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Decrease in Delta Sleep in Growth Hormone Deficiency Assessed by a New Power Spectrum Analysis

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Summary: Seven pituitary dwarfs between 18 and 28 years old with congenital absence of growth hormone, i.e., isolated growth hormone deficiency (IGHD), were examined with polysomnography. Power spectrum analyses of the delta band showed a significant decrease in power in the delta sleep in the IGHD patients compared with the controls. Power spectrum analyses add a new dimension to the description of sleep, as it evaluates, not only frequency of the electroencephalogram (EEG) in time but also the amplitude of the EEG signal. This means that sleep of same quantity can have different powers; for example, 15 min of stage 4 in one person can have another quality than 15 min of stage 4 in another person. An additional observation was that the power in the delta band in the normal young controls showed a correlation to age, with significant decrease within a 10-year period. **Key Words:** Power spectrum analysis—Sleep—Delta rhythm—Growth hormone deficiency.

The relationship between nocturnal growth hormone (GH) secretion and delta sleep (stage 3 + 4) is poorly understood although there is growing evidence of a correlation between peak GH secretion and the occurrence of delta sleep (1–7). Methodological problems could be one of the reasons for the difficulty in establishing a correlation, as measuring integrated hormone concentrations in the blood by multiple blood sampling during the night inevitably disturbs the sleep. Reports on sleep in children with GH deficiency (GHD) have also yielded contradictory results (8–10). Orr et al. (8) found no difference in delta sleep in GHD children and controls. Taylor and Brook (9) reported decrease in delta sleep in children with psychosocial dwarfism due to malnutrition, but no GH values were given. Wu and Thorpy (10) reported increased stage 3 and normal stage 4 sleep in 7 children with GHD, but some had undergone pituitary surgery and the control group was not optimal.

The aim of the present study was to determine if there were qualitative, i.e., power,

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differences in the delta sleep in GH-deficient young adults and normal subjects, using a novel power spectrum analysis.

METHODS

Patients

Seven pituitary dwarfs 18 to 28 years old were examined. Their only defect was isolated growth hormone deficiency (IGHD) or almost absent GH as the maximum plasma GH concentration produced during a clonidine stimulation test as less than 5 ng/ml (median peak value 2.4 ng/ml, normal above 30 ng/ml). Plasma somatomedin C concentration was subnormal in six patients and borderline in one (median 12.4 nmol/L). In all the patients, the diagnosis of IGHD was initially established in their childhood by slow growth velocity, retarded bone age, and abnormal insulin hypoglycemia tests. All had been treated with human growth hormone in their childhood. The secretion of the other pituitary hormones was normal: plasma prolactin, thyroid function (plasma TSH, T3, T4), adrenal function [30 min adrenocorticotropic hormone (ACTH) test], gonadal function [follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol and testosterone plasma concentrations]. None had previous central nervous system (CNS) surgery nor had received CNS irradiation; none had suffered from CNS infection. To make sure none had adenomas in the pituitary gland or other pathologies, all patients had a cerebral computed tomography (CT) scan performed prior to the study. This revealed a normal hypothalamic area with a normal width of the third ventricle. The size and appearance of the sella turcica was normal in all. They had been drug free for a minimum of 6 months prior to the study. Other than the IGHD, they were healthy in every respect.

Controls

The controls were normal adults, closely age (±6 months) and sex matched with the patients. They were free of sleep disturbances and did not abuse alcohol or drugs, nor were they receiving medication; in fact, none had ever been hospitalized.

Recording procedure

Patients and controls were asked to keep a regular sleep–wake schedule 7 days prior to the final polysomnographic recordings, which were performed on 2 consecutive nights. The electroencephalogram (EEG) was recorded with an 8-channel, portable tape recorder (Oxford 9000, Oxford Medical Ltd., Abingdon, U.K.). The frequency response for the recorder was 0–35 Hz, with an input range of 600 μV peak–peak (pp). The EEG was recorded between silver chloride cupelectrodes placed over the central region (C3) with reference to an electrode over the mastoid process (A2). The electrooculogram (EOG) and electromyogram (EMG) from the submental muscles were recorded simultaneously. Bedtime was selected freely in the period between 2200 and 2400h. "Lights out" time was marked on the tape by pressing a time marker. The subjects could sleep as long as they wanted and final wake time was indicated the same way.

