

DEPRESSION, SLEEP DISTURBANCES AND ANXIETY IN PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS: A LONGITUDINAL COHORT OBSERVATION

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SUMMARY

Background: Depression, sleep disturbances and anxiety may affect almost half of the population of patients with multiple sclerosis (MS) and they are major determinants of poor quality of life in young adults. The aim of our study was to assess their incidence in patients with MS in Poland, and whether they change during longitudinal observation in routine clinical practice.

Subjects and methods: We included 53 consecutive patients with relapsing-remitting form of MS in this prospective study, who were treated in our department. All patients were examined at the entry to the study and after at least three or more years after study start with 4 standardized questionnaires and clinical scales that were validated in Polish patients: Athens Insomnia Scale (AIS), Epworth Sleepiness Scale (ESS), Hospital Anxiety and Depression Scale (HADS) and Expanded Disability Status Scale (EDSS). The data from the two time-points were compared.

Results: At the entry to the study daytime sleepiness, nighttime insomnia, depression episodes and anxiety were observed in 11.3%, 13.2%, 11.3% and 28.3% of patients, respectively. At the end of the study higher proportion of patients reported any form of drowsiness, depression, insomnia or anxiety, however, the differences were not statistically significant. Except for anxiety, higher proportion of patients reported definite disorders, with the rise from 3.8% to 13.2% having depression and rise from 9.4% to 15.1% having insomnia. Moderate or pathological drowsiness was not reported initially, but it was reported in 5% and 2.5% patients, respectively, at the study end.

Conclusions: The incidence of sleep and mood disturbances in Polish patients with MS is quite high, and it is comparable to other studies in patients with MS. Possible mood changes or sleep disturbances in individual patients should be routinely monitored by clinicians.

Key words: multiple sclerosis - sleep disturbances - sleep disorders – depression – anxiety

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INTRODUCTION

Multiple Sclerosis (MS) is a chronic, inflammatory, demyelinating-neurodegenerative disease of the central nervous system of unknown etiology. MS affects about 2.5 million people around the world, with higher prevalence in northern European countries and among women (Pugliatti et al. 2006, Zwibel & Smrka 2011). The course of the disease varies among patients, but inevitably leads to physical and cognitive disability. MS is the primary non-accidental cause of disability among young adults and middle-aged people (Zwibel & Smrka 2011). First symptoms most often appear in the age of 20-40 years, which concerns the life-period with the highest professional and social activity of the individuals. Motor or cognitive disability is an important factor affecting the quality of life of MS patients, however, they are more pronounced in the later stages of the disease. At earlier stages, when there is no or minor motor disability, psychological and emotional disturbances may play a key role in limiting daily functioning.

Episodes of depression may appear during a lifetime in around half of the population of patients with MS (Paparrigopoulos et al. 2010). They occur

most often at the onset of the disease (Palasik et al. 2009), thus they are major determinants of poor quality of life of young patients. Severe depression occurs in 15-30% of patients with MS, which is 3-10 times more often than in healthy population (Pucak et al. 2007). Depression in MS may be related to the awareness of the incurable disease or to the progressive loss of function, but may also be the result of functional changes in the central nervous system or adverse effects of therapy (Giordano 2011, Raison 2006). Moreover, patients with MS may be affected also by sleep disturbances and anxiety (Attarian 2009). Although they are rarely diagnosed and treated, they can affect up to 25-40% of patients (Florkowski et al. 2009).

The aim of our study was to assess, to what extent sleep disturbances, depression or anxiety occur in patients with MS and whether they change during longitudinal observation in routine clinical practice.

SUBJECTS AND METHODS

We included 53 consecutive patients (60.4% women; mean age 32±10 years) with relapsing-remitting form of MS who were treated with disease modifying drugs in

our hospital and who had no cognitive deficits. Initial characteristics of the study group is given in the Table 1. Study has been approved by our Institutional Ethics Committee and it conforms to the provisions of the Declaration of Helsinki in 1995. Patients gave informed consent and were informed that their anonymity should be preserved.

