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ORIGINAL PAPER

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Periodic limb movements during sleep in alcohol dependent patients

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Abstract Complaints of sleep disturbances are common among alcohol dependent patients during subacute abstinence. Recovered patients may show persistent sleep abnormalities for months or even years. In the present study we studied the issue whether periodic limb movements in sleep and disturbances of nocturnal respiration are more frequent in alcohol dependent patients than healthy subjects and may be of predictive value for sustained abstinence vs. relapse after withdrawal.

Forty alcohol dependent patients spent three nights in the sleep laboratory at three time points: 2 to 3 weeks after withdrawal (T0) and at follow-up investigations 6 (T1) and 12 (T2) months after discharge from the hospital. Measurements of PLMS-arousal index and nocturnal respiration were performed during the first laboratory night of each measurement point.

Alcohol dependent patients displayed a significantly enhanced PLMS-arousal index at T0 compared to age- and gender-matched healthy subjects, whereas no alterations of nocturnal respiration were found.

The PLMS-arousal index at T0 was significantly elevated in patients who relapsed during the next 6 months compared to abstinent patients. In a discriminant function analysis the PLMS-arousal index classified 55 % of the patients correctly with respect to outcome after 6 months. It correctly predicted 80 % of abstainers and 44 % of the patients who relapsed.

According to neurobiological models of the generation of PLMS and the etiopathology of alcohol dependence a genetically determined vulnerability of the dopaminergic system is discussed as a factor underlying an increased risk of relapse in a subgroup of alcohol dependent patients.

Key words alcoholism · relapse · periodic leg movement · sleep

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Introduction

Alcohol dependent patients often complain of sleep disturbances during periods of drinking as well as during acute withdrawal and subacute or chronic abstinence [22, 26]. Recovered alcoholic patients may show persistent sleep abnormalities for months or even years [41]. The sleep disturbances are documented by polysomnography as reduced total sleep time, loss of delta sleep, impaired sleep efficiency and REM (rapid eye movement) sleep abnormalities. We [21] and others [23] have shown that REM sleep abnormalities (increased "REM pressure" = REM % Sleep period time (SPT)↑, REM latency↓, 1. REM density↑) at admission predicted later relapse in nondepressed alcoholic patients after discharge from the hospital. Furthermore, the amount of the reduction of subjectively experienced sleep quality is prognostic for early relapse in alcohol dependent patients [9, 10, 19, 38]. Several other well-recognized causes of disturbed sleep such as periodic leg movements in sleep (PLMS) and sleep-disordered breathing may also contribute to the sleep disturbances associated with alcohol dependence [1, 2, 11, 28, 32, 36, 39, 40].

We report here data on PLMS and nocturnal respiration which were collected in a longitudinal study of polysomnographically recorded sleep in alcohol dependent patients (preliminary report: [20]; complete data set: [21]). Our study did not primarily aim at PLMS. However, the increased PLMS-arousal indices found in the patients prompted us to scrutinize the issue. Besides comparing patients with healthy controls, another focus of the present paper is the question whether indices of

PLMS and nocturnal respiration are predictive for the further course of the alcohol disorder.

Methods

Subjects

The subjects comprised 40 patients with primary alcoholism (see Table 1) and 30 healthy controls stratified for age and gender. The patients were consecutively recruited (age 43 ± 9 years, 72.5% males). They had been admitted for treatment of alcoholism to our department, which offers a 21-day inpatient treatment program. Subjects were asked to participate in 3 consecutive nights of polysomnography recorded during the third week of hospitalization (T0) and at 6 (T1) and 12 (T2) months follow-up after discharge. All subjects underwent a medical and psychiatric investigation and physical examination. All patients met the criteria for alcoholism using DSM-III-R criteria (diagnoses were made with a structured clinical interview = SCID, German version, [45]). Primary alcoholism refers to patients without another psychiatric illness or significant medical problem prior to the onset of alcoholism. We excluded patients with psychotic features, clinically significant cognitive impairment, antisocial personality disorder, substance abuse other than alcohol and major medical problems (i. e., cirrhosis of the liver). All patients were free of psychoactive medication for a minimum of 7 days prior to the investigation in the sleep laboratory.

The study was approved by the local ethical committee and all subjects/patients gave informed written consent prior to inclusion.

