ORIGINAL ARTICLE

SLEEP DISORDERS IN RELAPSING-REMITTING MULTIPLE SCLEROSIS PATIENTS

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Tetiana A. Odintsova, Oksana O. Kopchak
KYIV MEDICAL UNIVERSITY, KYIV, UKRAINE

ABSTRACT

The aim: Our study aimed at evaluating the relationships between sleep disorders (SD), cognitive impairment (CI), anxiety and depression in patients with relapsing-remitting multiple sclerosis (RRMS).

Materials and methods: One hundred and five patients with RRMS (80 females and 25 males) aged from 22 to 67 years (mean age: 41,8±10,7; EDSS:3,5±1,6; disease duration (DD): 10,3±8,5 years) were enrolled into the study. All participants completed questionnaires on sleep (the Pittsburgh Sleep Quality Index /PSQI), cognitive functions (The Montreal Cognitive Assessment /MoCA), anxiety (Hamilton Anxiety Rating Scale /HAM-A), depression (Beck Depression Inventory/ BDI).

Results: According to PSQI score the patients were divided into two groups: with (n=42) and without SD (n=63). The patients with SD were older (45,36±1,66 vs 39,41±1,27, p=0.005), had higher EDSS score (3,98±0,26 vs 3,14±0,19, p=0,008), BDI (13,79±1,14 vs 8,96±0,86, p=0,0009) and HAM-A (24,52±1,42 vs 16,56±0,99, p<0,0001) scales compared with patients without SD. The frequency of anxiety (p=0,0034) and depression (p=0,038) was significantly higher in RRMS patients with compared to those without SD. No significant difference was found in gender, DD and MoCA score. In patients with SD significant negative correlation between MoCA and BDI score (r = -0,42, p<0,005) was found. In the group of patients without SD significant negative correlation between MoCA and EDSS (r = -0,27, p=0,03), MoCA and BDI (r = -0,26, p=0,043),) MoCA and HAM-A (r = -0,25, p=0,041) score was detected.

Conclusions: Insomnia type SD in RRMS patients were associated with older age, higher EDSS score and presence of anxiety and depression.

KEY WORDS: Multiple sclerosis, sleep disorders, cognitive impairment, anxiety, depression

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INTRODUCTION

Multiple sclerosis (MS) is a chronic progressive inflammatory autoimmune neurodegenerative disease of central nervous system (CNS) and it is considered to be the most prevalent neurological disability of young adults, often leads to severe physical or cognitive incapacitation [1]. The severity of disability in MS patients is increased not only by motor disorders and other neurological deficit, but by the presence of cognitive impairment (CI), psycho-emotional disorders, like anxiety and/or depression, and sleep disorders (SD) [2]. The frequency of SD in the MS population ranges from 47 to 62%, with a higher prevalence in women [3]. SD in MS can be either secondary due to numerous psychological or physical symptoms or primary [4]. In either of the two cases, a bidirectional relationship exists between MS and SD. Many factors like sex hormones, genetic mechanisms, psychosocial factors, certain physical factors that disrupt sleep, such as pain or bladder dysfunction may contribute to SD differences in female and male patients. SD in women are predominantly associated with depression and anxiety, whereas in men those are associated with pain [5]. MS patients prevalently suffer from insomnia, which is characterized by difficulties of falling asleep, maintaining sleep and early awakenings, inability to sleep as much as desired, which are predominantly accompanied by asthenia, excessive daytime sleepiness and/or disruption of daily activities [6, 7]. In order to establish the diagnosis of SD the foresaid symptoms must be present at least 3 nights per week for minimum three consecutive months [8].

