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Fatigue, sleep disturbances and circadian rhythm in multiple sclerosis

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Abstract. The aim of this study was to investigate whether fatigue and sleep disturbances in multiple sclerosis (MS) patients might be due to disrupted circadian sleep wake regulation. Actigraphy and a multiple sleep latency test (MSLT) were performed in 16 MS patients with both prominent sleep complaints and fatigue. Actigraphy scores did not differ from control values, whereas sleep onset latency values were altered in subgroups of MS patients. No evidence was found for a generalized circadian disturbance in MS patients.

Key words: Fatigue – Sleep – Circadian rhythm – Multiple sclerosis

Introduction

Fatigue and sleep disturbances are frequent and disabling symptoms in multiple sclerosis (MS) [3, 9]. However, there is at present no clear explanation for the mechanism underlying these symptoms.

The possibility that both fatigue and sleep disturbances in MS patients might be caused by disrupted circadian sleep wake regulation was investigated in the present study. Under physiological circumstances, various rhythmic phenomena occur in a synchronized way. These phenomena include, for example, deep body temperature, sleep wakefulness and rest activity. The hypothalamic suprachiasmatic nucleus (SCN) plays an important role in the entrainment and synchronization of several rhythms to the 24-h day. Visual information on the environmental 24-h light dark cycle is mediated directly to the SCN through the retinohypothalamic tract and possibly also indirectly via the geniculohypothalamic tract. In addition, the SCN receives neuronal input from the

raphe nucleus, and hormonal input, i.e. melatonin, from the pineal gland. The SCN outputs, resulting in the synchronization of rhythms, are less well described, but include projections within the hypothalamus and to the thalamus [6]. As the optic nerve, containing the retino-hypothalamic fibres, is often affected in MS patients, one may presume that a reduced input to the SCN leads to disturbances in the circadian timing of, amongst others, sleep wakefulness and rest activity. Moreover, rhythms might be disturbed by lesions (plaques) in the periventricular area of the hypothalamus i.e. in the region of the SCN or its efferents. Likewise, disturbed circadian rhythms in Alzheimer patients have been attributed to degeneration of the SCN [10], although degeneration of the optic system also offers an alternative explanation in this condition.

To evaluate the hypothesis we performed actigraphy and a multiple sleep latency test (MSLT) in a selected group of MS patients [2, 5]. Actigraphy is a non-invasive and patient-friendly way to evaluate the amplitude and stability of the rest activity cycle, as well as the occurrence of naps or sleep fragmentation [12]. The MSLT evaluates the time it takes to fall asleep during hours one is normally awake. As mood disturbances may coincide with and contribute to fatigue and sleep disturbances, depressive symptoms were evaluated as well. In addition, the human leucocyte antigen (HLA) type was assessed in order to determine its possible relationship to sleep disturbances, since an increase in daytime naps has been related to a possible similar genetic susceptibility for MS and the narcolepsy-cataplexy syndrome [13].

Patients and methods

Out of a group of 60 patients with definite MS who visited the outpatient clinic in February 1991, 16 were selected on the basis of both prominent fatigue and prominent sleep disturbances, which were evaluated using the Fatigue Severity Scale (FSS) and the

Sleep-Wake Experience List [4, 11]. Criteria for selection were a score of at least 5 on the FSS and the presence of at least two of the following six chronic sleep wake complaints: difficulty in initiating sleep, difficulty in maintaining sleep, early morning awakening, difficulty in waking up, tiredness on waking up, daytime sleepiness.

These patients were 9 women and 7 men. Their mean age was 43 years, range 29–67. Thirteen patients had a lowered visual acuity as determined with the Snellen chart. The FSS score ranged from 5 to 6.67 (mean 5.9). Eight patients had two types of chronic sleep wake complaints, while 6 patients had three and 2 patients had four types of these complaints. Their disability, expressed using the Expanded Disability Status Scale (EDSS) ranged from 2.0 to 7.5 (mean 5.5). Eight patients were in a relapsing-remitting phase of the disease and 8 were in a (relapsing-) progressive phase. None of the patients was studied during an acute relapse and none had received immunosuppressive medication, including corticosteroids, in the 3 months preceding the study.