Design

The polysomnographic recordings were performed exactly as described previously [21]. The first night served to adapt the subjects to the laboratory and to screen for sleep apnea and PLMS. The data reported in the present communication comprise those recorded in the first of three nights the patients and controls spent in the sleep laboratory. The clinical outcome was determined at 6 and 12 months follow-up after discharge from the hospital. Relapse was defined as any reported consumption of alcohol between hospital discharge and follow-ups, based on a separate standardized interview with the patients and confirmed by determination of blood alcohol level or elevated hepatic enzyme level. Abstinent patients were reinvestigated in the sleep laboratory at the 6 month (T1) and 12 month (T2) follow-ups.

Statistics

Descriptive statistical parameters include presentation of means and standard deviation. For group comparison the two-tailed t-test was used. Furthermore, repeated measures analysis of variance (ANOVA) corrected according to the method of Greenhouse and Geiser [25] was used. Correlations were computed according to Pearson (two-tailed).

Discriminant function analysis with cross-validation by a leave-one-out scheme was used to quantify the predictive power of the PLMS index.

Table 1 Clinical and demographic characteristics of patients with primary alcoholism (means ± SD)

	Patients	Controls
Age (years)	43±9	43±9
Sex (males in %)	72.5%	67%
Duration of alcoholism (years)	13±8	–
21-Hamilton Depression Rating Scale (T0)	4±5	–
Free of medication before T0 (days)	16±7	–
No. days drank in prior 6 months (180 days)	120±71	–
Daily alcohol consumption per drinking day (g)	191±128	–
GGT, IU (admission)	162±242	–
GOT, IU (admission)	36±30	–
GPT, IU (admission)	30±23	–

Sleep

Sleep was registered between lights out (11:00 pm) and lights on (07:00 am) using standard procedures (EEG: C4-1; C3-A2; horizontal EOG, submental EMG). For a detailed description of the algorithms used for recording of sleep parameters in our sleep laboratory, see [35]. The method to calculate "REM pressure" is described in detail elsewhere [21]. Mercury strain gauges on chest and abdomen were used to monitor respiratory effort and thermistors at the nose and mouth were used to monitor air flow. Leg movements were monitored bilaterally with surface EMG electrodes over the anterior tibialis muscles. Oxygen saturation was monitored by pulse oxymetry. The recordings were scored for the sleep stages and respiratory measurements using standard techniques [8, 14, 34]. The respiratory disturbance index was calculated as the number of apneas plus hypopneas per hour of sleep (SPT = sleep period time). Anterior tibialis EMG activity was scored as PLMS if the activity occurred during sleep, lasted 0.5 to 5 seconds, and occurred in a series of at least 4 movements separated by intervals of more than 5 seconds and less than 90 seconds [13]. The PLMS-arousal index was calculated as the number of minutes with PLMS followed by EEG arousal divided by the number of hours of sleep (TST). EEG arousal is defined as a sudden EEG frequency acceleration lasting a minimum of three seconds.

Results

Comparison of patients (T0) vs. age- and gender-matched controls

Data from 40 patients were compared with 30 age and sex-matched healthy controls concerning sleep data of the first laboratory night. While the PLMS-arousal index was significantly higher in patients than in controls, the apnea-hypopnea index did not differ between patients and controls (see Table 2, Fig. 1). There were no differences in sleep continuity between patients and controls. However, sleep architecture was significantly altered in

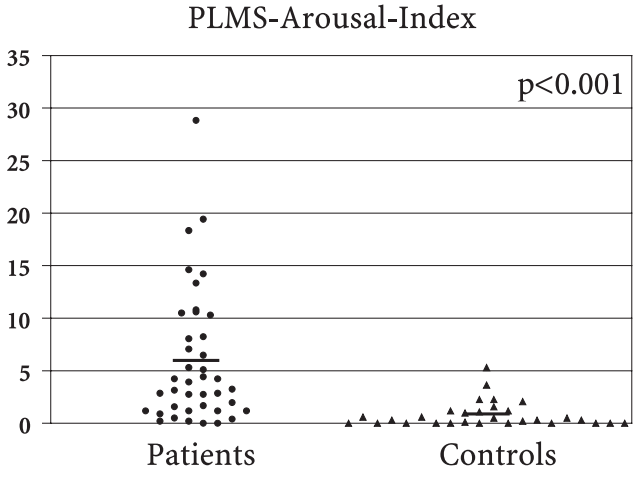

Fig. 1 PLMS-arousal index (T0): patients vs. controls.