The disease-modifying drugs or symptomatic therapies in MS also contribute to the development of SD. It was reported that sleep disturbance is a common complaint of patients with RR-MS receiving high doses of intravenous methylprednisolone [9]. Intake of IFN-β by RR-MS patients affects sleep continually, can increase fatigue, depression and negatively influences on the quality of life in general. Since this drug causes restlessness during sleep and difficult awakenings, both at initiation stage and after a chronic use, proving that these effects are not adaptive. However, the following side effect is reportedly cancelled by symptomatic therapies [10, 11], which can improve modulation of cytokines level and/or restore circadian secretion of melatonin and its suppressed metabolism [12]. Administration of glatiramer acetate leads to frequent awakenings during the night and daytime drowsiness due to increasing of anxiety and irritability, the typical side effects of the drug [13]. On the contrary, treatment with natalizumab or cannabinoids generally improves quality of sleep [14, 15]. Penner I.K. et al. demonstrated that natalizumab

administration had positive influence on fatigue, daytime sleepiness, cognitive function, depression and a quality of life in general from baseline to a year later [14]. Meuth S.G. et al. state that cannabis-based extracts improve general sleep disturbances as well as spasticity- and pain-related SD, but sudden discontinuation of such therapy caused interrupted sleep in 16% patients [15].

The relationships between sleep quality and clinical manifestations of MS is contradicting and not yet fully understood.

Our study aimed at evaluating the relationships between sleep disorders, cognitive impairment, anxiety and depression in patients with RRMS.

THE AIM

Our study aimed at evaluating the relationships between sleep disorders (SD), cognitive impairment (CI), anxiety and depression in patients with relapsing-remitting multiple sclerosis (RRMS).

MATERIALS AND METHODS

The current study consisted of one hundred and five patients with RRMS (80 females and 25 males) aged from 22 to 67 years (mean age 41,8±10,7). The maximum EDSS score was 6,0 with the mean score 3,5±1,6. Among the participants the minimum disease duration (DD) was one year and the maximum was forty-seven years (mean DD 10,3±8,5 years). All patients were diagnosed RRMS according to McDonald's Criteria 2010 [16]. A medical history was obtained from all the participants. The examination consisted of a standard clinical evaluation, neurological examination, the application of neuropsychological questionnaires, laboratory tests (complete blood count, biochemical parameters, TSH), MRI of brain and spinal cord. All the participants were screened for education. Education was divided into two categories: higher secondary school and higher vocational training for 18+ years/ university. To evaluate level of disability in MS patients Kurtzke's Expanded Disability Status Scale (EDSS) was applied. Mild disability equals 1-3,5 points, moderate – 4-6 points and 6,5-8 stand for severe disability [17]. The instrument applied to screen for SD presence and evaluate the quality of sleep was the Pittsburgh Sleep Quality Index (PSQI). PSQI scale consists of 19 items and 7 components: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, daytime dysfunction. According the test results 0-15 points mean absence of SD, 16-25 points – mild SD, 26-35 points – moderate SD and 36-45 points – severe SD [18]. The Montreal Cognitive Assessment (MoCA) was applied for assessment of cognitive functions. MoCA is a screening instrument composed of eight sections including visuospatial/executive functions, naming, memory, attention/processing speed, language, abstraction, delayed recall (short-term memory), orientation and education. The scale score is interpreted as: 30-26 points – no CI; 25-18 points – mild CI; <18 points – severe CI [19]. To find the presence and measure the severity of perceived anxiety symptoms we used Hamilton Anxiety Rating Scale (HAM-A). The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Each item is scored on a scale from 0 (not present) to 4 (severe), with a total score range of 0–56, where 0-13- absence of anxiety, 14-17 indicates mild severity, 18–24 – moderate severity and ≥ 25 – severe anxiety [20]. Presence of depression was assessed by the means of Beck Depression Inventory (BDI). BDI is a 21-item self-report measure that taps major depression symptoms according to diagnostic criteria listed in the Diagnostic and Statistical Manual for Mental Disorders. Each answer is scored on a scale value from 0 to 3. Mean score 0–9 stands for absence of depression, 10–18 indicates mild depression, 19–29 – moderate depression and 30–63 – severe depression [21].

Recruitment criteria were as follows: patients older than 18 years with RRMS in stage of remission, EDSS less than 6,5 points, with SD in form of insomnia, without intake of sleep-modifying medications, absence of nocturnal pelvic disorders, absence of infectious diseases.

