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# FEATURES OF SLEEP DISTURBANCES IN MULTIPLE SCLEROSIS PATIENTS

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## *SUMMARY*

***Background**: Sleep disturbances in multiple sclerosis (MS) have received little research attention despite the potential influence it may have on the impact of the disease. The aim of this study was to evaluate the prevalence of sleep disturbances in a Lithuanian community sample of individuals with the relapsing remitting multiple sclerosis (RRMS) and its relation with depression, anxiety, and health related quality of life (HRQoL).*

***Subjects and methods**: The examined group consisted of 137 RRMS outpatients. The following questionnaires were used: the original socio-demographic questionnaire, Medical Outcomes Study Sleep (MOSS) measure, Hospital Anxiety and Depression Scale (HADS), and HRQoL measure. The relationship of objective sleep disturbances was evaluated with multivariate linear regression, adjusted to socio-demographic and clinical data.*

***Results**: Sleep disturbances were present in 45.3 percent of patients. According to the HADS-D, depressive symptoms were present in 21.9 percent, according to the HADS-A, anxiety symptoms were present in 19.7 percent of study participants. Mean value of Physical and Mental component of HRQoL respectively constituted 40.4 and 44.5. We observed the relationship between sleep disturbances and gender, age, EDSS, prevalence of depression and anxiety, and Physical and Mental component of HRQoL.*

***Conclusions**: Our research was limited by narrow number of study participants and could be accepted only as preliminary study. The study investigated only RRMS patients, therefore investigation of other clinical forms of MS could provide more exhaustive data related with sleep disturbances. The investigation included only outpatients group, therefore research of inpatients could provide more comprehensive data. Sleep disturbances in our study were common in RRMS, and they related with female gender, older age, higher disability status, prevalence of depression and anxiety, and worse HRQoL. The treatable causes of sleep disturbances in RRMS should be identified and cured. However, further research are requested to confirm these findings.*

***Key words:** relapsing remitting multiple sclerosis - sleep disturbances – depression – anxiety - quality of life*

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## INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system that affects approximately 2.5 million people around the world (Courtney et al. 2009, Langer-Gould et al. 2006). Individuals with MS are at risk of increased co-morbidity associated with sleep problems. Studies to date suggest that persons with MS may have significantly more sleep problems than the general population, though prevalence estimates range from 25 percent to 54 percent (Najafi et al. 2013, Veauthier et al. 2013). Also depression and anxiety may accompany MS, with prevalence up to 50 percent (Alschuler et al. 2012, Ó Donnchadha et al. 2013, Sarısoy et al. 2013).

Health-related Quality of life (HRQoL) is impaired in multiple sclerosis subjects. In addition, based on the generic HRQoL measure, and the Short Form (36) Health Survey (SF-36), MS patients have poorer HRQoL than patients with other chronic disorders such as Parkinson's disease, epilepsy, and diabetes mellitus (Łabuz-Roszak et al. 2013). Despite the importance of this construct, HRQoL in MS has generally received little attention (Kes et al. 2013).

Because the link between sleep and mood disorders and HRQoL is not clear in MS, the aim of the study was to evaluate the frequency of sleep disturbances and its relation with depression, anxiety, and HRQoL in Lithuanian RRMS patients. To our knowledge, this is the first study that has examined sleep disturbances in Lithuanian MS patients.

## SUBJECTS AND METHODS

Data were collected through a self-report survey of individuals recruited through the Lithuanian University of Health Sciences (LUHS).

### Subjects

One hundred and ninety seven MS patients were approached for the study; 166 expressed an interest in participating, and 137 met study inclusion criteria and gave their written consent. All patient anonymity was preserved. The study was conducted from January 2011 to January 2012.

Inclusion criteria for MS patients were 1) a diagnosis of RRMS, 2) Expanded Disability Status Scale (EDSS) score (Kurtzke 1983) of 0 to 7.0, 3) no relapse for at least 30 days prior to screening and during the study, and 4) no chronic steroid treatment (>30 days) for 6 months prior to study entry.

Exclusion criteria were 1) age less than 18 years, 2) cognitive or psychiatric conditions that could preclude compliance with informed consent or study procedures, 3) presence of other significant neurological difficulties (other than MS), 4) presence of significant pulmonary, otorhinological disorders, or other medical disorders, and 5) significant abnormalities on screening laboratory investigations.