Table 2 Sleep variables, PLMS-arousal index and apnea-hypopnea index (T0): patients (n = 40) vs. healthy controls (n = 30)

	Patients (t0) (n = 40)	Controls (n = 30)	t-test* t =	df =	p-value
PLMS-arousal index	5.9±6.4	0.84±1.2	4.9	42.8	**0.000**
PLMS index without arousal	23.7±26.4	4.6±6.3	4.4	44.7	**0.000**
Apnea-hypopnea index	1.4±1.5	1.3±1.9	0.2	68	0.816
Sleep variables					
Sleep continuity					
Sleep efficiency (%)	79.4±8.3	82.1±10	–1.3	68	0.210
S-2 latency (min)	24.5±15.7	25.5±28.4	–0.2	68	0.857
Time awake (% SPT)	12.8±8.5	11±7.6	0.9	68	0.351
No. of awakenings	26.1±12.4	21.9±9.7	1.56	68	0.123
Sleep architecture					
Stage 1 (% SPT)	11.6±5.7	8.7±4.5	2.3	68	**0.022**
Stage 2 (% SPT)	52.5±8.8	56.3±8	–1.9	68	0.066
Stage 3 + 4 (% SPT)	1.4±3.9	4.4±5.4	–2.6	68	**0.011**
REM (% SPT)	21.3±6.4	19.9±5	0.9	68	0.345
REM sleep					
REM latency (min)	64.2±33	88.3±34.1	–3.0	68	**0.004**
Total REM density (%)	35.9±11.6	25.7±8.6	4.2	67.9	**0.000**
1st REM period duration (min)	21.7±15	14.6±12.3	2.1	68	**0.038**
1st REM density (%)	32.2±14.9	19.73±9.3	4.3	65.9	**0.000**
REM pressure	1.11±1	–0.82±0.8	3.7	68	**0.000**

* Student's t-test (two-tailed)

patients (increased stage 1 % SPT and decreased stages 3 + 4 % SPT). Furthermore, patients exhibited an increased REM sleep pressure.

Predictive value of the sleep variables at T0 for outcome at the 6 month follow-up

At follow-up after 6 months, 23 patients had relapsed and 10 patients had remained abstinent. Seven patients were not available for further study at the time of follow-up. The two-tailed t-test showed a significantly higher PLMS-arousal index in the patients who relapsed within 6 months after withdrawal (see Table 3, Fig. 2).

Analysis of the adaptation nights demonstrated that patients who relapsed at the 6 month follow-up exhibited a significantly higher REM pressure at T0 than patients who remained abstinent (see Table 3).

In order to assess the predictive power that the PLMS-arousal index can provide, we performed a discriminant function analysis for the PLMS-arousal index and the dichotomy abstinence/relapse. The PLMS-arousal index classified 55 % of the patients correctly (figures for cross-validation step). It correctly predicted 80 % of abstainers and 44 % of relapsers.

No significant correlation was found between the PLMS-arousal index and REM pressure, neither with respect to the total group of patients ($r = 0.115$, $p = 0.484$) nor with respect to the group of relapsed patients ($r = -0.036$, $p = 0.871$).

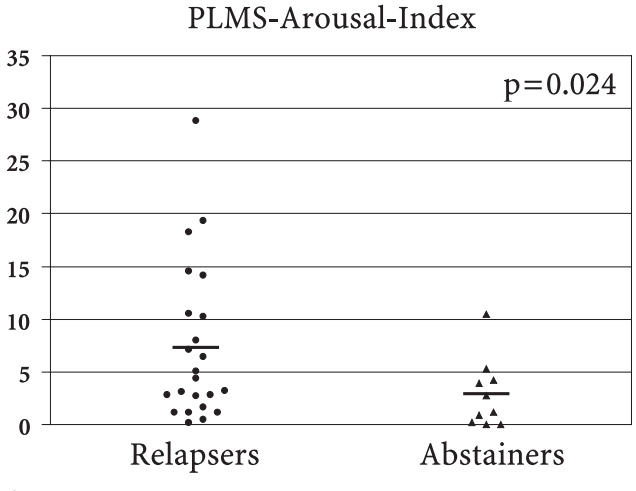

Fig. 2 PLMS-arousal index (T0): relapsers vs. abstainers.

Sleep variables, PLMS-arousal index and apnea-hypopnea index during the course of one year of abstinence

Ten patients remained abstinent up to one year, the time of the second follow-up, and could thus be studied by polysomnography at both follow-up investigations at 6 and 12 months. ANOVA revealed no significant alterations during the time of follow-up of one year. There was a non-significant trend towards a normalization of the PLMS-arousal index (see Fig. 3).

