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# Daytime sleepiness is not increased in mild to moderate multiple sclerosis: a pupillographic study

Birgit Frauscher[a], Robert Egg[a], Elisabeth Brandauer[a], Hanno Ulmer[b], Thomas Berger[a], Werner Poewe[a], Birgit Högl[a,*]

[a]*Department of Neurology, Medical University of Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria*
[b]*Department of Statistics, Informatics and Health Economics, Medical University of Innsbruck, Austria*

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**Abstract**

*Background*: Daytime sleepiness has been described in multiple sclerosis (MS); a combination of MS and narcolepsy has also been observed in a few case reports. In this study, we investigated daytime sleepiness in a general sample of MS patients compared to healthy controls with the pupillographic sleepiness test (PST) and the Epworth and Stanford sleepiness scales (ESS, SSS).

*Methods*: A PST was performed in consecutive MS patients and controls. Additionally, a questionnaire including the ESS and the SSS was applied.

*Results*: Sixty-one MS patients (29 men and 32 women, age 34.5±8.3 years, mean disease duration 7.4±6.6 years, expanded disability status scale (EDSS) 1.7±1.2 (mean ± sd)) and 42 age-matched controls (13 men and 29 women, age 36.9±12.9 years) participated in this study. In the MS group, the pupillary unrest index (PUI) was 5.0±2.0, the ESS 7.4±3.5 and the SSS 2.4±1.2, whereas in the control group, the PUI was 4.7±1.8, the ESS 8.4±4.0 and the SSS 2.4±1.2 (mean ± sd). These differences were not significant. No correlation was found between PUI and the ESS or the SSS. Furthermore, no correlation was found between EDSS and sleepiness measured by PUI, ESS and SSS.

*Conclusion*: In a general sample of MS patients with mild to moderate disease, there was no evidence for overall increased daytime sleepiness compared to healthy controls.

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*Keywords:* Multiple sclerosis; Daytime sleepiness; Pupillographic sleepiness test; Epworth sleepiness scale; Stanford sleepiness scale; Pupillary unrest index

## 1. Introduction

Narcoleptic symptoms in multiple sclerosis have been examined in a previous questionnaire study, in which 77% of 70 patients with multiple sclerosis (MS) answered positively to the question 'Do you have a tendency to fall asleep abruptly during the day?' and 56% experienced 'muscular weakness... associated with strong emotions... '. Nevertheless, none of the nine patients of this series who underwent polysomnography fulfilled the criteria of narcolepsy [1]. Several other case reports describe MS patients who suffer from excessive daytime sleepiness and additional symptoms of narcolepsy (cataplexy, sleep onset REM episodes) [2,3]. In a large case history review of a neurologic hospital, the association between narcolepsy and MS was very rare [4].

Increased daytime sleepiness in a wider range of MS patients has not been systematically investigated. The pupillographic sleepiness test (PST) [5–7] is a novel method for objective measurement of daytime sleepiness based on the evaluation of spontaneous pupillary oscillations in darkness, which has been validated in healthy persons [6] and patients with hypersomnia [7].

The aim of this study was to investigate daytime sleepiness in MS patients compared to controls by performing videopupillography and assessing the Epworth (ESS) [8] and Stanford (SSS) sleepiness scales [9].

* Corresponding author. Tel.: +0043 512 504 23890; fax: +0043 512 504 23842.
*E-mail address:* birgit.ho@uibk.ac.at (B. Högl).

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## 2. Methods

### 2.1. Study collective

Sixty-one consecutive MS patients [29 men (47%) and 32 women (53%)] from the Department of Neurology of Innsbruck Medical University (Innsbruck, Austria) were included in this study after informed consent was obtained. Forty-two age-matched healthy volunteers [13 men (31%) and 29 women (69%)] served as controls. Because controls were recruited from persons accompanying the patients, a female preponderance in this group emerged.

Exclusion criteria in this study were intake of any drugs on the day of the examination, consumption of caffeine or alcohol on the day of the examination or disturbed sleep in the two nights before pupillography.

The mean age of the 61 MS patients was $34.5 \pm 8.3$ years with a mean disease duration of $7.4 \pm 6.6$ years and a mean expanded disability status score (EDSS) of $1.7 \pm 1.2$. Fifty MS patients (82%) suffered from a relapsing-remitting disease, seven (11.5%) from the first attack of a laboratory-definitive MS, three (4.9%) from a secondary chronic progressive disease and one (1.6%) from a primary chronic progressive disease. Seven patients with relapsing remitting disease course were presently suffering from a relapse while they were studied. Nineteen patients (30%) were treated with β-interferon (10 received 8 million units of interferon-β-1b subcutaneously every second day, and five received 6 million of interferon-β-1a intermuscularly each week and four 44 μg interferon-β-1a subcutaneously every second day).

