatment in GHD patients did not find any change in delta activity after 6 months of treatment, as compared to baseline. No comparison was made with a placebo condition, and some patients experienced supraphysiologic IGF-I concentrations with mild side effects.

Two recent studies, conducted in patients previously treated by transsphenoidal surgery for pituitary tumours with or without suprasellar extension, have evidenced that hypothalamic involvement was associated with sleep fragmentation, resulting in shorter sleep duration, disturbed sleep architecture, and disturbed circadian movement rhythms, possibly via alterations of the suprachiasmatic nuclei [35, 36]. Though a hypothalamic involvement could not be excluded in four of our patients, none had suffered from compression of the optic chiasm and only one had received radiotherapy. Moreover, sleep variables were similar in those patients and in the other 9 patients (data not shown). Thus, it seems unlikely that hypothalamic alterations were involved in sleep disturbances observed in our cohort.

Our study has several limitations. The small sample size is an obvious weakness of the study, which involved a demanding and labor-intensive protocol and challenging recruitment criteria. Second, our cohort consisted mostly of middle-aged and older men (8/13 patients over 40 years old). In men, the earliest sign of aging of sleep is a dramatic decrease in delta activity that is apparent already by 40 years of age [37, 38]. Therefore, it is possible that the impact of rhGH treatment on sleep, and particularly SWS and delta activity, would have been more robust had we been able to recruit more young patients. A further limitation is that we did not record breathing parameters in these patients, and therefore could not control for the presence of sleep apnea. An increase in the prevalence and severity of sleep apnea could have contributed to the decrease in delta activity observed in our study. However, neither the distribution of sleep stages, nor the measures of sleep fragmentation (which would arguably increase in the case of worsening sleep apnea) were affected by treatment. The fact that the participants in the present study were only modestly overweight and did not gain a significant amount of weight during rhGH treatment also argues against a role of sleep apnea in the present findings. Finally, the only prospective study evaluating the incidence of sleep apnea in adult GHD patients treated with rhGH showed that treatment does not induce or aggravate sleep apnea [17].

CONCLUSION

In conclusion, although they need to be confirmed by larger studies, the present findings suggest that recombinant human GH treatment administered for 4 months may reverse some of the disturbances in the macro- and micro-architecture of sleep previously evidenced in adult patients with GHD. These findings add to a body of evidence indicating a central role of GHRH activity in modulating sleep quality.

