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Brain Morphology and Sleep EEG in Patients with Huntington's Disease

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Summary. In 12 patients with Huntington's disease, the relationship between brain morphology, nocturnal sleep EEG, and clinical variables was studied. Global cerebral atrophy did not significantly correlate with sleep parameters, whereas atrophy of the caudate nuclei was associated with reduced slow wave sleep and increased time spent awake. Several clinical parameters (e.g., anergia and thought disturbance scores of the Brief Psychiatric Rating Scale, illness duration and global clinical assessment) showed significant correlations with global cerebral atrophy. Similar studies in other neuropsychiatric disorders demonstrate associations between sleep alterations and brain morphological changes of different localizations, thus pointing to a complex relationship between both. It can be hypothesized that the caudate nuclei may be involved in sleep regulation; indirect evidence from studies with positron emission tomography (PET) point in the same direction.

Key words: Huntington's disease – Basal ganglia disorders – Sleep EEG – Cerebral atrophy – Caudate nuclei

Introduction

Since neuropsychiatric disorders are often characterized by abnormalities in both brain anatomy and function, cranial computed tomography (CT) and sleep EEG are important research tools in this field. Although it appears useful to study the relationship between sleep EEG parameters and cranial CT scan measures, few reports have focused on this topic. Ishibashi et al. (1987) observed correlations between cortical atrophy and decrease of slow wave sleep in chronic alcoholics, with a synchronous recovery of both parameters during abstinence. Van Kammen et al. (1988) found a correlation between ventricular enlargement and decreased slow wave sleep in schizophrenics. However, in patients with eating disorders, Lauer et al. (1989) observed an opposite relationship: patients with abnormally high ventricular brain ratios (VBR) exhibited significantly more slow wave sleep than patients with normal VBR values.

In the present study, the relationship between cranial CT measures and sleep EEG parameters (as well as selected clinical variables) was analyzed in patients with Huntington's disease. This disorder appears to be a suitable model for such investigation, since the underlying pathoanatomic and pathophysiologic alterations are relatively well known, compared with disorders like major depression or schizophrenia. Huntington's disease is accompanied by local changes in the basal ganglia region (atrophy of the caudate nuclei) as well as by a global cerebral atrophy, with enlargement of external and internal CSF spaces (Lange and Aulich 1986; Ott and Schuhmacher 1988). Sleep is also impaired, with more time spent awake, reduced slow wave sleep, and other abnormalities (Wiegand et al. 1989).

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Methods

Twelve inpatients with Huntington's disease were examined and treated in the clinic of the Max Planck Institute of Psychiatry, Munich (FRG). Table 1 gives selected demographic and clinical data for the sample. Five patients (Nos. 2, 3, 6, 7, 8) were drug-free; the wash-out period was more than 3 weeks in three cases and 1 week in two cases. Seven patients received medication with tiapride in doses ranging from 300 mg to 1200 mg daily, with additional medication in five cases (meclofenoxate 1000 mg in case 1; haloperidol 5 mg, amitriptyline 75 mg, sulpiride 100 mg in case 4; valproate 900 mg, clozapine 100 mg in case 9; trazodone 30 mg, trifluoperazin 3 mg in case 11; piracetam 2400 mg in case 12). For the sleep recordings, 12 age- and gender-matched healthy persons (mean age 45.3 ± 11.0 years) served as controls.

Cranial CT was performed in all patients with a General Electric Scanner 9800, using the 512 × 512 matrix and a 5-mm slice thickness. Measurements were carried out on two scans cut parallel to the glabella-inion line: (1) on a scan showing the insular cisterns, the third ventricle, and the anterior and posterior horns of the lateral ventricles; (2) on a scan through the region of the cella media of the lateral ventricles. All measurements were performed directly on the display screen, as described by Krieg et al. (1988). Distance measurements were carried out by using the "measure

Table 1. Demographic and clinical data

Patients	Age (years)	Duration of illness (years)	Global clinical assessment (%)	BPRS anxiety/ depression	BPRS anergia	BPRS thought disturbance	BPRS total score	TDRS score
1	57	6	30	8	21	9	45	44
2	46	4	70	7	7	4	24	36
3	55	10	40	9	20	7	43	43
4	46	3	30	5	18	10	42	34
5	30	2	60	18	13	7	44	42
6	31	1	90	16	5	4	31	13
7	48	4	30	10	22	6	46	47
8	54	1	80	10	10	6	33	31
9	42	7	50	18	21	12	67	21
10	41	4	60	10	11	5	41	34
11	36	2	80	12	16	6	53	28
12	53	12	30	7	18	12	46	47
$\bar{x} \pm SD$	44.9 ± 9.2	4.7 ± 3.5	54.2 ± 22.3	10.8 ± 4.3	15.2 ± 5.8	7.3 ± 2.8	42.9 ± 10.9	35.0 ± 10.6

distance" program; brain areas were measured on the basis of Hounsfield units by using the "density mask" program of the scanner (Zeumer et al. 1982; Schmauss and Krieg 1987).

