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The Effect of Neuroendocrine Secretion on Brain Morphology and EEG Sleep in Patients with Eating Disorders

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Summary. Neuroendocrine disturbances [low plasma levels of triiodothyronine (T3), high plasma concentrations of cortisol], morphological brain alterations [enlarged external cerebrospinal fluid (CSF) spaces, dilatation of the ventricles] and altered sleep patterns [fragmented sleep continuity, a reduction of slow wave sleep (SWS) or REM sleep] have been described in patients with anorexia nervosa and bulimia nervosa. The present study investigates to what degree these disturbances interact with each other. In ten anorexic and five bulimic patients cranial computed tomography (CT) to estimate the size of the CSF spaces, blood sampling to measure cortisol and T3 plasma concentrations, and all-night polysomnography were performed. In comparison with patients with normal CT scans, the patients displaying enlarged CSF spaces spent more time in SWS, and the duration of REM sleep was reduced. In the whole sample, a negative correlation was found between the amount of REM sleep and cortisol, whereas a positive association was found between the amount of REM sleep and the T3 level. In addition, the degree of brain shrinkage correlated positively with cortisol and negatively with T3. On the basis of these results, it can be assumed that in patients with eating disorders the disease process with its neuroendocrine alterations affects brain morphology as well as EEG sleep.

Key words: Eating disorder – Cranial computed tomography – Cortisol – Triiodothyronine – REM sleep

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Introduction

In both patients with anorexia nervosa and in normal-weight bulimic patients various endocrine and metabolic changes, such as low plasma levels of triiodothyronine (T3) and elevated plasma concentrations of cortisol, free fatty acids and ketone bodies, were found and regarded as a consequence of the behavioural disorder with self-induced starvation and malnutrition, respectively (e.g. [30, 31]). In cranial computed tomography (CT), enlarged external cerebrospinal fluid (CSF) spaces and dilated ventricles have been observed in the majority of patients with anorexia nervosa and also in a number of normal-weight bulimia patients [1, 19, 21, 22]. Due to the fact that high plasma cortisol levels and low T3 concentrations have been closely associated with brain shrinkage, hypercortisolism and hypothyroidism have been thought to be basically involved in the pathogenesis of the structural brain alterations [22, 23].

Several EEG sleep studies have reported a disturbed sleep pattern in anorexic patients, in particular a fragmentation of sleep continuity and a reduction of slow wave sleep (SWS) or REM sleep [5, 26, 29]. In bulimic patients the EEG sleep pattern was found to be largely indistinguishable from that of controls [26, 37]. In a study of ours [25], we were not able to replicate the above-mentioned observations in anorexic patients; however, in the patients with an eating disorder there was a much higher variance in sleep measurements as compared with controls.

In anorexic patients the endocrine and metabolic alterations as well as the structural brain abnormalities normalize with weight gain [22]. In addition,

the sleep structure of anorexics seems to improve after refeeding ([24]; our own unpublished data).

In a pilot study we asked the question whether endocrine disturbances, structural brain alterations and altered sleep patterns show a common interaction in patients with an eating disorder.

Patients and Methods

Ten female patients with anorexia nervosa (according to the criteria of Feighner et al. [9]) took part in the study, which was conducted at the Max-Planck-Institute of Psychiatry, Munich. In addition, five female patients with bulimia nervosa (according to the criteria of Russell [33]) were investigated, who, due to the severity of the bulimic symptomatology with one or more binges per day, were in need of hospital treatment. The patients had never received psychoactive medication. The clinical descriptions of these patients are given in Table 1.

Hormone analysis. Blood samples for hormone analysis (cortisol, T3) were collected at 10-min intervals from 8.30 to 9.30 a.m. after overnight fasting in 12 patients. Plasma for the analysis of cortisol and T3 was kept frozen at 30°C until analysed. Cortisol was measured as described earlier [6]. In the pooled plasma sample, the intra-assay variability was 4.5% and the interassay variability was 6.2% at an average concentration of 12.1 µg/dl. T3 was assayed by radioimmunoassay using kits supplied by Serono (Freiburg, FRG). In the pooled plasma sample, the intra-assay variability was 7.1% and the interassay variability was 8.2% at an average concentration of 0.85 ng/ml.