To quantify observed disturbances, we used 4 standardized questionnaires and clinical scales that were validated in Polish patients. Nighttime sleep disturbances were assessed with the Athens Insomnia Scale (AIS) and excessive sleepiness during the day with the Epworth Sleepiness Scale (ESS) (Soldatos et al. 2000, Johns 2000). AIS allows to quantify the symptoms of nighttime insomnia and contains 8 formulations that the patient evaluates on a scale from 0 to 3. Scores up to 9, 10 and above 10 indicate normal state, borderline and insomnia, respectively. In the ESS, the patient determines the probability of falling asleep during the day (on a 0-3 points scale) in the 8 presented situations. Scores in the range 11-14, 15-18 and above 18 indicate mild, moderate and pathological drowsiness, respectively. The level of anxiety and depression was determined with the use of Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith 1983). The HADS is self-explanatory and includes 7 questions about anxiety and 7 about depression. Each subscale can be scored from 0 to a maximum of 21 points. Scores up to 7, in the range from 8 to 10 and above 10 indicate normal state, mild anxiety or mild depression and anxiety or depression, respectively. To assess clinical severity of the disease we used Expanded Disability Status Scale (EDSS), in which dependence in mobility and functional deficits in selected systems: visual, brain stem, pyramidal, cerebellar, sensory, bowel and bladder, along with mental functions (Kurtzke 1983) are quantified. Score 0 is assigned to patients with normal neurological status, score up to 2 indicates minimal disability, not influencing daily functioning, scores over 4 indicate increasing limitations in walking and self-care, where score 9 indicates helpless bed patient. Score of 10 indicates death due to MS.

All scales were applied in all patients in two time-points, at the entry to the study and at least three or more years after start of the study. Differences between two examinations were analyzed with the use of Statistica 10.0 software (StatSoft Polska, Poland).

Normality of the data were verified with Shapiro-Wilk test. In the main statistical analysis paired t-test, Mann-Whitney U, Wilcoxon and McNemar tests were used, and a *p* value less than 0.05 was considered significant.

RESULTS

Median time of observation period was 4 years (range limits 3-6 years). Initial median EDSS was 1.5 points (range limits 0-5 points) and did not change during the study period; EDSS at the study end was 1.5 points (range limits 1-4.5, *p*=0.118).

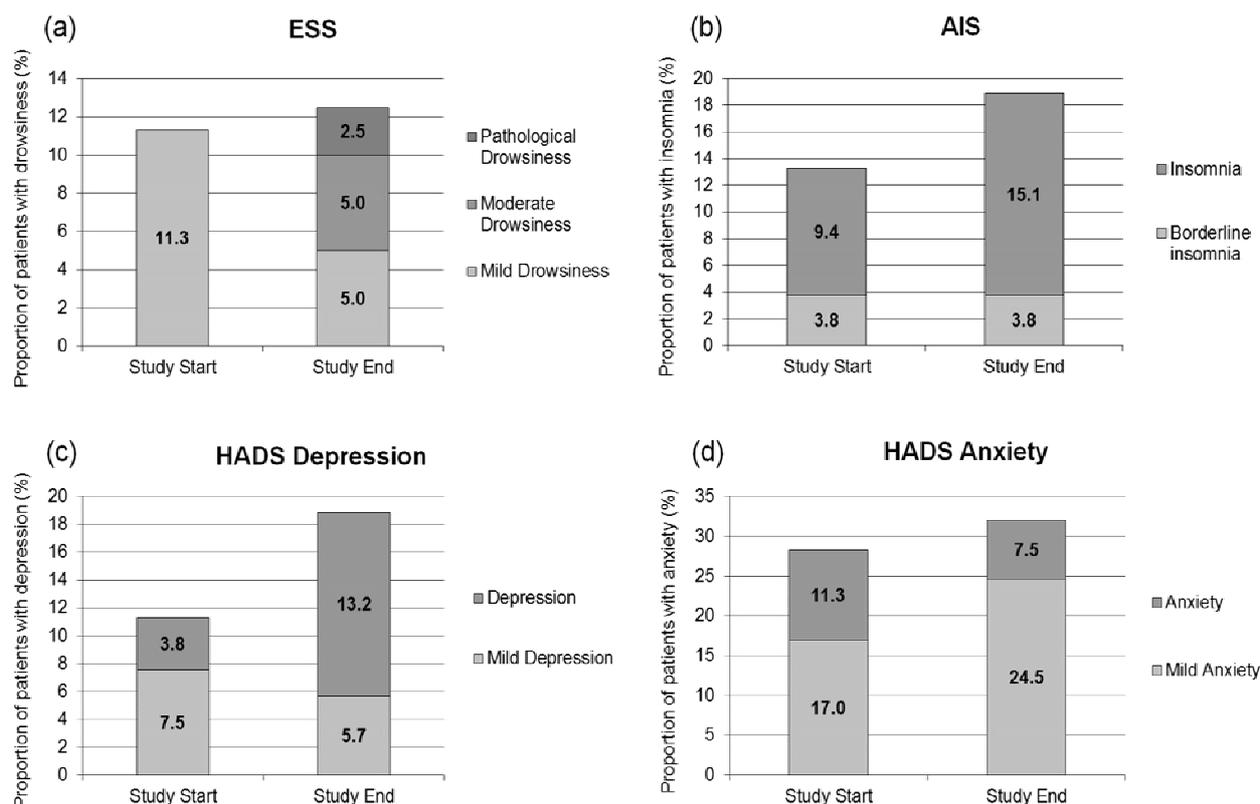
At the study start, daytime sleepiness, measured with ESS, was observed in 6 patients (11.3%), but its intensity was classified as mild drowsiness (Figure 1a). None of the patients were classified as having moderate or pathological drowsiness. Nighttime sleep disturbances, measured with AIS, were observed in 7 patients (13.2%), where 5 (9.4%) were classified as having insomnia and 2 (3.8%) were in borderline stage (Figure 1b). Depression episodes at the study start, measured with HADS, were observed in 6 patients (11.3%), where 4 (7.5%) had mild depression and only 2 (3.8%) were diagnosed as having depression (Figure 1c). Any form of anxiety, measured with the second part of HADS, was observed in 15 patients (28.3%), where 9 patients (17.0%) had mild anxiety and 6 patients (11.3%) had anxiety (Figure 1d).