Discussion

The goal of the present analysis was to assess the potential significance of PLMS and parameters of nocturnal respiration as predictors of outcome in alcoholic patients. To this end, data obtained in the adaptation nights

Table 3 Sleep variables, PLMS-arousal index and apnea-hypopnea index: relapsers vs. abstainers (6 months follow-up)

	Relapsers (T0) (n = 23)	Abstainers (T0) (n = 10)	t-test*	df	p-value
PLMS-arousal index	7.3±7.4	2.9±3.3	2.4	30.9	**0.024**
PLMS index without arousal	29.5±30.5	8.9±11.5	2.8	30.7	**0.009**
Apnea-hypopnea index	1.4±1.7	1.4±1	0.1	31	0.913
Sleep variables					
Sleep continuity					
Sleep efficiency (%)	79.9±8.5	77.3±8.6	0.8	31	0.426
S–2 latency (min)	23.2±12.6	23.6±11.9	–0.08	31	0.932
Time awake (% SPT)	13.6±9	14.4±8.8	–0.239	31	0.813
No. of awakenings	27.3±14.5	25.6±10.1	0.34	31	0.732
Sleep architecture					
Stage 1 (% SPT)	11.6±5.8	11±5.7	0.25	31	0.807
Stage 2 (% SPT)	50.3±9.4	56.5±6	–1.9	31	0.063
Stage 3 + 4 (% SPT)	1.9±4.8	0.1±0.3	1.2	31	0.238
REM (%SPT)	22.1±6.6	17.7±5.2	1.9	31	0.066
REM sleep					
REM latency (min)	58.7±34.6	82.3±34.6	–1.8	31	0.081
Total REM density (%)	38.3±10.8	32.4±12.9	1.4	31	0.183
1st REM period duration (min)	22.9±15.8	20.7±13.9	0.4	31	0.706
1st REM density (%)	35.7±14.7	26.5±15.7	1.6	31	0.118
REM pressure	0.25±0.93	–0.73±0.99	2.7	31	**0.011**

* Student's t-test (two-tailed)

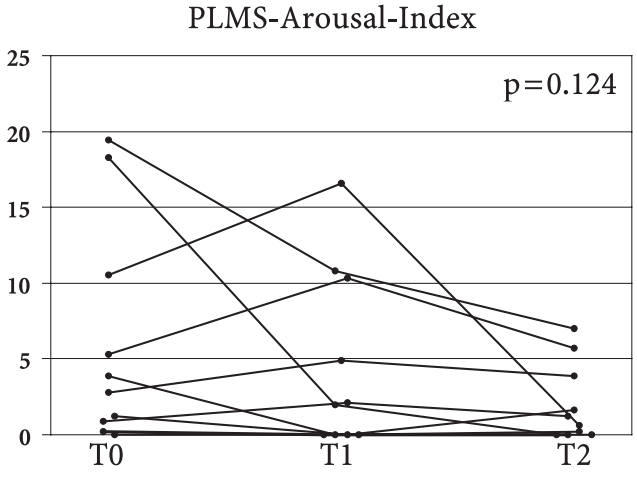

Fig. 3 PLMS-arousal index of abstainers: T0, T1, T2.

were analyzed. These adaptation nights are the first few nights within the total of three nights spent by the patients in the sleep laboratory at each of three assessment time points during the course of our longitudinal study of potential predictors of relapse in alcoholic patients: T0 (2–3 weeks of abstinence), T1 (follow-up at 6 months) and T2 (follow-up at 12 months). Several authors [7, 16, 32] did not find any adaptation effects of PLMS and parameters of nocturnal respiration. A collateral finding of the present study was that our initial result of a predictive value of REM pressure during baseline night at T0 for later relapse [21] could be replicated with data obtained during the adaptation nights. In contrast, sleep continuity did not differ between patients and controls in the adaptation nights, while significant differences in this parameter were found in the baseline night [21]. This distinction between the baseline and adaptation night is probably due to a general disturbance of sleep in an unfamiliar environment, the extent of which causes a ceiling effect that precludes the detection of more subtle differences between patients and controls. No significant alterations in polysomnography occurred over one year in 10 abstinent alcoholics. Our findings, however, are not comparable to the longitudinal studies of other authors [18, 43], due to the small sample size (n = 10). The main result of the present work is, however, that PLMS at T0 also appears to predict outcome in alcoholic patients. The PLMS-arousal index classified 55 % of the patients correctly. It correctly predicted 80 % of abstainers and 44 % relapsers.

The demographic and clinical variables of relapsed and abstinent patients did not differ significantly (see [21]).