Cranial computed tomography was carried out using a General Electric 9800 Scanner. Measurements were performed on three scans cut parallel to the glabella-inion line: (1) a low cut, showing the insular cisterns, the third ventricle as well as the anterior and posterior horns of the lateral ventricles; (2) a slice through the region of the cella media of the lateral ventricles; (3) a scan of the superficial cortex. Ventricular size was determined by calculating the ventricular brain ratio (VBR) and the size of the external CSF spaces by measuring the width of the insular cisterns, the interhemispheric fissure and the cortical sulci. The standardized procedure for assessing these parameters has previously been described in detail [22, 35] and was applied in this study. In respect to the size of the external CSF spaces, a width of 3–4 mm of the interhemispheric fissure and the sulci was defined as a "slight", a width of more than 4 mm as a "marked" degree of sulcal widening [22, 35]. According to our normative data, a VBR value exceeding 4.70% is defined as abnormal [22].

EEG sleep measurements. All patients slept for three consecutive nights in the sleep laboratory; nights 1 and 2 served for adaptation. Sleep was recorded between lights out (2315 hours) and lights on (0630 hours) using standard procedures (EEG, EMG, EOG; [32]). Polysomnograms of the 3rd night were visually scored according to standard criteria [32]). Sleep onset was defined as the first occurrence of a sleep spindle or a K-complex. Termination of the sleep period (SPT) was defined by the last occurrence of sleep stage 2, 3, 4, or REM. The absolute (min) and relative amount (%SPT) of each sleep stage [1, 2, 3, 4, REM, SWS (stage 3 + 4), as well as intermittent time awake] were then calculated.

All measurements were performed during the 1st week after hospital admission.

Statistical analyses were obtained by using Student's *t*-test (if variance was proved to be inhomogeneous, the formula corrected for small sample size was applied) and Pearson's correlation coefficient. The level of significance was set at 5% (two-tailed).

Results

Age distribution and the duration of illness in both samples of eating disorders did not differ; however, the mean body weight (%IBW) of the anorexic patients was, as expected, significantly lower. Out of the total sample, only two patients (13%) showed normal CT scans; five patients (33%) displayed either ventricular dilatation ($n = 4$) or enlarged external CSF spaces ($n = 1$); and in eight subjects (53%) both ventricular and sulcal size were abnormally high. The sleep measurements of both groups were similar, except for a decreased sleep efficiency in the bulimics. Furthermore, CT measures and endocrine parameters did not differ between the anorexics and bulimics (Table 1a).

Dichotomizing the total sample according to a VBR value of 4.7% (a higher value is considered to be abnormal), the following results were observed (Table 1b). The patients exhibiting an abnormal VBR value (seven anorexics, two bulimics) tended to show higher plasma concentration of cortisol ($P < 0.10$) and lower plasma levels of T3 ($P < 0.15$) than the patients with normal-sized ventricles. With regard to sleep data, in patients with ventricular dilatation the amount of SWS was increased, mainly indicated by a significantly higher amount of sleep stage 3 (mean ± SD: 44 ± 15 min vs 25 ± 15 min, $P < 0.05$), and REM sleep was decreased. However, this could not be proven statistically.

The VBR values were positively correlated with plasma cortisol levels ($r = 0.66$, $P < 0.02$) and negatively associated both with T3 ($r = -0.58$, $P < 0.05$) and the amount of REM sleep ($r = -0.62$, $P < 0.02$). The size of the external CSF spaces was found to be positively correlated with plasma cortisol ($r = 0.71$, $P < 0.05$) and negatively correlated with T3 values ($r = -0.69$, $P < 0.05$; due to data level of CSF measurements, Spearman rank correlation coefficients were calculated here). Plasma concentrations of cortisol were negatively correlated with T3 values ($r = -0.65$, $P < 0.05$) and the amount of REM sleep ($r = -0.80$, $P < 0.01$; see Fig. 1). A positive association was observed between T3 plasma levels and the amount of REM sleep ($r = 0.77$, $P < 0.01$; see Fig. 2). Re-analysing these significant correlations without the outlier values, the results again were proven. The relative amount of SWS was not associated with either CT measurements or endocrine parameters. The pa-