Participants were excluded if they were younger than 18, had progressive forms of MS, stage of exacerbation of RRMS or severe disability (EDSS score 6,5 – 8 points), severe depression, pelvic disorders, pregnancy, as well as patients treated with corticosteroids and INF-β, which could alter the study's parameters.

All the subjects provided written informed consent and the study was approved by the Institutional Ethics Committee.

Student's t-test (t) was applied for evaluating credibility between mean quantitative positions of two samples. Proportions were compared using $\chi 2$. The Pearson's correlation coefficient (r) between different indicators was analyzed. A value of $p<0,05$ was considered statistically significant.

RESULTS

The main complaints of the patients with RRMS were the following: inability to fall asleep, midnight awakenings, sense of psycho-emotional tension, inability to relax, inability "to turn off their head", presence of disturbing thoughts, anxiety, intermittent sleep, morning and daytime weakness, mood swings, increased irritability, fatigue, lack of energy during usual daily activities, memory decrease, vocabulary difficulties, inability to concentrate, decreased occupational performance. Neurological examination revealed brain stem disorders, pyramidal signs, pathological reflexes, increased muscle tone, impaired coordination (intention tremor, ataxia, missing the mark), sensory disorders (in particular, Lhermitte's sign).

According to the results of the brain MRI, the majority of the patients had multifocal lesions in the white matter, periventricular, cortical, juxtacortical, infratentorial areas, as well as lesions in the cervical segments of spinal cord.

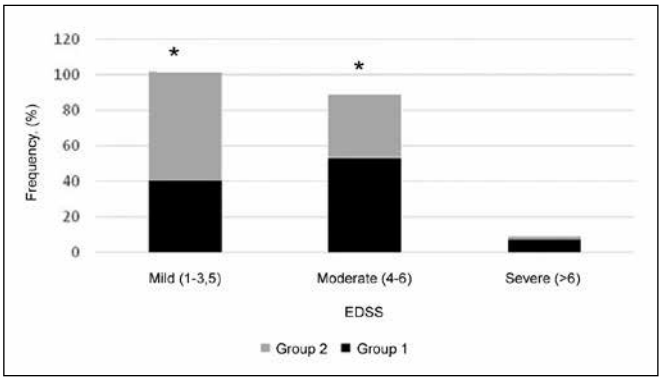

Fig.1. The frequency of different disability rate (according to EDSS) in the patients with RRMS of both groups
*-p= 0,005

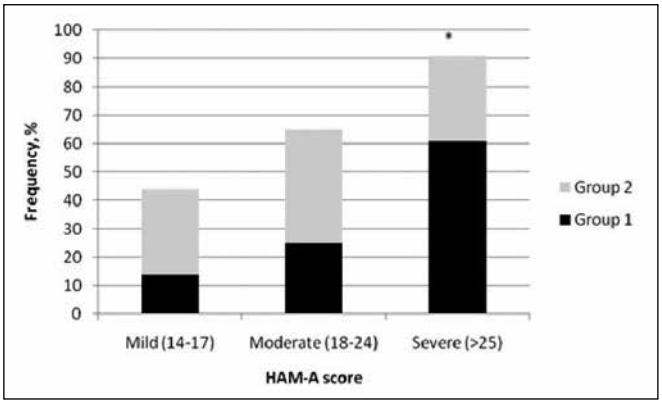

Fig.2. The frequency of various anxiety severity (according to HAM-A score) in the patients with RRMS of both groups
*-p<0,0001

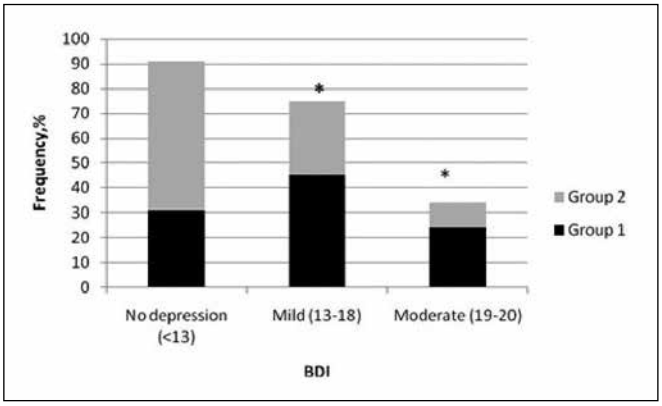

Fig. 3. The frequency of the various depression severity (according to BDI score) in the patients with MS of both groups
*-p=0,0001