At the end of the study we observed higher proportion of patients reporting any of examined disturbances, however, when we applied pair wise testing, the differences between two time-points were not statistically significant. In most observed parameters, except for anxiety, higher proportion of patients reported definite disorders. In HADS Depression scale, proportion of patients reporting depression raised from 3.8% to 13.2% (Figure 1c). Also higher proportion of patients reporting insomnia in AIS scale was observed, with a change from 9.4% to 15.1% (Figure 1b). In the ESS scale, the total proportion of patients with drowsiness raised only to 12.5%, however, the distribution of the intensity of drowsiness changed. None of the patients reported moderate or pathological drowsiness at the study start, but at the end it was 5% and 2.5% of patients, respectively (Figure 1a). In HADS Anxiety scale, the total proportion of patients reporting any form of anxiety did not alter during observation, with the change from 28.3% to 32% (Figure 1d).

Table 1. Baseline characteristics of the study group at the study start

	Women	Men	<i>p</i> value
Patients, n (%)	32(60.4)	21(39.6)	0.131
Age, years (mean±SD)	34.8±10.8	30.8±7.8	0.153
Time from first symptoms (years)	4(0-30)	3(0-25)	0.770
Time from diagnosis of MS (years)	2(0-19)	2(0-12)	0.733
EDSS (points)	1.75(0-5)	1.5(1-3.5)	0.411
Relapses during 1 year before	1(0-3)	1(0-2)	0.659

Note: otherwise indicated, data are given as median with range limits



AIS, Athens Insomnia Scale; ESS, Epworth Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale. Observed differences between two time-points were not statistically significant in all parameters (pairwise testing, McNemar test, $p > 0.05$)

Figure 1. Proportions of patients with MS (N=53) reporting any symptoms of insomnia, drowsiness, anxiety or depression at the two time-points of the study

DISCUSSION

Our study shows, that incidence of depression, anxiety or sleep disturbances among patients with MS is higher than it is expected in general population of healthy individuals. Longitudinal observation showed some worsening of these comorbidities, although in statistical testing the difference did not reach significance level, what in our opinion could be the result of the small sample size and short period of the observation. Janssens et al. in several-years observation of MS patients also did not find changes in severity of depression, anxiety or sleep disturbances (Janssens et al. 2006), however, they pointed out that usage of disease modifying treatment leading to only slight progression or lack of disability may be connected to small or no changes in the mood or sleep.