Aldrich and Shipley [3] have discussed several possibilities to explain the association between drinking behavior and PLMS, which also represent potential explanations for the results of the present study. First, this association might be due to toxic effects of alcohol on the CNS [12]. Chronic alcohol abuse produces a variety of perturbations of brain function, some of which appear to be mediated by effects on the inhibitory neurotransmitter gamma-aminobutyric acid. Thus, a reduced inhibition of an intrinsic subcortical pacemaker may be the neurophysiological basis of PLMS [13]. Second, alcohol ingestion may trigger PLMS in susceptible individuals. Third, subjects with symptoms related to PLMS, such as restless legs, may use alcohol to experience relief from their symptoms. Then patients may, in particular, use alcohol to promote sleep. Fourth, PLMS may be a consequence of alcohol-induced sleep disturbance rather than a primary cause of sleep disturbance. Sleep

disruption with frequent arousals and increased amounts of light non-REM sleep may increase the likelihood that PLMS occur.

It is unlikely that peripheral neuropathy related to alcohol use is responsible for the association we observed, since Aldrich and Shipley [3] already found no correlation between extent of PLMS and severity of alcoholism, although the latter is clearly associated with peripheral neuropathy.

Our results do not allow us to identify which of these various potential explanations is correct. On the basis of the anamnestic information available from the patients in the present study, it is, however, very unlikely that a substantial percentage of the patients suffered from PLMS-related symptoms such as restless legs or had an increased vulnerability for such symptoms that might have been aggravated or triggered by alcohol abuse. Furthermore, the extent of PLMS in relapsers was significantly higher than that in abstainers, although sleep continuity and sleep architecture were not different (see Table 3). This suggests that sleep disturbances per se are insufficient to explain the association of alcoholism and PLMS. Thus, we consider perturbations of neurotransmitter functioning induced by chronic alcohol abuse and/or withdrawal the most likely explanation for the enhanced PLMS-arousal index in alcoholic patients and, by inference, also for the increased vulnerability to relapse in the subgroup with the highest PLMS-arousal index.

Several authors [5, 30–32] have conjectured on the basis of pharmacological studies that a compromised dopaminergic activity or reduced sensitivity of dopamine receptors in the brain might be responsibe for PLMS. This hypothesis is supported by the beneficial effects of dopamine agonists in the treatment of PLMS in patients with restless legs syndrome [27, 42] and narcolepsy [6]. On the other hand, a large body of evidence supports the important role of the dopaminergic system for the initiation and maintenance of drug addiction and craving [24]. While acute alcohol consumption might increase the dopamine-mediated activation of the reward system in the brain, chronic abuse might rather lead to a diminished dopaminergic activity [33]. Thus, given its purported association with PLMS, decreased dopaminergic neurotransmission might be envisaged as one potential cause of the enhanced PLMS-arousal index in chronic alcoholic patients. In accordance with this hypothesis is the increased amount of PLMS found in Parkinson's syndrom, a well-established example of central dopamine deficiency [17, 44]. On the other hand, PLMS appear to be reduced in schizophrenia [15, 29], a condition with hypothesized dopamine overdrive in susceptible brain areas [4]. Thus, withdrawal might not only induce a protracted syndrome of serotonergic dysfunction [21] but also a protracted syndrome of dopaminergic dysfunction in alcoholics that is responsible for increased PLMS indices. Patients with a particular pronounced increase in PLMS might tend to "treat" this condition and the associated sleep disturbance by alcohol ingestion, which might explain the greater likelihood for relapse in these patients. Alternatively or in addition, a perhaps genetically determined vulnerability of the dopaminergic system might pose an increased risk of relapse to this subgroup of alcoholic patients.

Earlier findings that alcoholic patients exhibit an enhanced amount of sleep-disordered breathing [2, 11, 28, 39, 40] were not replicated in the present study. One likely explanation is that increased sleep-disordered breathing is age dependent: Aldrich et al. [2] reported that only 3 % of alcoholics below the age of 49 years exhibited sleep-disordered breathing while this abnormality was found in 75 % of the patients with an age over 60 years. Since the mean age of patients in our study was 45 years, an increased extent of sleep-disordered breathing, if any, would not be expected to become statistically significant.

In conclusion, the present study provides evidence that an enhanced PLMS-arousal index is found in alcoholic patients after a short period (2–3 weeks) of abstinence, the extent of which predicts the outcome. This finding may have important clinical implications: first, polysomnography of alcoholics should include leg movement monitoring. Second, treatment, for example, with a dopamine agonist for PLMS should be considered for patients presenting with a clearcut elevation of PLMS-arousal index, since such patients may tend to treat their PLMS-associated arousal and consequent sleep disturbance by alcohol ingestion [37].

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