The following cranial CT parameters were assessed:

FH/CC quotient (FH = greatest distance between the frontal horns; CC = shortest distance between the heads of the caudate nuclei. A value beneath 0.18 is considered abnormal) (Lange and Aulich 1986)

CC/OT quotient (CC = shortest distance between the heads of the caudate nuclei; OT = outer table of the skull at the same level)

FHBR (frontal horn brain ratio: area of the frontal horns of the lateral ventricles divided by the area of the brain × 100)

VBR (ventricular brain ratio: area of the lateral ventricles divided by the area of the brain × 100)

CSFBR (cerebrospinal fluid spaces brain ratio: area of the internal and external cerebrospinal fluid spaces divided by the area of the brain × 100. For this measure the mean value of the values assessed for the two scans was calculated).

In contrast to FH/CC, CC/OT and FHBR, which primarily quantify the regional degenerative process in the caudate nuclei, the CSFBR relates the total area of the cerebrospinal fluid spaces (i.e, ventricular system, cisterns, sulci, and fissures) to the brain area, and is therefore a measure of global brain atrophy. Owing to unreliable results, linear measurements for evaluating the width of cortical sulci were not carried out.

In addition, the cranial CT scans were visually evaluated by experienced neuroradiologists not directly involved in this study. A control group was not established since the performance of X-ray cranial CT in healthy control subjects was rejected by the local ethical committee.

After an adaptation night in the sleep laboratory, nocturnal sleep was recorded polysomnographically between lights out (23:00) and lights on (7:00) using a 17-channel Nihon Kohden 4417 EEG machine, including the following parameters: EEG (C3-A2/C4-A1), EOG (horizontal), and EMG (submental). The sleep polygraphs were scored visually according to standard criteria (Rechtschaffen and Kales 1968) by a rater unfamiliar with the cranial CT scan data. In the evaluation of sleep recordings, the following definitions of sleep parameters were used:

- Sleep period time: time from sleep onset until final awakening
- Sleep onset latency: time from lights out until the appearance of stage 2 sleep
- Sleep efficiency: ratio of total sleep time to time in bed
- Stages awake, 1, 2, SWS (= sum of stage 3 and 4), REM are expressed in percentages of sleep period time
- REM latency: time from sleep onset to the first occurrence of REM sleep
- REM density: percentage of 3-s "mini-epochs" of REM sleep containing at least one rapid eye movement related to the total number of "mini-epochs" of REM sleep.

The degree of motor disturbances was measured by means of the Tardive Dyskinesia Rating Scale (TDRS, Simpson et al. 1979) which range from 0 (= no involuntary movements) to 220. For the assessment of psychopathology, the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) was used. Of the five BPRS subscales, only the anxiety/depression, anergia, and thought disturbance scores were included in the present analysis. The total BPRS score has a minimum of 18 (= no psychopathology) and a maximum of 126. The scores of the subscales range from 4 to 28. In addition, a global clinical assessment was performed by means of the Karnofsky index (Gross et al. 1987; maximum: 100% = no symptoms, no impairment; minimum: 10% = dying).

Statistical analysis was obtained by computing Spearman's rank correlation coefficients. In addition, group statistics were performed using Mann-Whitney's U-test. The level of significance was set at 5% (two-tailed).

Results

In Table 2, selected cranial CT measurements are listed. The majority of patients had pathologic cranial CT scans; cranial CT measurements (FH/CC quotient and CSFBR, respectively) and visual evaluation showed good correspondence.

Table 3 shows the sleep EEG variables of the patients and matched healthy controls. In patients, sleep efficiency was reduced by increased nocturnal wakefulness and a higher number of nocturnal awakenings. Sleep onset latency tended to be longer, and there was a trend towards reduced slow wave sleep. There were no significant differences between medicated and drug-free patients.

Table 2. Cranial CT measurements

Patients	Caudate atrophy		Global cerebral atrophy	
	FH/CC	Visual	CSFBR	Visual
1	1.30	++	19.6	++
2	1.46	++	9.9	+
3	1.38	++	22.5	++
4	1.97	(+)	22.2	++
5	1.72	+	11.2	+
6	1.67	(+)	4.8	−
7	1.45	+	28.3	+
8	1.80	(+)	7.9	−
9	1.51	+	31.4	++
10	1.17	++	11.7	(+)
11	1.60	+	13.5	+
12	1.40	++	25.8	++
$\bar{x} \pm SD$	1.54 ± 0.23		17.4 ± 8.7	

Visual evaluation of cerebral atrophy: − absent; (+) minimal; + moderate; ++ marked