In the 42 controls, the mean age was $36.9 \pm 12.9$ years.

### 2.2. Pupillography

Infrared videopupillography was performed in a quiet and dark basement room between 11 a.m. and 1 p.m. or between 3 p.m. and 5 p.m. The patients or controls were placed in a comfortable sitting position using a chin rest. Infrared video images of the pupil were digitized in real time (25 Hz) for a duration of 11 minutes by a frame grabber board and analysed mathematically after artifact elimination. The result of the frequency analysis by fast Fourier Transformation is given in a power value for the frequency range $< 0.8$ Hz as a mean of the entire measurement. Outcome parameters of the infrared videopupillography are the mean pupil diameter (mm) and the pupillary unrest index (PUI) as measures of pupillomotor instability in darkness. The PUI is calculated as an integrated sum of the slow movements of the pupillary margin during 11 minutes. Values are reported in millimeters per minute. The more unstable the position of the pupillary margin, the higher the value of the PUI. A high PUI is characteristic for increased daytime sleepiness. In 349 healthy subjects aged 20–60 years, a pupillographic valdidation study showed a mean PUI of 4.5 mm/min [10].

In patients with a history of optic neuritis, visual evoked potentials (VEPs) were performed prior to pupillography. In patients with unilaterally pathological VEPs, pupillography was performed on the healthy side. Patients with bilaterally pathological VEPs were excluded from the study. To detect an afferent deficit, a swinging flashlight test was performed in all MS patients before pupillography [11] by the same neurologist (R.E.). If the swinging flashlight test was pathological on one side, the healthy eye was examined.

### 2.3. Rating scales

The Epworth Sleepiness Scale (ESS) [8] and the Stanford Sleepiness Scale (SSS) [9] were applied in personal interviews. The ESS is an 8-item questionnaire in which the probability to fall asleep is assessed for eight different everyday situations. Every question is rated from 0 to 3 points. The maximum total score is 24 points. The SSS was applied directly before pupillography and describes the current state of sleepiness. It is rated from 1 (meaning that the subject is fully alert) to 7 (meaning that the subject is excessively sleepy). Disease severity was assessed by the expanded disability status scale (EDSS) [12], and depression by the Beck Depression Inventory (BDI) [13].

### 2.4. Statistics

All statistical analyses were performed using the SPSS statistical analysis program (SPSS 10.0, Chicago, IL, USA). Data are reported as means $\pm$ standard deviation. The variables were tested for normal distribution using the Kolmogorow Smirnov test. Regarding the main variables, ESS and PUI fulfilled the condition of normal distribution, whereas SSS was not normally distributed. To analyse differences between mean values of MS patients and healthy controls we used the Mann–Whitney *U*-test if the variables were not normally distributed and the *t*-test if the variables were normally distributed. In addition, analysis of variance was used to control for gender and age effects in ESS and PUI. Data were analysed for correlation by the Pearson correlation test if normally distributed and the Spearman correlation test if not normally distributed. *P*-values $< 0.05$ were considered statistically significant.

## 3. Results

In MS patients, the mean ESS, SSS and PUI were in the range of normality (ESS $7.4 \pm 3.5$; SSS $2.4 \pm 1.2$; PUI $5.0 \pm 2.0$). Compared to controls (ESS $8.4 \pm 4.0$, SSS $2.4 \pm 1.2$, PUI $4.7 \pm 1.8$), there was no significant difference in daytime sleepiness. An ESS $> 10$ was achieved by 26.2% of the MS vs. 38.1% of the control group. This difference was not significant. There was also no significant difference in the Beck depression score between both groups. The results are shown in Table 1. In addition, age and gender did

Table 1
Results reported as means ± std (range) in MS patients vs. healthy controls

| | MS patients ($n=61$) | Controls ($n=42$) | $p$ value ($t$-test)* | Age and sex adjusted p value (ANOVA) |
|---|---|---|---|---|
| Age | 34.5±8.3 (18–58) | 36.9±12.9 (20–61) | 0.23 | |
| Epworth sleepiness score (ESS) | 7.4±3.5 (0–16) | 8.4±4.0 (0–17) | 0.16 | 0.20 |
| Stanford sleepiness score (SSS) | 2.4±1.2 (1–4) | 2.4±1.2 (1–4) | 0.78 | # |
| Pupillary unrest index (PUI) | 5.0±2.0 (2.0–10.3) | 4.7±1.8 (1.7–10.8) | 0.40 | 0.76 |
| Pupil diameter | 6.3±1.0 (3.4–8.5) | 6.6±0.9 (4.9–8.0) | 0.15 | 0.023 |
| Beck depression score | 5.7±5.7 (0–29) | 4.7±4.7 (0–17) | 0.45 | # |

*$P$-values for SSS and Beck depression score were calculated using Mann–Whitney $U$-test; for all other variables $t$-test was used. #Due to the non-normal distribution, an age and gender adjusted analysis of variance (ANOVA) was not applicable. Univariate comparisons did not show significant effects of age and gender on SSS and Beck depression score.

not show a significant effect on the above-mentioned variables. The PUI of both groups is illustrated in Fig. 1.