Polysomnographic MSLT recordings were performed at 1000, 1200, 1400 and 1600 hours [2]. Each recording lasted 20 min and, if asleep, patients were awoken at the end of this period. Sleep-onset latency (SOL) was scored as the time between closing of the eyes and the first epoch (30 s) of any stage of sleep [7]. SOL values were compared with values determined previously in our laboratory in 40 healthy controls (21 women, 19 men) whose age ranged from 24 to 78 years (mean 50). A sleep wake diary was kept during the week before the MSLT, including the time of going to bed and waking up and the number of hours sleep per night. In a short sleep interview, special attention was paid to symptoms of the narcolepsy-cataplexy syndrome and the sleep apnoea syndrome.

A blood sample was collected from all patients to type for HLA-A, -B, -C and -DR. The prevalence of the different antigens in patients was compared with data collected from 1080 healthy blood donors.

The Beck Depression Inventory (BDI) was administered to all patients to assess depressive symptoms [1]. A BDI score of 17 was used as the cut-off point for depression.

Following MSLT a 7-day actigraph was recorded in all patients, for which purpose an actigraph was worn on the wrist [5]. The small (57 × 46 × 22 mm) and light (70 gm) actigraph, a miniaturized version of the one described by Witting et al. [12], continuously counts wrist movements and stores them hourly in a solid-state memory. After recording, the data can be transferred to a computer for further analysis. The movement counts give an indirect assessment of the sleep wake state of the subject. Hourly scores of the actigraph were analysed using a chi-square periodogram, and the parameters interdaily stability (IS), intradaily variability (IV), mean of the ten most active (M10) and mean of the five least active (L5) hours were computed [12]. IS can be interpreted as the strength of coupling between the rest activity rhythm and its supposedly stable *Zeitgebers*, e.g. light and darkness. IV gives an indication of the fragmentation in the rest activity rhythm, and reflects the number of transitions between sleeping and waking during the 24-h cycle. If fragmentation occurs, M10 and L5 give additional insight in the character of the fragmentation, as these measures reflect daytime naps and night-time awakenings respectively [12].

The partners of the patients were asked to participate as controls. As only 8 partners volunteered (5 women, 3 men, aged 19–61 years), the results of 8 male students, aged 20–31 years, were added after confirming that they did not differ statistically from the results of the partners (Mann-Whitney: $P = 0.67$ for IS, $P = 0.17$

for IV, $P = 0.60$ for M10 and $P = 0.06$ for L5). The trend in L5 could be traced to a habit of staying up very late for one or two nights, occurring in a few students and slightly increasing their L5 parameter.

All statistical comparisons were performed using a Mann-Whitney test or a Spearman rank correlation, with a significance level of 0.05.

Results

Multiple sleep latency test

In several patients sleep stages 1 and 2 but neither deep sleep nor rapid eye movement (REM) sleep were recorded in any of the patients. Means and standard deviations of SOL are presented in Table 1. No significant differences between the patient and control group were found, but a trend for an interaction between SOL and HLA type emerged: HLA-DR 2 positive patients had shorter SOL than controls, while HLA-DR 2 negative patients had longer SOL than controls. This trend reached significance for SOL at 1600 hours in the comparison between HLA-DR 2 negative patients and both controls ($P < 0.01$) and HLA-DR 2 positive patients ($P < 0.02$). Although these significances might be attributed to the large number of tests, all comparisons point in the same direction. According to the diary, several patients took short naps during the day, but none of them on a regular basis; the number of hours per sleep varied from 4 to 7. In the interview none of the patients reported narcoleptic symptoms. Heavily snoring or apnoeas were neither mentioned by the patients themselves nor by their partners.