Power spectrum

The power spectrum plot gives a three-dimensional presentation of the analyzed EEG signal.

The x-axis shows the analysis time in hours with a resolution of 30 s; the y-axis shows

the frequency in the range of 0–25 Hz with a resolution of 0.5 Hz. The third axis shows the power, presented in colors, with red indicating the maximum value.

The recorded tape was replayed via the Oxford 9000 replay and display system. The output signal from channel (C3) was connected to a computer system, which performed the power spectrum analysis. The computer was especially designed for this purpose, and it converted the EEG signal into digital values and stored it on a hard disk. There was no filtration of the signal before spectral analysis. The only filter of the signal was determined by the frequency range of the recorder (0–35 Hz). The sampling frequency was 2,000 Hz, and with a replay speed of 40 times real-time, corresponds to a sampling frequency of 50 Hz in real-time. For each recording, a 100 μV pp calibration signal on the tape was used to calibrate the signal level. Artifacts could be rejected manually before the spectral analyses. It mostly concerned big movement artifacts, as a common artifact such as muscle activity is found in a much higher frequency range and does not interfere with the analysis of delta activity.

Analysis

The power spectrum analysis was performed by using auto regressive (AR) modeling (11). The dynamic range in the power spectrum was optimized by the use of an amplification of 20 dB/decade in frequency of the input signal. This was performed because of the natural drop in EEG amplitude for increasing frequencies. For the used frequency range (0–5 Hz) the amplification factors had the following values: 0.5 Hz 1.00, 1.0 Hz 2.00, 2.0 Hz 3.99, 3.0 Hz 5.96, 4.0 Hz 7.91, and 5 Hz 9.83.

Every 30 s the signal power in each 0.5-Hz frequency band was calculated and converted into a color, which is in the color scale shown in Fig. 1. The color scale is linear and ranges the power from 0 to an entered maximum value which was the same in each analysis and was set to 3828 μV^2 = 3.58 log μV^2. The color red represents signal power equal to or greater than this value.

Sleep scoring

All subjects had their sleep records scored manually and blindly the traditional way, according to the criteria of Rechtschaffen and Kales (12). These data are to be published elsewhere (28).

Statistics

For statistical analysis, a Mann–Whitney nonparametric test was used. Correlation was calculated using Spearman's rank correlation test.

Ethics

The protocol was approved by the Regional Committee of Medical Ethics. All subjects gave informed consent to participate.

RESULTS

Power spectrum analysis of the delta band for each subject is presented in a color display. Figure 1 shows the power in the delta band in a GH-deficient patient in relation to the quantitative sleep pattern; Fig. 2 shows the same for a normal subject. The computer could only display 8 h of sleep at a time, so in order to limit the number of illustrations, only the first 8 h of sleep are visualized here.

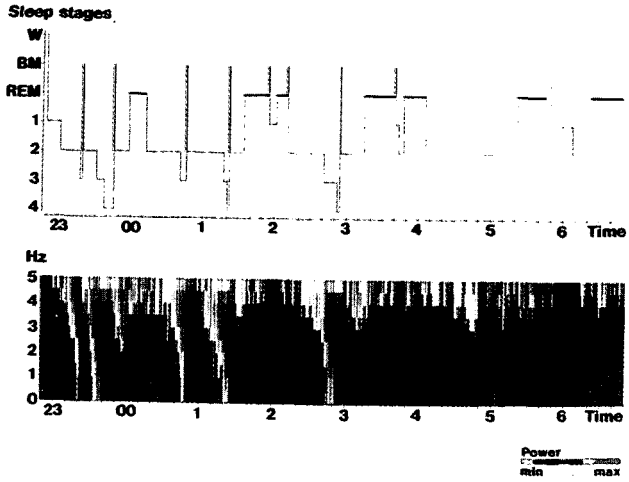

FIG. 1. Upper: Quantitative sleep stage distribution in a GH-deficient patient. Lower: Power spectrum plot of the delta band in the same sleep period in the same patient.