All study procedures were approved by the Bioethics Board of LUHS. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

The age range of participants (n=137) was between 18 and 74 years (mean age 44.7±12.9 years).

There were 99 women (mean age 42.6±14.6 years) and 38 men (mean age 45.2±12.3 years).

### Methods

Information on sleep disturbances was collected using the Medical Outcomes Study Sleep (MOSS) measure (Hays & Stewart 1992). We assessed a number of other variables that could act as potential confounders in the relationship between sleep disturbances and depression, anxiety and HRQoL.

These included gender, age, place of residence, education, marital status, professional activity, disease duration, Expanded Disability status Scale (EDSS) (Kurtzke 1983), treatment of RRMS, Hospital Anxiety and Depression Scale (Zigmond & Snaith 1983), and SF-36 (Tarlov et al. 1989, Vickrey et al. 1995).

The MOSS measure was designed to evaluate six sleep constructs. The scale has been validated in large populations and presented normative scores available for comparison (Hays et al. 2005, Tarlov et al. 1989). The sleep scale was scored as recommended (Spritzer & Hays 2003) and descriptive statistics were generated to describe demographic and sleep status. Scores on the MOSS subscales ranged from 0 to 100, with the exception of sleep quantity. Higher scores on the MOSS reflected more of the attribute indicated by the subscale name. A single indicator of mild, moderate, or severe sleep problems was calculated from item 12 of the MOSS measure based on recommendations (Manocchia et al. 2001).

Neurological examination was performed and the level of disability established using EDSS (Kurtzke 1983).

The HADS is a self-assessment screening questionnaire for anxiety and depression. Patients are asked to choose one response from the four given per question. The questions related to anxiety, marked ‘A’ (7 questions), and depression, marked ‘D’ (7 questions), are given alternately. The scores (from 0 to 3) for each question for ‘A’ and separately for ‘D’ are added to obtain two results: for anxiety and for depression. A total score of 0 to 7 indicates no abnormality, 8-10 is borderline, and 11 and above suggests anxiety or depression (Zigmond & Snaith 1983).

HRQoL was assessed with the SF-36 Health Survey. It has been used frequently in this patient population, and is considered to be the gold standard among generic measures to assess HRQoL in MS patients [13]. On this measure, individual item responses are combined into scores on eight subscales or health concepts (physical functioning, role participation with physical health problems, bodily pain, general health, vitality, social functioning, role participation with emotional health problems, and mental health). Eight subscale scores are then combined into two component summary measures; the physical component summary (PCS) score and the mental component summary (MCS) score, both ranging from 0 to 100. The PCS and MCS scores are converted into norm-based scores: for the general population, the mean for each summary score is 50 and the standard deviation is 10. Higher scores indicate better HRQoL (Ware et al. 1993, 2008).

### Statistical analyses

Statistical analyses were performed using the program SPSS 15. Descriptive statistics were used to summarize study subjects' social and clinical characteristics data. Data was expressed as mean ± standard deviation (SD) or percentages. Some scores did not fit a normal distribution, therefore non-parametric tests were used. The correlation between results of the tests was analysed using Spearman and Pearson correlation analysis and unpaired *t*-tests, as appropriate in MS subjects. Multiple linear regression was used to model the relationship of sleep disturbances (dependent variables – sleep disturbance present/absent =0/1) with the two component summary scores for depression, anxiety and HRQoL, adjusting for gender, age, residence, education, marital status, professional activity, duration of the disease, EDSS, and treatment of MS in RRMS patients (independent variables). P value of $<0.05$ was taken as significant.

## RESULTS

The social and clinical characteristics of the study subjects are presented in Table 1.

Mean scores on the MOSS measure indicated that women with RRMS had more sleep disturbances and overall sleep problems than men with RRMS (all comparisons $p<0.01$). Women also ranked sleep adequacy worse ($p<0.001$) despite reporting less snoring ($p<0.01$) and more hours of sleep per night than men ($p>0.05$). Mean scores of respiratory problems/shortness of breath in women was significantly higher than compared to men ($p<0.01$). Daytime somnolence was also higher in women with RRMS than in men ($p<0.05$). When using the MOSS single indicator of sleep problems, as defined by Manocchia (Manocchia et al. 2001) 8.1 percent of the RRMS population had mild, 15.3 percent moderate, and 21.9 percent severe sleep problems (Table 2).