According to PSQI the participants were divided into two groups: group 1 – with SD (n=42); group 2 – without SD (n=63). Analyzing the results of PSQI the most frequent indicators of SD were difficulties of falling asleep (25/60% patients), problems with maintaining sleep (23/55%), early awakenings (12/28%), restlessness and/or seizures of lower extremities (17/40%), daytime drowsiness (11/26%), lower daytime productivity (22/52%). None of the patients experienced nocturnal urinary problems, sleep-related breathing disorders (sleep apnea syndrome) or episodes of disorientation during the night. Based on this questionnaire, three levels of SD were observed: mild, moderate and severe. Mild SD were present in 18 (43%) patients, moderate – in 14 (33%) and severe SD – in 10 (24%) participants. 27 (64%) patients of the group 1 were older than 40 years, whereas in the group 2 this number was 31 (48%), so in proportion there is a tendency of developing SD coherent with aging, demonstrating a significant difference between groups according to the age of patients (p=0,005). Thus, the mean age of the group 1 (45,36±1,66) was substantially lower in comparison to the group 2 data (39,41±1,27). The group 1 consisted of 35 (83%) females, and 45 (71%) females were included in the group 2, which demonstrates no valuable difference.

We also considered the influence of higher education availability on presence of SD in MS patients. There were 17 (40%) patients with higher education in the group 1, as opposed to 39 (61%) people in the group 2. Thus, the frequency of patients with higher education was significantly lower in SD group of patients as comparing to those without SD (χ^2=8,82; p=0,003). The education level showed significant difference in both groups concerning its possible influence on sleep quality.

The group 1 demonstrated the following EDSS results: 17 (40%) patients had mild disability, 22 (53%) – moderate and 3 (7%) had severe level of disability; meanwhile 39 (62%) patients had mild disability, 23 (36%) – moderate and only one (2%) had severe disability in the group 2 (Fig1). The number of participants with mild level of disability was significantly lower meanwhile the moderate level of disability was much greater in the first group of patients with MS in comparison with patients of the second group (χ^2=10,7; p=0,005). The mean EDSS score was substantially higher (p=0,008) in SD group (3,98±0,26) comparing to those without SD (3,14±0,19).

The duration of disease did not differ significantly in both groups (11,62±1,35 in the group 1 and 9,44±1,03 in the group 2), hence its impact on development and severity of SD was irrelevant (p>0,05).

According to the MoCA score, 26 (62%) patients with SD had CI of different severity; meanwhile this indicator was 40 (63%) in patients without SD. The data of our study does not confirm the correlation between of SD and CI parameters (r=-0,25, p=0,10). No substantial difference was found in both groups since results were almost identical according to MoCA score (p=0,95).

In accordance with extended expertise, among the patients of the first group no CI was found in 16 (38%) individuals, 23 (55%) had mild and 3 (7%) had severe CI. Among those participants with mild CI the lowest parameters were found in such domains: visuospatial/executive functions (23/100%), memory (14/61%) and abstraction (12/52%); language (8/35%) and attention (7/30%) had relatively higher rates. All the patients with severe CI had poor performance in all cognitive domains with the lowest rate in memory and language.

The HAM-A scale results revealed the presence of anxiety in the patients with RRMS. There were 36 (86%) patients

suffering from anxiety in the group 1, among which 5 (14%) had mild, 9 (25%) – moderate and 22 (61%) had severe anxiety. Whereas, in the second group 37 (59%) had anxiety disorder, including 11 (30%) with mild, 15 (40%) – with moderate and 11 (30%) with severe level ($p<0,0001$) (Fig.2). Hence, the mean HAM-A score was 24,52±1,42 in the first group and 16,56±0,99 in the second ($p<0,0001$). Substantial positive correlation was found between HAM-A score and PSQI score ($r=0,47$, $p=0,003$), which indicates that presence of SD in patients with MS is strongly associated with anxiety level.