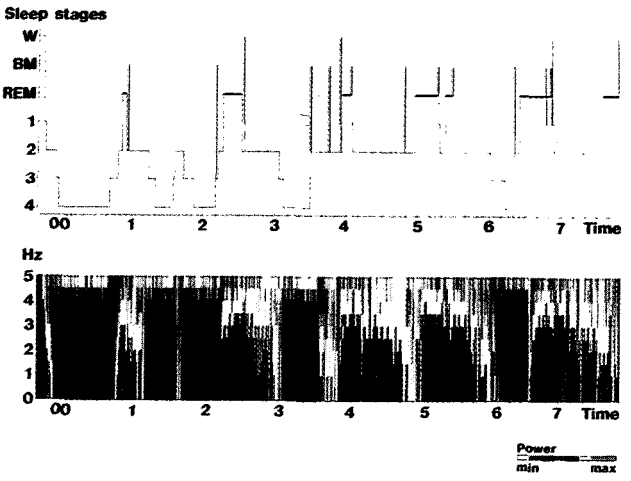

FIG. 2. Upper: Quantitative sleep stage distribution in a normal subject. Lower: Power spectrum plot of the delta band in the same sleep period.

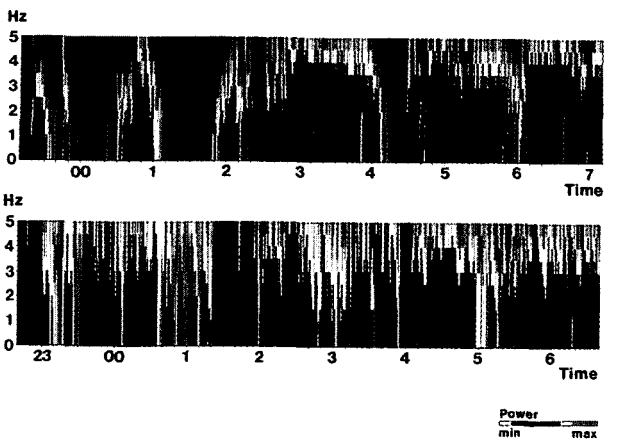

FIG. 3. Upper: Power spectrum plot of delta bands in a normal subject aged 28 yr. Lower: a GH-deficient patient aged 28 yr.

The difference between power in the delta sleep in a GH-deficient patient and a control is obvious from the color spectrum (Fig. 3), but for statistical analysis, numerical figures are necessary. To get a numerical value for the power in the delta band in patients and controls, the area of red color was computed automatically in the 0–3 Hz band for the whole sleep period. This area was computed for every 30 s so that an astronomical figure emerged for each record. The power for each subject is therefore given in relative figures. The power in the delta band in the two groups is illustrated in Table 1. The power in the delta range of 0–3 Hz was significantly decreased in the GH-deficient patients compared with the controls ($p < 0.01$).

Three of the GH-deficient patients had reoccurrence of delta sleep at the end of their sleep, demonstrated here by high power in the 0–3 Hz band. Only 1 of the controls had this phenomenon.

Another observation was that the power in the delta band (0–3 Hz) decreased with age in the normal subjects from 18 to 28 years old, the correlation being significant ($p = 0.01$). The correlation between age and power in the delta sleep in normal subjects is shown in Fig. 4. There was no correlation between power in delta sleep and age in the IGHD patients.

DISCUSSION

Power spectrum analysis of EEG is not a new technique (13–23). It has previously been illustrated as compressed spectral array (landscape of mountains) where the amplitude has been visualized graphically in such a way that a high amplitude at a given time could hide information about the amplitude to a later time merely by shadowing.

TABLE 1. *Power in delta band*

GH-deficient patients					Controls			
Case no.	Age (yr, mo)	Sex	Nights 1 and 2[a]	Mean	Mean	Nights 1 and 2[a]	Sex	Age (yr, mo)	Case no.
DW 1	18.09	F	184,7 561,0	372,8	809,8	821,0 798,5	F	18.08	N 1
DW 2	20.0	F	418,0 413,6	415,8	869,2	857,4 881,0	F	19.02	N 2
DW 3	20.06	F	736,5 579,8	658,2	771,0	680,3 861,6	F	19.11	N 3
DW 4	20.07	M	141,2 159,9	150,6	574,1	693,2 455,0	M	20.08	N 4
DW 5	24.05	M	45,2 317,0	181,1	505,9	425,7 586,0	M	24.05	N 5
DW 6	28.01	M	288,1 369,0	328,6	468,7	520,7 416,6	M	27.07	N 6
DW 7	28.07	M	224,9 259,4	242,2	479,3	531,2 427,3	M	28.02	N 7

[a] The figures are relative values.