**Table 1.** Characteristics of RRMS study subjects

| Variable | Mean±SD, range, or N (%) |
|---|---|
| Gender, female | 99 (72.3%) |
| Age, years | 44.7±12.9, 18–74 |
| Residence, urban | 77 (56.2%) |
| Education (>12 years) | 67 (48.9%) |
| Marital status (living with a partner) | 82 (59.9%) |
| Professional activity | 35 (25.5) |
| Disease duration, years | 12.6±8.7, 0.5–33.5 |
| EDSS | 3.8±2.1, 0.5–6.5 |
| Immunomodulating treatment | 108 (78.8%) |
| Sleep problems | 62 (45.3%) |
| HADS | |
| Depression | 30 (21.9%) |
| Anxiety | 27 (19.7%) |
| Quality of life | |
| Mental component score | 44.5±14.1 (18.5-67.4) |
| Physical component score | 40.4±12.3 (17.7-67.3) |

SD = standard deviation; N = number of participants;
EDSS = Expanded Disability Status Scale;
HADS = Hospital Anxiety and Depression Scale

Responses to the sleep disorders indicated that both women and men with RRMS had significantly higher levels of sleep disorders in the age group of >45 years ($p<0.001$). Regarding gender differences, women with RRMS under the age of 45 reported higher levels of insomnia symptoms, though it was not significant.

According to HADS, depressive symptoms were present in 30 of RRMS patients (21.9 percent). Mean HADS-D score was 6.3±4.1 points. Anxiety was present in 27 RRMS patients (19.7 percent). Mean HADS-A result was 7.7±3.5 points.

Mental component scores were similar in men and women (44.88±13.2, and 44.21±12.85, unpaired t-test $p>0.05$). However, physical component scores in the male group were higher compared to women (45.34±14.25, and 36.27±12.33, unpaired t-test $p<0.05$). The eight SF-36 subscale scores and two SF-36 summary scores for RRMS subjects are presented in Table 3.

Multiple linear regression was used to model the relationship of sleep disturbances (dependent variable – sleep disturbances present/absent =0/1) with the two component summary scores for depression, anxiety and HRQoL, adjusting for gender, age, residence, education, marital status, professional activity, duration of the disease, EDSS and treatment of MS in RRMS patients (independent variables). In our study, sleep disturbances were associated with gender, age, EDSS, depression, anxiety, Mental and Physical component scores of HRQoL in RRMS patients (Table 4).

However, disturbances were not associated with residence, education, marital status, professional activities, disease duration, and immunomodulating treatment.

**Table 2.** Comparison of MOSS scale domain scores between females and males

| Characteristics | RRMS women (N = 99) Mean (SD) | RRMS men (N = 38) Mean (SD) | p |
|---|---|---|---|
| Sleep disturbance (initiation and maintenance) | 38.22 (25.02) | 31.33 (21.52) | <0.01 |
| Snoring | 29.51 (33.02) | 36.26 (31.08) | <0.01 |
| Respiratory problems/Shortness of breath | 17.39 (25.21) | 11.57 (21.00) | <0.01 |
| Sleep quantity (hours/night) | 7.12 (1.48) | 6.91 (1.68) | >0.05 |
| Sleep adequacy | 45.34 (25.36) | 56.51 (25.36) | <0.001 |
| Daytime somnolence | 40.21 (24.79) | 36.42 (23.75) | <0.05 |
| Sleep problems' index | 41.31 (22.13) | 32.46 (15.93) | <0.01 |

MOSS = Medical Outcomes Study Sleep measure; RRMS = relapsing remitting multiple sclerosis; N = number of participants;
SD = standard deviation

**Table 3.** Norm-based scores of the SF-36 for 137 RRMS study subjects

| SF-36 subscale or summary score | Mean±SD, range | |
|---|---|---|
| Physical functioning | 36.4±12.8 | 14.5-57.3 |
| Role physical | 37.0±12.5 | 18.3-56.5 |
| Bodily pain | 43.3±9.5 | 23.8-63.2 |
| General health perception | 45.4±12.3 | 23.7-65.1 |
| Vitality | 44.4±11.3 | 18.5-72.5 |
| Social functioning | 36.6±13.8 | 15.9-61.2 |
| Role emotional | 35.8±13.7 | 8.1-56.7 |
| Mental health | 43.2±10.4 | 17.0-66.2 |
| Physical component score | 40.4±12.3 | 17.7-67.3 |
| Mental component score | 44.5±14.1 | 18.5-67.4 |