No correlations could be found between PUI and ESS (rho = −0.09) (Fig. 2) and PUI and SSS (rho = 0.01) in the general sample. The same was true in the MS group (correlation of PUI and ESS (rho = −0.005), PUI and SSS (rho = 0.05)) and in controls (correlation of PUI and ESS (rho = −0.11), PUI and SSS (rho = −0.10)). Furthermore, in the MS group, no correlation was found between disease severity (EDSS) and sleepiness measured by PUI

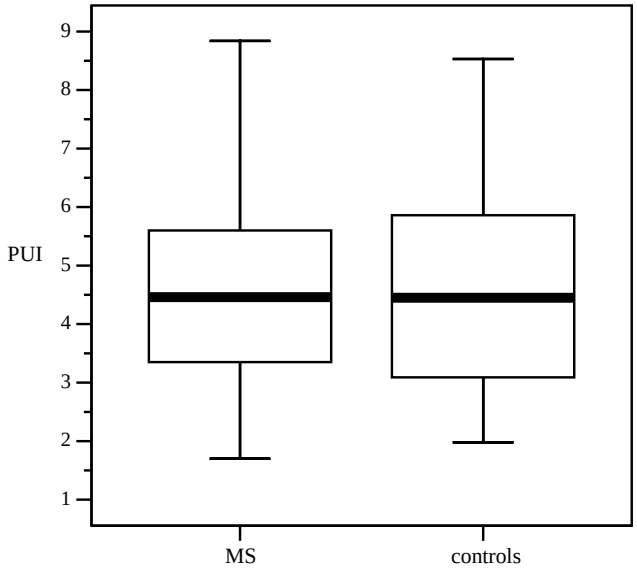


Fig. 1. Box plot illustrating the mean pupillary unrest index (PUI) [mm/min] in the MS vs. the control group.

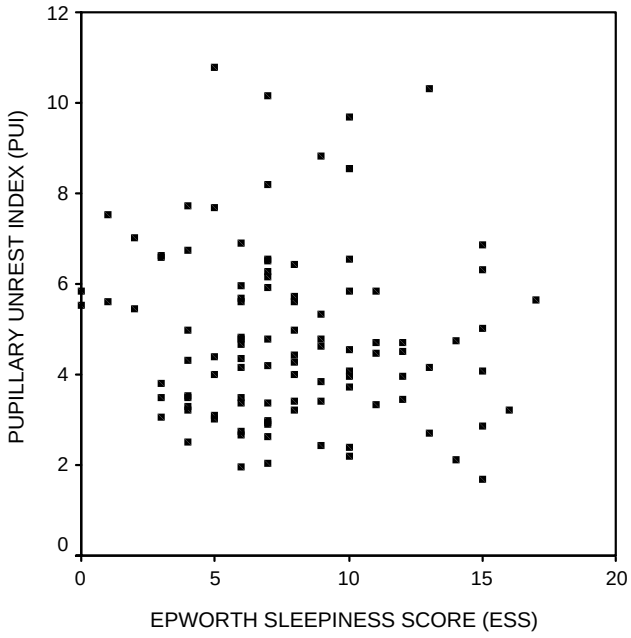


Fig. 2. Scatter diagram illustrating the correlation between the Epworth sleepiness score (ESS) and the pupillary unrest index (PUI) in the 103 subjects of this study. No correlation was found.

(rho = 0.03), ESS (rho = −0.01), and SSS (rho = −0.06). In our data, a positive correlation between ESS and SSS (rho = 0.21; $p<0.05$) was found.

There were also no significant differences between MS patients presently suffering from a relapse vs. patients not suffering from a relapse while they were studied concerning ESS ($p=0.63$), SSS ($p=0.90$) and PUI ($p=0.10$).

In a subgroup analysis of patients receiving β-interferon ($n=19$) vs. patients without β-interferon ($n=42$), β-interferon receiving patients had an ESS of 8.0±4.2, a SSS of 2.4±1.3, a PUI of 5.1 ± 2.3 and a pupil diameter of 6.0±1.1, whereas the patients without interferon had an ESS of 7.1±3.1, a SSS of 2.5±1.2, a PUI of 4.9±1.9 and a pupil diameter of 6.4±1.0 (mean ± std). These differences were not significant.