Table 3. Sleep variables in patients vs healthy controls

	Patients ($n=12$)	Controls ($n=12$)	P
Sleep period time (min)	412.4 ± 57.2	418.0 ± 13.1	ns
Sleep onset latency (min)	39.3 ± 36.0	16.3 ± 14.8	<0.10
Sleep efficiency (%)	80.6 ± 12.4	91.6 ± 4.5	<0.01
No. of awakenings	19.9 ± 11.3	9.7 ± 6.1	<0.01
Stage awake (%)	9.7 ± 6.5	4.7 ± 4.0	<0.05
Stage 1 (%)	10.7 ± 6.4	9.1 ± 5.9	ns
Stage 2 (%)	53.6 ± 10.9	56.3 ± 6.3	ns
Slow wave sleep (%)	4.7 ± 3.3	9.8 ± 8.2	<0.10
REM sleep (%)	19.0 ± 5.2	18.6 ± 4.3	ns
REM latency (min)	72.8 ± 45.8	76.8 ± 21.4	ns
REM density	24.5 ± 13.7	25.0 ± 9.3	ns

Table 4. Intercorrelations between cranial CT measurements

	FH/CC	CC/OT	FHBR	VBR
CC/OT	−0.79**			
FHBR	−0.72**	0.93**		
VBR	−0.44	0.73**	0.83**	
CSFBR	−0.34	0.65*	0.80**	0.94**

*$P<0.05$; **$P<0.01$

Table 4 shows the intercorrelations between the cranial CT variables. FHBR, CC/OT, VBR, and CSFBR were closely intercorrelated; the same held true for FHBR, CC/OT, and FH/CC, whereas the FH/CC quotient lacked significant correlations with VBR and CSFBR. Thus, of the five cranial CT parameters, only the FH/CC quotient (reflecting local, illness-specific changes), and the CSFBR (reflecting global cerebral atrophy) will be included in the following analysis.

According to Table 5, both local and global cerebral atrophy measures did not correlate significantly with age, but clearly correlated with illness duration. Clinical parameters (e.g., global clinical assessment and BPRS anergia, thought disturbance, and total score) correlated significantly with global cerebral atrophy (CSFBR), but not with caudate atrophy (FH/CC quotient). There was no significant correlation of cranial CT measures with the degree of movement disturbance (TDRS score). The BPRS anxiety/depression subscore did not correlate with the cranial CT measures.

Table 6 shows the correlations between cranial CT parameters and selected sleep variables. Caudate atrophy clearly correlated with less slow wave sleep and more time spent awake, whereas global cerebral atrophy showed no significant correlations with sleep parameters. Sleep duration, stages 1 and 2, and REM parameters did not have any relationship to cranial CT measures.

In order to corroborate the results of the correlational analysis, a group statistical analysis was performed between subjects with a high vs low degree of atrophy [grouping values were the respective medians of the FH/CC quotient (1.49) and the CSFBR (16.6)]. In general, the observations resembled those reported above. Owing to the small subsample size, these data are not reported in detail here.

Discussion

The majority of patients in the present study had global cerebral atrophy as well as local atrophy of the caudate nuclei which corresponds to findings from earlier neuroradiological studies on Huntington's disease (Lange and Aulich 1986; Ott and Schuhmacher 1988). The respective measurements (CSFBR and FH/CC) correlated highly with duration of illness, whereas correlations with age were less pronounced and not significant. It can, thus, be concluded that the neuroanatomical alterations are closely illness-related and not merely a reflection of age effects.

Table 5. Correlations between cranial CT measurements and clinical variables

	Age	Duration of illness	Global clinical assessment	BPRS anxiety/ depression	BPRS anergia	BPRS thought disturbance	BPRS total score	TDRS score
FH/CC	−0.39	−0.71**	−0.37	0.21	−0.35	0.00	−0.17	−0.51
CSFBR	0.34	0.76**	−0.78**	−0.14	0.91**	0.73**	0.78**	0.43

**$P<0.01$

Table 6. Correlations between cranial CT measurements and sleep variables

	Sleep period time	Stage awake (%)	Stage 1 (%)	Stage 2 (%)	SWS (%)	REM (%)
FH/CC	0.04	−0.78**	−0.27	0.27	0.60*	0.26
CSFBR	−0.25	0.51	−0.05	−0.15	−0.35	0.14

*$P < 0.05$; **$P < 0.01$

The patients exhibited an impaired nocturnal sleep pattern with reduced sleep continuity, less sleep efficiency, more time spent awake and a tendency towards less slow wave sleep and longer sleep onset latency. These findings are in line with previous studies on sleep in Huntington's disease, e.g. by Hansotia et al. (1985). Results on nocturnal sleep and its relationship with several clinical parameters obtained in a larger sample will be described and discussed elsewhere in more detail (Wiegand et al., in press). A previous report has already focused on movements during nocturnal sleep in Huntington's disease (Wiegand et al. 1989).