The assessment of BDI score revealed that in the group with SD 13 (31%) patients had no depression, 19 (45%) – mild depression and 10 (24%) – moderate one, severe level was not detected; whilst in the group without SD 38 (60%) patients had no signs of depression, 19 (30%) – mild, 6 (10%) – moderate, severe depression was not found as well (Fig. 3). There was significant difference concerning the frequency of depression's severity between the two groups of patients with MS ($p=0,0001$). The mean BDI score was 13,79±1,14 in the first group and 8,96±0,86 in the second ($p=0,0009$). Significant positive correlation between BDI and PSQI score was found ($r=0,37$, $p=0,047$), which indicates positive relationship between depression and SD, as well as the possible contribution of depression into the development of SD.

In both groups of patients with MS substantial negative correlation between MoCA and BDI score was detected (in the first group $r = -0,42$, $p<0,005$; in the second group $r=-0,26$, $p=0,043$ correspondently).

In the second group of patients the evidence of negative influence of disability, depression and anxiety on cognitive performance was found. According to the results of MoCA test, 23 (36%) participants (subgroup I) had unimpaired cognition, 30 (48%) (subgroup II) had mild CI and 10 (16%) (subgroup III) had severe CI. In accordance with EDSS score, 17 patients had mild disability and 6 had moderate in the subgroup I; 17 had mild, 13 – moderate disability in the subgroup II; in the subgroup III mild disability was in 6 patients and moderate – in 4 individuals. Thus, noteworthy correlation between MoCa and EDSS score was found ($r = -0,27$, $p=0,03$). As for HAM-A score, among patients without SD and CI (subgroup I) 11 participants had no anxiety, 3 patients – mild anxiety, 5 had moderate and 4 – severe; in the subgroup II 13 patients were without anxiety, 6 – with mild anxiety, 7 – with moderate and 4 had severe anxiety; in the subgroup III 4 patients had mild anxiety, 3 – moderate and 3 had severe level of anxiety. Noteworthy negative correlation between MoCA and HAM-A score was found in the patients without SD ($r = -0,25$, $p=0,041$).

DISCUSSION

Insomnia was prevalent in RRMS patients and associated with older age, that is congruent with the previous study [22]. Our findings show significant difference of education level concerning its possible influence on sleep quality in patients with RRMS. This result is consistent with data of Alhazzani A.A. et al. that the level of education is considered as a risk factor for development of insomnia on a condition of absence of depression [23]. We found no valuable difference between both groups concerning gender, that does not match with previously reported results that SD in MS patients are prevalently associated with female gender [9].

We failed to find any significant association between insomnia and duration of the disease in RRMS patients, that corresponds to data of other investigators *[22]*. At the same time in our study patients with MS and SD had higher score on EDSS, that does not concur with findings of Čarnická Z. et al [22].

In both groups of RRMS patients no significant difference was found according to MoCA score, unlike the results of other studies reporting the influence of sleep quality on cognitive function [24, 25]. Concurrent, all the RRMS patients with SD in the presence severe CI had poor performance in all cognitive domains with the lowest rate in memory and language. In patients with MS, in general, memory impairment was present in 40-60% cases already on early stages of the disease [26], information processing speed disorder was common in 12-25% of patients, executive functions were impaired in 19 % of MS [26, 27]. Thus, the more frequently affected domains were memory, attention, information processing speed and executive functions [28, 29]. Significant association between sleep disturbance and cognitive dysfunction was found in some studies [30-32]. In a systematic review by Hughes, A.J. et al., in particular, memory, executive functions were mostly affected in patients with SD [30]. Sleep disturbance was considered the predictor of future cognitive decline in MS; results of systemic review highlight the need to integrate sleep assessment into routine MS care. Interventions aimed treating sleep disturbance may offer promise for improving cognitive dysfunction in MS [30]. In patients with MS insomnia can additionally impact their vigilance, cognition, motivation and attention, greater amounts of sleep loss correlate with daytime sleepiness, poor cognitive performance and expressed fatigue [8, 33].