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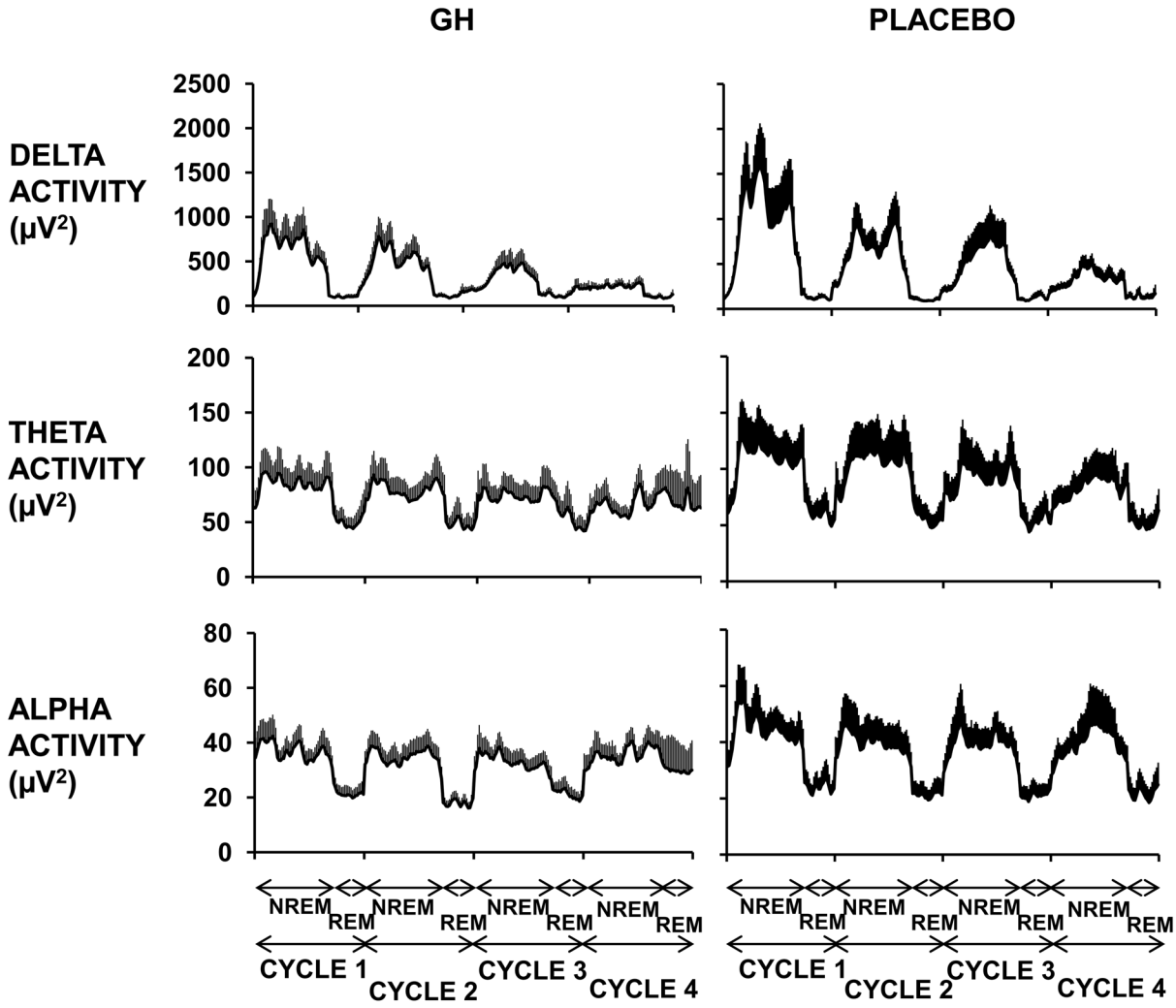

Fig. 1.

Mean profiles (+SEM) of absolute EEG spectral power in the delta, theta and alpha ranges during the first four NREM-REM cycles in GHD patients under rhGH (left) and placebo (right).

Table 1

Sex- and age-specific instructions for rhGH administration.

	Men ≤ 45 years	Men > 45 years	Women ≤ 45years	Women > 45 years
Initial dose (mg/day)	0.2	0.1	0.3	0.3
Increments (mg/day)	0.2	0.1	0.2	0.1
Max. dose (mg/day)	0.6	0.4	0.7	0.6

Table 2

Clinical characteristics of the patients None of the patients had visual field defects at presentation.

Subj., Sex	Age (yrs)	BMI (kg/m^2)	Diagnosis, Onset	Treatment (yrs before)	Adrenal	Additional hormonal replacement therapy		
						Thyroid	Gonad	ADH
1, M	64	25.0	NFPA, AO	Surgery (2)	CA 37.5 mg/d			
2, M	60	23.2	NFPA, AO	Surgery (7)	HC 25 mg/d			
3, M	28	17.8	Idiopathic, CO	n/a			T im 250mg/3wks	
4, F	70	24.1	Prolactinoma, AO	Surgery (14)	HC 35 mg/d	T4 125 μg/d	E2-PRG transd	
5, M	69	30.1	NFPA, AO	Surgery (8)	HC 20 mg/d	T4 150 μg/d	T im 250 mg/mo	
6, M	22	21.4	Idiopathic, CO	n/a	CA 37.5 mg/d	T4 150 μg/d	T im 250mg/3wks	
7, M	47	32.7	Idiopathic, CO	n/a	CA 25 mg/d	T4 125 μg/d	T oral 120 mg/d	
8, M	36	44.0	Neurosarcoidosis, AO hypothalamic infiltration	n/a	HC 20 mg/d	T4 200 μg/d	T im 250 mg/mo	DDVAP nasal 20 μg/d
9, M	47	26.7	Idiopathic, CO	n/a	HC 20 mg/d	T4 100 μg/d	T im 250mg/2wks	
10, M	30	29.5	Cranio, AO	Surgery (7)	CA 37.5 mg/d	T4 50 μg/d	T im 250 mg/2wks	DDVAP nasal 20 μg/d
11, M	27	24.0	Cranio, AO	Surgery (7)	HC 25 mg/d,	T4 125 μg/d	T im 300 mg/3wks	DDVAP nasal 15 μg/d
12, M	51	28.4	Histiocytosis, AO	RT (3)	HC 20 mg/d	T4 75 μg/d	T im 200 mg/2wks	
13, M	54	34.4	NFPA+ pituitary apoplexy, AO	n/a	HC 20 mg/d	T4 75 μg/d	T transd 5 mg/d	DDVAP oral 100 μg/day