More time spent awake and a reduced amount of slow wave sleep were both associated with a reduced FH/CC quotient. Relationships between impaired nocturnal sleep and cerebral atrophy in neuropsychiatric conditions of various etiologies have been reported by several authors. Schneider et al. (1982) found clear correlations between poor sleep quality, especially reduced slow wave sleep, and ventricular enlargement in patients suffering from ischemic lesions. In a preliminary study, Ishibashi et al. (1987) reported on an association between improvement of cortical atrophy and increase of slow wave sleep during remission in abstinent chronic alcoholics. In schizophrenic patients, van Kammen et al. (1988) found that stage 4 sleep correlated negatively with VBR measures. In eating disorders, on the other hand, Lauer et al. (1989) reported on a higher amount of slow wave sleep in patients with cerebral atrophy than in patients displaying no cranial CT alterations. However, it must be taken into account that in eating disorders the cranial CT scans may reflect "pseudoatrophy" rather than real loss of brain tissue, in contrast to various other neuropsychiatric conditions, including Huntington's disease.

Although the results of most studies seem to point in the same direction, a more detailed analysis reveals considerable differences regarding the localization of brain atrophic changes which correlate with impaired sleep. In the study by Schneider et al. (1982) on patients with ischemic lesions, only ventricular enlargement correlated with sleep disturbance, whereas cortical atrophy showed no relationship with sleep parameters. The same applies to van Kammen's (1988) data obtained in schizophrenic patients. The data of Ishibashi et al. (1987) on chronic alcoholics, however, point to a more important role of cortical atrophy in this context. Our own results suggest that for the impairment of sleep in patients with Huntington's disease, local (and, thus, illness-specific) atrophy of the caudate nuclei seems to be more decisive than global cerebral atrophy.

For a conclusive interpretation of these results, too little is as yet known about the relation between brain morphology and sleep. It must be remembered that cortical atrophy generally yields a diminished EEG amplitude, since the EEG mainly reflects cortical electrical activity. Such a relationship has been observed in patients with Huntington's disease who exhibit a low-voltage waking EEG that correlates with cortical atrophy (Scott et al. 1972). Using the amplitude criterion of slow wave sleep (Rechtschaffen and Kales 1968) can thus be expected to lead to an artifactural reduction of this sleep stage (indicating diminished EEG synchronization) in patients with cortical atrophy. However, contrary to this expectation, the present study revealed that slow wave sleep reduction did not correlate with the CSFBR parameter (which includes cortical atrophy) but with the FH/CC quotient indicating local atrophy of the caudate nuclei, which is not likely to influence the EEG amplitude in general. Considering that sleep regulation encompasses a large variety of anatomic and functional systems distributed throughout the brain, it may be fruitful to study possible direct or indirect links between basal ganglia function and sleep. Further evidence for such an association comes from studies with positron emission tomography (PET) in depressed patients and normal controls. Patients with major depression exhibit a low metabolic rate in the caudate nucleus (Baxter et al. 1985; Buchsbaum et al. 1986); as in Huntington's disease, slow wave sleep is known to be frequently reduced in depression. In a recent PET study, Buchsbaum et al. (1989) demonstrated changes in the metabolism of the caudate nucleus during sleep in healthy volunteers.

The very high correlations between global cerebral atrophy (CSFBR) and clinical variables (global clinical assessment and the BPRS subscales anergia and thought disturbance) are an interesting side-aspect of the present study. We did not observe a significant correlation between psychopathology and caudate atrophy. This is not in agreement with the report of Bamford et al. (1989), who found close relationships between caudate atrophy and several neuropsychological variables indicating cognitive impairment in Huntington's disease. The discrepancy of results may be attributed to the rather global nature of the psychopathometric scales, as compared with the more specific neuropsychological methodology applied by Bamford et al.

Thus, the general clinical state as well as part of the psychopathological symptomatology of these patients seem to be closely linked to global cerebral atrophy. Both the anergia and thought disturbance subscales of the BPRS reflect aspects of dementia. There is also an interesting parallel to the findings of van Kammen et al. (1988), who observed a correlation between VBR and negative symptoms in schizophrenia. In contrast, anxiety/depression did not correlate with cranial CT measures indicating an independence of more pronounced affective symptoms and brain morphological alterations in Huntington's disease.

It thus becomes evident that the relation between brain morphology and sleep in neuropsychiatric disorders is quite complex. The interpretation of such associations is complicated by the fact that cranial CT scans do not allow differentiation between atrophy and pseudoatrophy. For a corroboration of the present findings, a longitudinal analysis of sleep, cranial CT and psychopathology, would be of great value. In order to evaluate sleep EEG and cranial CT scan changes associated with the illness progression, a follow-up of the patients is under consideration.

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