SF-36 = Short Form (36) Health Survey; SD = standard deviation

**Table 4.** Relation between sleep disturbances and demographic and clinical data of RRMS subjects

| Independent variables | | Exp. B | 95% CI for Exp. B | |
|---|---|---|---|---|
| | | | Minimal | Maximal |
| Gender | Female | 2.232 | 1.112 | 4.287 |
| | Male | 1.00 | | |
| Age | >45 years | 3.256 | 1.372 | 5.962 |
| | ≤45 years | 1.00 | | |
| EDSS | ≥4 scores | 3.178 | 1.248 | 5.887 |
| | <4 scores | 1.00 | | |
| HADS-D | ≥11 scores | 2.965 | 1.223 | 5.769 |
| | <11 scores | 1.00 | | |
| HADS-A | ≥11 scores | 3.362 | 1.133 | 5.885 |
| | <11 scores | 1.00 | | |
| Mentalcomponentscore | <50 scores | 2.881 | 1.227 | 5.557 |
| | ≥50 scores | 1.00 | | |
| Physicalcomponentscore | <50 scores | 3.676 | 1.363 | 6.221 |
| | ≥50 scores | 1.00 | | |
| Constant | | 0.000 | | |

Dependent variable: sleep disturbances present/absent (0/1); Exp. B = Expired B; CI = Confidence Interval;
HADS-D = Hospital Anxiety and Depression Scale - Depression; HADS-A = Hospital Anxiety and Depression Scale - Anxiety

## DISCUSSION

According to resources, up to 55 percent of MS patients could suffer from sleep disturbances. The results of our study have confirmed this. We observed sleep problems among 45.3 percent of the examined RRMS patients. This is significantly higher than the prevalence estimates of sleep problems in the MOSS population (33.1 percent) of chronically ill patients (Manocchia et al. 2001) and similar to the estimate published by Tachibana in a small MS population (Tachibana et al. 1994). Data from Stanton similarly found in 60 individuals with MS that 53 percent had middle insomnia (night wakening) and 58 percent had terminal insomnia (early awakening) (Stanton et al. 2006). Taken together, these studies indicate that over 50 percent of individuals with MS experience significant sleep problems.

As reported by other authors, and not mentioned in our study, the frequency of sleep disturbance was independent of sex and age. Our study indicates that women with RRMS appear to be at a higher risk of sleep disturbance than men, and older participants significantly more often claim the prevalence of sleep problems. Although some researchers observed a correlation between sleep disturbances and EDSS or disease duration, we could only confirm it partially: we found a strong correlation between sleep disturbances and EDSS; however, data relating to sleep problems and RRMS duration was statistically insignificant.

Similarly to other authors, we found that immunomodulating therapy was not associated with sleep problems. Some researchers have reported that such therapy could induce or intensify sleep disorders (Mendozzi et al. 2010), but our study did not confirm this. We found no association between therapy and the results of most questionnaires. We only observed a relationship between immunomodulating therapy and HADS-D results: people treated with immunomodulators had a significantly lower score than untreated individuals. Other recent studies also suggest that immunomodulating therapy neither causes nor exacerbates depression among MS patients (Borras et al. 1999, Walther & Hohlfeld 1999), but there are reports about an association between such therapy and mood disorders (Mohr et al. 1997, Neilly et al. 1996).

Some authors provide data about correlations between sleep disturbances and professional activities. The results of Labuz-Roszak (Labuz-Roszak et al. 2012) suggested that a professionally active lifestyle could protect from insomnia, anxiety and depression and improve HRQoL. Consequently, MS patients who do not work are at greater risk of developing either sleep and mood disorders or lower HRQoL. However our study could not confirm these results.

A limitation of our study is that it is cross-sectional. For this reason, causation cannot be determined. We cannot determine if disturbed sleep will impede mental health or if RRMS patients with poor mental health status will have more sleep difficulties because of their health status. The relationship may be bidirectional as noted in studies in the general population (Lai et al. 2013, Milette et al. 2013, Maaskant et al. 2013, Girschik et al. 2013).