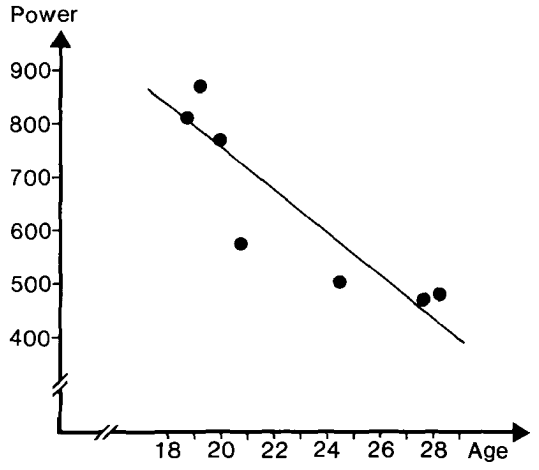

FIG. 4. Correlation between age and power in delta sleep in normal subjects.

Amplitude is given in μV and power in μV^2. The higher the amplitude of an EEG signal, the higher the power. In the power spectrum presented here, no information is hidden because the third dimension, i.e., the power, is illustrated in color.

Amplitude of an EEG signal is correlated to the underlying neuronal activity in the cerebral cortex. The higher the sum of postsynaptic potentials the higher the amplitude and again the higher the power. So power spectrum analysis of sleep EEG adds a new dimension (quality) to sleep. Whether higher neuronal activity and thereby higher power is equal to a better quality of sleep is left unanswered.

Within the same subject, we registered differences in power from night to night in the delta sleep (Table 1), and the interindividual variance was greater than expected from the quantitative variance (in min) of the delta sleep. It should be noted that the agreement between the automatic detection of delta activity and the manual scoring of delta sleep was above 90%, which is in accordance with analog systems of color density spectral array (24,25). The power spectrum analysis was set to give the color red for power equal to or greater than a given maximum value. It means that delta activity of lower power value would give another color. For example, in 1 patient especially, (DW 5), the difference between first and second night power cannot be explained by a "first night effect" concerning the quantity of delta sleep because the difference in delta sleep between the 2 nights was only 11 min. The significance of variance in power during sleep remains to be explored. This is in contrast to the power in awake EEG, where the amplitude of the α rhythm is very constant day by day interindividually, and therefore, it is also a constant power.

There are several external factors that can influence amplitude of an EEG signal: a thick skull or thick skin can decrease the amplitude in some cases. This study showed that patients with GHD had significantly decreased power in their delta sleep compared with sex- and age-matched normal subjects ($p < 0.01$). In this case, it is not likely that the decreased power is caused by a thick skull in view of the fact that patients who lack GH have decreased bone formation and very low skin resistance.

No power spectrum analyses of sleep in GHD have ever been carried out in humans. An animal study (26), however, demonstrated that adminstration of GH-releasing factor into the third ventricle in rats increased the power in the lower frequency band. This is

in accordance with our study in which patients with very low GH values had low powers in the 0–3 Hz frequency band.

The significance of low power in the delta sleep in GH-deficient adults is poorly understood. It could be that the delta sleep should reach a certain level of power in order to trigger the neurotransmitters to facilitate neurosecretion (i.e., GH). This is supported by an animal study (27) in which GH secretory periodicity was correlated to the power spectrum analyses of sleep EEG in adult rats. After sleep deprivation of the rats, the GH secretion increased in relation to increased sleep. This could explain some of the paradoxes with occurrence of delta sleep without a significant rise in GH, i.e., the power in the delta sleep is simply too low in the later sleep cycles to trigger any GH secretion.

Another noticeable finding in our study was the correlation between age and delta power in normal young subjects, with a significant decline in power within a 10 year period. Delta sleep declines quantitatively by age to disappear in old age as does GH secretion (5–6). In our controls, the decline in power in the delta sleep was much faster than the expected decline in minutes of delta sleep in this age group. In fact, the quantitative decline in delta sleep in minutes was nonsignificant in this group (unpublished observations). For the correlation between power and age in delta sleep (Fig.4), one could argue that a curved line should be approximated, but the data for this were too few. When more data are collected, an asymptotic curve will probably emerge.

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