Table 1. Clinical characteristics, sleep measures, CT measures and endocrine parameters in patients with eating disorders

	Anorexia nervosa ($n = 10$)	Bulimia nervosa ($n = 5$)	VBR ≤ 4.70% ($n = 6$)	VBR > 4.70% ($n = 9$)
Age (years)	20.6 ± 2.8	23.8 ± 2.8	24.0 ± 2.5	20.1 ± 2.5**
Duration of illness (months)	40.1 ± 32.0	68.8 ± 24.9	60.2 ± 37.2	42.7 ± 28.3
Body weight (% IBW)	70.7 ± 5.9	92.0 ± 10.6***	79.2 ± 7.0	76.9 ± 15.9
Sleep period time (SPT; min)	418.0 ± 20.9	419.1 ± 29.1	422.3 ± 8.0	415.7 ± 29.3
Sleep efficiency (%)	93.3 ± 4.6	86.2 ± 5.5**	92.0 ± 6.9	90.3 ± 5.4
Slow wave sleep (% SPT)	17.5 ± 8.2	17.6 ± 8.8	13.2 ± 9.6	20.4 ± 5.8*
REM sleep (% SPT)	20.2 ± 6.4	18.3 ± 4.1	22.7 ± 6.3	17.4 ± 4.3*
Enlargement of external CSF spaces (n)				
None	1	2	2	1
Slight	3	3	3	3
Marked	6	0	1	5
Ventricular brain ratio (VBR; %)	7.0 ± 4.1	4.5 ± 2.5	2.6 ± 0.6	8.5 ± 3.0
Cortisol (μg/dl)	17.8 ± 7.4	9.8 ± 3.9	10.1 ± 3.6	18.7 ± 7.2*
Triiodothyronine (T3; ng/ml)	0.75 ± 0.20	0.80 ± 0.25	0.89 ± 0.17	0.70 ± 0.20

* $P < 0.10$; ** $P < 0.05$; *** $P < 0.01$
IBW = ideal body weight; VBR = ventricular brain ratio

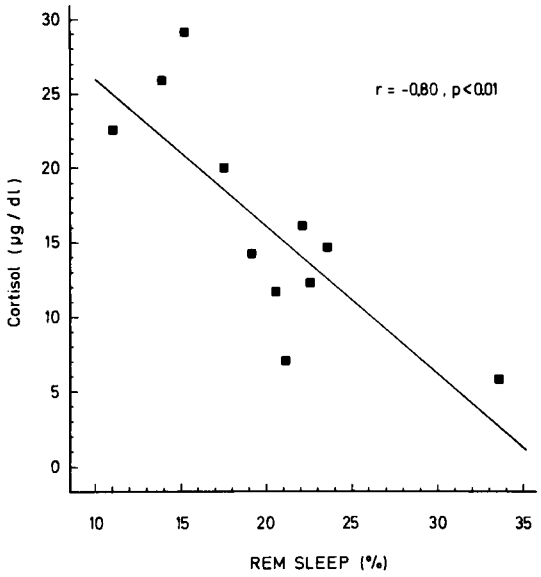

Fig. 1. Correlation between plasma cortisol (μg/ml) and amount of REM sleep (% SPT) in patients with eating disorders ($n = 11$)

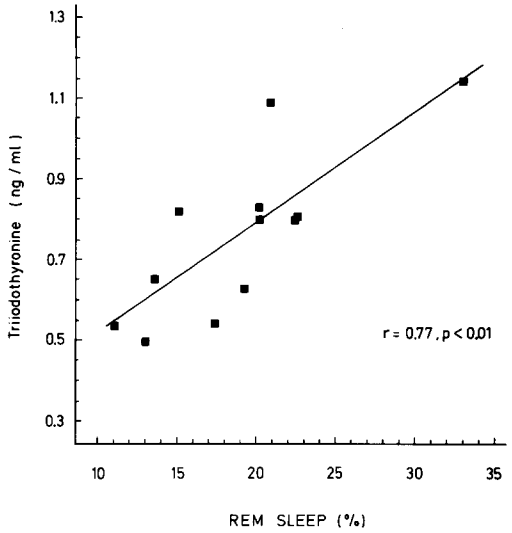

Fig. 2. Correlation between plasma triiodothyronine (ng/dl) and amount of REM sleep (% SPT) in patients with eating disorders ($n = 12$)

tient characteristics (age, body weight, duration of illness) as well as indicators further assessed for malnutrition (plasma concentration of free fatty acids, ketone bodies) did not show any association with the EEG sleep and CT measurements and, therefore, are not reported in detail here.