NFPA non-functioning pituitary adenoma, *Cranio* craniopharyngioma, *AO* adult-onset, *CO* childhood-onset, *RT* radiotherapy, *CA* cortisone acetate, *HC* hydrocortisone, *T4* L-thyroxine, *T* testosterone, *E2* estradiol, *PRG* progesterone, *DDAVP* desmopressin, *transd* transdermal.

Table 3

Mean (±SEM) values of sleep variables in 13 patients with pituitary GHD after 4 months of placebo or rhGH treatment.

	Placebo	GH	p level GH vs Placebo
Time of lights out	23h32±12 min	23h44±18 min	0.470
Time of lights on	07h54±19 min	07h34±20 min	***0.092***
Time in bed (min)	504±13	471±17	0.216
Sleep period time (min)	479±11	431±19	**0.005**
Sleep latency (min)	15±4	21±8	0.423
Total sleep time (min)	422±20	384±25	0.223
Sleep efficiency (%)	84±3	82±4	0.635
WASO (min)	57±16	47±12	0.191
REM sleep (min)	80±9	67±8	0.879
REM sleep (%)	19±2	17±2	0.588
Stages I+II (min)	261±13	248±15	0.376
Stages I+II (%)	63±4	66±4	0.542
Stages III+IV (min)	95±19	69±19	0.110
Stages III+IV (%)	18±4	17±4	0.455
Delta activity (μV^2)*	794±219	559±125	**0.048**
Theta activity (μV^2)*	102±25	82±17	0.376
Alpha activity (μV^2)*	40±7	35±5	0.542

*Spectral power is reported as the average absolute power during NREM sleep in the first 6 hours of sleep; *WASO* wake after sleep onset; *REM sleep* rapid eye movement sleep; *NREM sleep* non-rapid eye movement sleep.

Table 4

Review of studies evaluating the impact of hGH treatment on sleep in adult GHD patients

Authors	n	Patients	Protocol	Results
Astrom et al., 1990 [14]	8	Young adults with CO-isolated GHD	PSG before and after 6 months hGH treatment No placebo control. No spectral analysis.	↓ total sleep time ↑ REM sleep No change in SWS duration
Nolte et al., 2002 [15]	5	Patients with AO-GHD due to pituitary disease	PSG after 1 yr rhGH treatment and after 6 months withdrawal No placebo control. No spectral analysis.	*rhGH*: normal stages I, II, SWS duration; ↓ sleep efficiency and REM sleep *rhGH* withdrawal: ↓ SWS duration
Schneider et al., 2005 [16]	18	CO-GHD patients	PSG before and after 6 months rhGH treatment. No placebo control. Spectral analysis.	No differences in sleep parameters. Supraphysiologic IGF-1 levels in 10 patients.
Peker et al., 2006 [17]	19	AO-GHD patients	PSG before and after 6 months rhGH treatment No placebo control. No spectral analysis.	No differences in sleep parameters
Ismailogullari et al., 2009 [9]	12	Women with AO-GHD due to Sheehan's syndrome	Parallel group design PSG before and after 6 months rhGH treatment, and *vs* 8 patients on placebo. No spectral analysis.	No differences in sleep parameters
Morselli et al. (present study)	13	9 adults with AO-GHD 4 adults with CO-GHD	Randomized cross-over design PSG after 4 months treatment rhGH *vs* placebo Spectral analysis.	*rhGH vs placebo*: ↓ sleep period time (earlier wake up) ↓ SWS intensity (delta activity)

CO childhood onset, *AO* adult onset, *PSG* polysomnography, *REM* rapid eye movement, *SWS* slow wave sleep.