Suffering from sleep problems was associated with an increased risk of depression, anxiety and lower HRQoL. The results of our study also confirmed this. The quality of sleep is especially important to people with MS, because, recent studies suggest that good sleep is necessary for proper brain function and plasticity. According to some authors, slow wave sleep is important for downscaling the synaptic strength of new brain circuits being a consequence of the plastic process to energetically sustainable baseline level, beneficial for learning and memory (Bamer et al. 2010, Tononi & Cirelli 2006).

Sleep has been linked to other co-morbidities in MS such as pain, depression, and fatigue (Stanton et al. 2006, Fleming & Pollak 2005), and some evidence suggests that sleep is especially important in MS to maximize brain plasticity, a particularly important process in individuals with a neurodegenerative disease (Kraft & Brown 2007). The relations between sleep disturbances in MS patients and depression and anxiety are extensively analysed. However, a unified approach is not reached. Our study clearly confirmed that sleep disturbances in RRMS patients are strongly related with the prevalence of anxiety and depression. However, more exhaustive trials are requested to identify relations between mood and sleep disorders in RRMS patients (Labuz-Roszak et al. 2013, Feinstein 2006, Cowan 2007).

The relationship between sleep complaints and poorer mental health, such as depressed mood, is also consistent with findings from epidemiological studies of sleep in the general population (Lee et al. 2013, Schubert & Coles 2013, Kudlow et al. 2013), and in patients with other medical conditions (e.g. arthritis, chronic pain) (Roehrs et al. 2013, Finan et al. 2013, Engstrøm et al. 2013).

Epidemiological and electroencephalographic (EEG) sleep studies have shown a role for sleep disturbances in the pathogenesis of depression (Araghi et al. 2013, Lee et al. 2013, Fairholme et al. 2013). However, there is longitudinal data to suggest that an increase in depressive symptoms worsens sleep quality (Shahsavand-Ananloo et al. 2013). While the mechanisms involved in MS patients remain unexplored, studies in depressed patients show that abnormalities in the hypothalamic-pituitary–adrenal (HPA) axis are associated with nighttime awakenings, and light slow wave sleep (Tomfohr et al. 2012).

Our study reports that sleep disturbances are predictors of HRQoL in RRMS, as captured by the widely used SF-36 questionnaire. HRQoL is an important measure of health status in RRMS patients, especially because MS patients' symptoms can affect so many aspects of daily living (Klevan et al. 2013).

Our patients had an important reduction in HRQoL of approximately one standard deviation below general population norms for both summary measures. As a comparison, our mean MCS score (44.5) for MS patients was lower than that previously reported in treated rheumatoid arthritis patients (50.4) and dialysis patients (46.6), and our mean PCS score (40.4) was similar or somewhat higher than that previously reported for rheumatoid arthritis and dialysis patients (37.4 and 33.1) (Kosinski et al. 2002, Fukuhara et al. 2003).

Disturbed sleep appears to have a negative impact not only on mental but on physical summary scores for HRQoL in RRMS as well. From self-reported questionnaire data, poor sleep quality is common in RRMS, and is associated with lower HRQoL (Lobentanz et al. 2004, Merlino 2009). Specifically, lower SF-36 physical and mental summary scores (indicating poorer HRQoL) are reported in patients with subjective poor sleep quality (Tachibana et al. 1994).

Given the high prevalence and potential effect of sleep on overall disease impact, future studies of sleep disturbance in MS and development of successful interventions in this population are of great need. It may be true that sleep improving interventions will also have an impact on depressive, anxiety symptoms and psychosocial functioning, as well as HRQoL. Clinicians should routinely ask about sleep and include treatment of sleep disorders in a comprehensive care plan for MS patients.

Our research was limited by narrow number of study participants and could be accepted only as preliminary study. The study investigated only RRMS patients, therefore investigation of other clinical forms of MS could provide more exhaustive data related with sleep disturbances. The investigation included only outpatients group, therefore research of inpatients could provide more comprehensive data.

## CONCLUSIONS

Our study demonstrated that sleep disturbances are related with female gender, older age, higher EDSS scores, prevalence of depression and anxiety, as well as with worse mental and physical health status (assessed with the mental and physical domain of the SF-36) in RRMS. These findings suggest that it would be useful to include sleep evaluation and treatment of sleep disturbances in the treatment of RRMS patients. It is possible that with adequate treatment of sleep disorders, mental and physical HRQoL, and other clinical symptoms of RRMS, such as depression and anxiety, may improve. Further work in this area is in progress.

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