Discussion

The similarity of the EEG sleep pattern in anorexic and bulimic patients, as well as the results regarding brain morphology and endocrine measurements, closely resemble the observations reported earlier, including the reference data of control subjects [22, 23, 25]. The focus of the present pilot study, however, was to investigate whether there is an interaction between endocrine parameters, brain morphology and sleep during the acute state of anorexia nervosa as well as bulimia nervosa. Comparing the patients with a normal VBR value with those displaying ventricular dilatation, the latter group tended to spend more time in SWS but less time in REM sleep. Furthermore, patients with ventricular enlargement

displayed high levels of cortisol and low concentrations of T3. These observations, obtained by dichotomizing the patient sample according to the criterion of a normal versus an enlarged ventricular system, became more obvious when analysing the respective interactions. This resulted in the finding that low T3 plasma levels and elevated cortisol serum concentrations were associated with a reduced amount of REM sleep as well as with an enlargement of internal and external CSF spaces.

To our knowledge the influence of a low T3 level on sleep regulation has not yet been described in the literature. A low T3 concentration, which in anorexia nervosa and bulimia nervosa is regarded as an adaptive response of the organism to chronic or intermittent starvation, reflects down-regulated metabolic processes [31]. It seems likely that a T3-mediated reduction of metabolic processes mainly affects those sleep structures – i.e. REM sleep – in which metabolic rates normally increase. Such a rise of metabolism during dream (REM) sleep has been reported in healthy volunteers by assessing the regional glucose metabolism [13] and during desynchronized sleep in animals by measuring the regional cerebral blood flow [10].

With respect to our finding of a close association between elevated plasma cortisol levels and a low amount of REM sleep, it is of special interest that Born et al. [2] and Fehm et al. [8] found a reduced amount of REM sleep after the application of corticosteroids. Furthermore, a diminished amount of REM sleep was reported by Gillin et al. [11] after ACTH application and by Holsboer et al. [15] after intravenous injection of corticotropin-releasing hormone (CRH). Thus, it is most likely that the limbic-hypothalamic-pituitary-adrenal hormones modulate neurotransmission in neurons involved in the basic regulation of sleep.

Of course, one can critically remark that in the present investigation cortisol was measured in a sample which had been collected immediately after morning awakening. However, it is well known that patients with eating disorders – especially with anorexia nervosa – have an increased 24-h cortisol secretory pattern [3, 6], the degree of which may be well reflected by the plasma levels measured by us.

According to these results resembling prior observations that a low T3 secretion and hypercortisolism are associated with enlarged CSF spaces [17, 18, 22, 34], it can be hypothesized that malnutrition-induced endocrine alterations not only affect brain morphology but also diminish the amount of REM sleep in patients with eating disorders. On the other hand, it can also be speculated that not malnutrition per se but an increased release of endogenous CRH [4, 12, 16], the anorectic effect of which is well documented [20, 28], causes the behavioral, endocrine, neuroanatomical and EEG sleep alterations. It is also likely that a mutually synergising effect of CRH hypersecretion and of malnutrition with its secondary consequences leads to the respective abnormalities in patients with eating disorders.

Finally, one has to consider the possibility that brain shrinkage directly affects the physiological regulation of sleep, especially since it was demonstrated that an enlargement of internal and external CSF spaces is associated with a diminished regional cerebral blood flow [36].

Regardless of the discussion of cause and effect of the behavioural and biological changes in patients with eating disorders, this study gives hints that neuroendocrine disturbances, morphological brain alterations and the state of nutrition influence EEG sleep patterns as intervening variables. In our opinion, this circumstance should be taken into consideration when analysing the polysomnograms of those psychiatric disorders which display disturbances in neuroendocrine activity and enlarged CSF spaces as, for example, is the case in major depression [7, 14, 27, 34].

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