In our study presence of SD in RRMS patients is strongly associated with anxiety level. These findings are consistent with data provided by other investigators, which consider anxiety and stress as possible contributors to the development or progression of SD immensely due to brain mediators' malfunction [33]. We revealed positive correlation between depression and insomnia, that matches data of Bahmani D.S. et al., that emphasize the crucial effect of depression on the quality of sleep, and vice versa the deterioration of depressive disorders with presence of insomnia [32].

In both groups of RRMS patients substantial negative correlation between MoCA and BDI score was found. This finding is in accordance with previous studies, that state the influence of depression on the ability to learn, process information, impairs memory and practical skills. It predominantly occurs in case of location of lesions in temporal lobe, as the hippocampus and the amygdala, the structures

responsible for converting a short term-memory into a long term-memory, learning new skills and emotional reactions, can be damaged at the same time [34, 35]. Nocity V. et al. in their study revealed that poor sleep quality is associated with fatigue, higher scores of BDI and Self-Administered Anxiety Scale in MS patients [7].

All the mentioned above associations between SD, CI, anxiety and depression in MS patients can be explained by the fact, that sleep disruption affects CNS on the cellular level. Oligodendrocytes (OL) are the only cells of CNS with a function of myelination; hence any external or internal influence on those has crucial consequences. Maturation of OL depends on circadian cycle, disruption of which can be caused by SD or created artificially (common "disorder" in shift work). Neurodegenerative diseases associated with a disrupted sleep/wake cycle contribute to the volume of the white matter loss [25, 36, 38]. Philips T. and Rothstein J. D. reported that decreasing of sleep quality and duration has a negative influence on myelination due to OLs' dysfunction (disruption of myelin sheath and prevention of lactate transmission to axons) [24, 25].

In patients with RRMS without SD the evidence of negative influence of disability, depression and anxiety on cognitive performance was found. Our results are congruent with previous studies, according to which disability has crucial role in the development and deteriorating of CI in MS patients, but is often overlooked by physicians due to the vivid picture of neurological deficit [38]. Other authors connect MS with anxiety, since anxiety can be present independent of type, disease duration, level of disability or age and it deteriorates cognitive function and quality of sleep [39, 40].

The main strengths of our study are strict inclusion criteria and its use of a design adapted to evaluate sleep and psycho-emotional disorders, as well as the relationships between them, applying questionnaires. Although, several limitations need to be discussed. First, this study's cohort was only composed of RR-MS patients. Relapsing-remitting form is the most widespread form of MS. Therefore, our results cannot be generalized to SD prevalence in progressive forms of MS. Secondly, we had patients only with insomnia, restless leg syndrome and sleep apnea syndrome were absent in the study participants according to PSQI. Thirdly, SD were revealed only by applying the PSQI, not by other sleep quality questionnaires (Epworth Sleepiness Scale).

CONCLUSIONS

Insomnia type SD are prevalent in RRMS patients and are associated with older age, higher EDSS score and presence of anxiety and/or depression. Therefore, all MS patients with anxiety and/or depression should be screened for presence of SD since they tend to deteriorate patients' psycho-emotional condition and cognitive performance. The results of our study emphasize on the importance of interventions targeted at revealing sleep disorders and improving sleep quality in patients with MS for improvement of their non-motor symptoms and quality of life in general.

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ORCID and contributionship:
Oksana O. Kopchak: 0000-0003-2666-0616 [A,C,E,F]
Tetiana A. Odintsova: 0000-0003-2455-6778 [B,C,D]

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CORRESPONDING AUTHOR
Tetiana A. Odintsova
Kyiv Medical University
2 Boryspilska st., 02099 Kyiv, Ukraine
tel: +380689723808
e-mail: t.odintsova@kmu.edu.ua

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