## 4. Discussion

The few existing studies and case reports on daytime sleepiness [14,15] or daytime sleepiness plus associated cataplexy in MS [2,3] yielded ambiguous results. A small number of single case observations showed hypersomnia [15] or narcoleptic symptoms in MS patients [2,3]. Poirier and co-workers reported daytime sleep attacks in MS [1]. In their study, sleepiness was assessed qualitatively (present/absent), but not using a quantitative scale. One single study used an objective measurement for daytime sleepiness (the multiple sleep latency test (MSLT)) in a small number of 16 MS patients with both prominent fatigue and prominent sleep disturbances [14]. In contrast to the results mentioned

above [1–3,15], increased daytime sleepiness was not found in the MS group.

The foremost result of our study is a lack of difference between MS patients and healthy controls in regard to daytime sleepiness when characterized objectively via pupillographic sleepiness test as well as subjectively using ESS and SSS.

The mean ESS of our patients is in the range of normality. In another study of 50 MS patients with a mean EDSS of $3.8 \pm 1.5$ the ESS was $9.7 \pm 2.9$ [16]. A study of Rammohan and co-workers performed in 72 patients with a mean EDSS level of 3.3 (range 0–6) showed a mean ESS of 9.5 (range 1–20) [17]. The different disability scores may account for these differences.

In a subgroup analysis of patients receiving β-interferon ($n = 19$) vs. patients without β-interferon ($n = 42$), there was no significant difference regarding ESS, SSS, PUI or pupil diameter.

We sought to avoid selection bias by investigating a relatively large group of MS patients with different courses of disease, taken consecutively from an MS outpatient department. No pre-selection concerning sleep disorders was performed.

Few explanatory hypotheses for hypersomnia or narcoleptic symptoms in MS patients exist. There might be a similar genetic susceptibility or an accidental association between both diseases [3]. Another possible cause of narcoleptic symptoms in MS could be brainstem or diencephalic lesions affecting sleep-wake regulating structures [18].

The failure to demonstrate increased daytime sleepiness in MS makes a connection between the inflammatory processes present in MS and overall increased sleepiness unlikely. It is known that increases of systemic mediators of inflammation like TNF-alfa and IL-6 may trigger sleepiness [19]. However, our data indicate that in unselected MS patients the background central nervous system inflammatory activity is not sufficient to cause significant differences in sleepiness compared to normal subjects.

Mean EDSS of the MS patients taking part in our study was $1.7 \pm 1.2$, indicating relatively mild disability status. Therefore, we could have missed a potential correlation between disease severity and sleepiness in more severely affected patients. Similarly, there was no correlation between duration of disease ($7.4 \pm 6.6$ years) and measures of sleepiness.

In the subgroup of patients receiving β-interferon no increased daytime sleepiness was found. This finding is in contrast to the literature reporting somnolence in rabbits receiving interferon [20]. However, this effect was dose-dependent and took place in otherwise healthy animals. It may well be argued that in MS patients treated with β-interferon the beneficial anti-inflammatory effect outweighs a potential sleep-inducing effect of β-interferon as an inflammatory cytokine.

The mean PUI of our healthy subjects is in line with normal values for the PST in healthy men and women given by Wilhelm et al [10]. Age distribution of our subjects (range 20–61 years) was comparable to that study.

A possible drawback of this study is that gender matching was not performed for patients and controls. However, gender does not influence PUI [10]. Moreover, after correction for gender and age, there were no differences in PUI, ESS and SSS. Another possible drawback of our study could be that pupillography was not performed at the same time in all subjects. Nevertheless, no examination was performed between 1 and 3 p.m. during the physiological post-lunch dip in daytime alertness [21].

No correlations were found between ESS and PUI or SSS and PUI. The PST is an objective measure of sleepiness, whereas the ESS and SSS are regarded as subjective measures of sleepiness. There is ongoing controversy regarding the application of subjective and objective measures of daytime sleepiness [22,23]. According to Johns, the ESS is more suitable for measuring daytime sleepiness than the maintenance of wakefulness test (MWT) and the multiple sleep latency test (MSLT) [22], whereas Chervin considers the MSLT as gold standard [23]. This controversy is mirrored by the lack of correlation present in our study, since our data suggest that subjective perception of sleepiness (as measured by ESS and SSS) does not necessarily match the objectively measured PUI.

In further studies, anatomical distribution of MS lesions and sleepiness should be investigated. We cannot rule out that in our series brain structures involved in sleep-wake regulation like the brainstem or diencephalon were spared in a fashion not typical for MS patients in general, since patients had a mild disease stage and magnetic resonance imaging findings were not included in the analysis. A longitudinal study on sleepiness in MS patients with various courses of disease and treatments could help characterize patients more at risk of developing daytime sleepiness.

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