HLA types

Four patients (25%) were HLA-DR 2 positive, approximating the prevalence in the blood donor group (28%). Compared with the blood donor group the prevalence of the A1 antigen was twice as high in the patient group (63% versus 32%). The A1 antigen was not related to SOL values, depression scores or actigraphy results.

Depression scores

Six patients (38%) were moderately to severely depressed (BDI > 17). Compared with the non-depressed patients, the depressed patients had no different mean EDSS (5.5 versus 5.6), while their mean FSS score was somewhat higher (6.2 versus 5.8) as was their mean SOL (17.8 versus 16.8 min).

Table 1. Mean sleep-onset latency (and standard deviation)

	<i>n</i>	1000 hours	1200 hours	1400 hours	1600 hours
Multiple sclerosis (MS) patients	16	18.1 (4.9)	18.3 (3.7)	15.9 (5.7)	16.4 (6.1)
Controls	40	18.3 (3.6)	16.3 (4.8)	15.5 (4.9)	14.7 (5.0)
HLA-DR 2+ MS patients	4	14.8 (8.6)	16.0 (6.2)	12.7 (5.9)	9.3 (7.6)
HLA-DR 2– MS patients	12	19.3 (2.6)	19.0 (2.5)	17.0 (5.5)	18.8 (3.0)

Table 2. Circadian parameters from actigraphy (mean and standard deviation). IS, Interdaily stability; IV, intradaily variability; L5, mean of the five least active hours; M10, mean of the ten most active hours

	<i>n</i>	IS	IV	L5	M10
MS patients	16	0.64 (0.13)	0.54 (0.17)	13 (5)	143 (29)
Controls	16	0.58 (0.12)	0.55 (0.16)	21 (12)	148 (19)

Actigraphy

Means and standard deviations of IS, IV, L5 and M10 are presented in Table 2. No significant differences between the control group and the patient group were found, although patients showed a trend for a lower L5 ($P < 0.07$).

Discussion

No clear differences in circadian activity level between MS patients selected for fatigue and sleep disturbances and controls were found. The trend towards a lower average of least active hours (L5) in patients seems to be attributable to the slightly increased L5 in a few students. Thus the actigraph data do not support a loosened coupling of the rest activity cycle to *Zeitgebers*, from this it can be inferred that sleeping and waking occur with a 24-h synchronization comparable to that in healthy controls. Also fragmentation of the sleep wake pattern, in the form of naps or arousals from sleep, did not occur significantly more in MS patients than in healthy controls.

Our data indicate that a lesion in the optic nerve – in our sample 13 patients had lowered visual acuity – is not a sufficient condition for circadian rhythm disturbances. Since we did not find clearly disturbed circadian rhythms, the SCN itself is also not likely to be affected in the majority of MS patients.

Daytime SOL values were altered in subgroups of MS patients. Although only 25% of the patients were HLA-DR 2 positive, HLA-DR 2 positive patients tended to have shorter SOL than controls. However, neither the MSLT nor the interview showed evidence for the narcolepsy-cataplexy syndrome. Both the narcolepsy-cataplexy syndrome and MS are associated with the presence of the HLA-DR 2 antigen [13]. On the other hand, HLA-DR 2 negative MS patients tended to have longer SOL than controls. This might be interpreted in terms of arousal level: although one feels sleepy, the arousal level is too high to actually fall asleep. It might therefore be fruitful to address arousal level disturbances rather than circadian rhythm disturbances in future research on sleep complaints in MS patients. In contrast to the findings of Rumbach et al. [8], we could not demonstrate short SOL values in HLA-B8 positive ($n = 5$) or HLA-B14 positive ($n = 1$) MS patients.

The number of patients with depressive symptoms was higher than could be expected on the basis of the estimated prevalence of 10–20% in the population medically ill [1]. This might be due to our selection of patients

on FSS scores: it has been observed before that symptoms of depression and fatigue overlap in MS patients [9].

In conclusion, our data do not support the hypothesis of a generalized circadian disturbance in MS patients leading to fatigue and sleep disturbances, but rather point to differences in arousal levels.

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