Patients with MS are at higher risk of sleep disturbances (Bamer et al. 2008). In our study 13.2% patients suffered from sleep disturbances at the study start and this proportion did not significantly change till the end of the observation (18.9%). Data from the literature are not unequivocal in that matter. Some authors report higher numbers, where prevalence of sleep disturbances in patients with MS is estimated at 25-54%. Opposingly,

Merkelbach et al. reported pathologic drowsiness to be present in 20% of patients with MS (Merkelbach et al. 2011), which is similar to our results. Such differences may depend on the studied symptoms which occur in MS patients, and are defined as sleep disturbances, such as: insomnia, sleep-related movement disturbances, sleep-disordered breathing, narcolepsy, rapid eye movement sleep behavior disorder (Koppa et al. 2007). Another factor attributing to different results may be immunomodulatory treatment, which may decrease sleep disturbances (Pokryszko-Dragan et al. 2013).

Anxiety can occur in 25-40% patients with MS. In our study anxiety was the most stable parameter observed longitudinally, where at the study start almost 30% of patients had anxiety and this number did not change in the time of the observation. Piusinska-Macoch et al. reported the trend of reduction of anxiety symptoms during treatment (Piusinska-Macoch et al. 2010) and Giordano et al. reported the reduction of anxiety during the half-year follow-up (Giordano et al. 2011). According to Wilken et al. anxiety in patients with MS is a psychological reaction to the presence of the disease (Wilken & Sullivan 2007). Properly treated symptoms of multiple sclerosis usually do not cause anxiety disturbances in patients.

According to epidemiological studies, depressive episodes may occur even twice as often in patients with MS than in the general population. The risk is the highest during relapses of the disease, where depression may occur in 40-50% of patients. In our study the incidence of depressive episodes was rather low, but during the study we noted substantial rise, although not significant, of the proportion of patients with depressive disturbances (from 11.3% to 18.9%), especially with definite depression (from 3.8% to 13.2%). Similar incidence (21%) of depression in patients with MS reported Sayao (Sayao 2011), whereas Janssens et al. reported the presence of depression among patients with MS to be comparable with the controls (Janssens et al. 2003). Giordano et al. suggested a low intensity of depressive symptoms and their stability over a six-month period (Giordano et al. 2011). Controlling of the symptoms of depression is very important, because according to Pucak et al., depression in self-assessment of patients with MS had a greater impact on their quality of life than severity of disability (Pucak et al. 2007). In addition, depression may be an important factor delaying the correct diagnosis of MS with all the consequences (Byatt et al. 2011).

The quality of life is a subjective concept and scales are the generic instruments that may be less sensitive for changes in depression, sleep disturbances and anxiety in patients with relapsing-remitting multiple sclerosis. Used scales are validated tools to assess studied disturbances among MS patients and are often used in scientific research, as well as in clinical practice (Pokryszko-Dragan et al. 2013, Carnicka & Kollar 2015, Stanton et al. 2006). T. Ziemssen suggested to use of Beck Depression Inventory as a screening test for depression at the time of diagnosis of MS, and to increase the diagnostics in patients with higher scores than 12 (Ziemssen 2009).

There are some limitations of this study. The study was performed in one center, located in the highly urbanized city. The follow-up time between two time points was not consistent in all patients, what may affect test results. Additionally a small study sample may not be representative for the general population of patients with MS in Poland. Moreover, patients during the study were treated with different types of immunomodulatory therapy.

CONCLUSIONS

The incidence of sleep and mood disturbances in Polish patients with MS is quite high, even with appropriate access to disease modifying treatment, and it is comparable to other studies in patients with MS. Possible mood changes or sleep disturbances in individual patients should be routinely monitored by a clinician. The incidence of anxiety up to 30% and depressive episodes close to 20% in general population of patients with MS should be of interest of treating physicians.

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Data analyses and interpretation: Weronika Bulska and Ewa Krzystanek;
Writing of the manuscript: Paulina Brozek, Marta Brachmanska, Katarzyna Rabczko, Weronika Bulska, Marta Ciulkowicz, Ewa Krzystanek;
Multiple edits of the manuscript drafts: Ewa Krzystanek;
Literature research: Paulina Brozek, Marta Brachmanska, Katarzyna Rabczko, Ewa Krzystanek;

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