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ORIGINAL ARTICLE

Fatigue and depression influence the prevalence of anxiety in patients with multiple sclerosis

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Abstract

Background There is scarce information in Middle-Eastern Europe regarding the prevalence of anxiety in patients with multiple sclerosis (pwMS) and its association with different clinical-demographic factors.

Objective We aimed to determine the prevalence of anxiety in Hungarian MS patients and to analyze associated factors.

Materials and methods We evaluated 260 PwMS with the STAI-5 anxiety questionnaire. Fatigue (FIS), depression (BDI-II) and cognition (BICAMS) were also measured. Patients underwent standard neurological evaluations to evaluate Expanded Disability Status Scale (EDSS), and also measured the fine motor skills of the hand with the 9-hole peg test (9HPT), and the walking distance with the 25-foot walking test (T25FW).

Results We identified 23.1% ($N=60$) of the patients with anxiety (only state, trait or both forms concurrently). According to our two univariate, multivariable logistic regression analysis, fatigue and depression are strongly associated with both state and trait anxiety. In the absence of fatigue, the odds of trait anxiety are 82% lower (OR: 0.18; 95% CI: 0.06–0.53; $p=0.002$), while in the case of pwMS without depression, the odds are reduced by 81% (OR: 0.19; CI95%= 0.07–0.51, $p=0.001$). This association with fatigue (OR: 0.33; CI95%= 0.13–0.85, $p=0.021$) and depression (OR: 0.14; CI95%=0.06–0.35; $p<0.001$) can also be statistically verified on state anxiety. Importantly, a significant association with state anxiety was found in SPSM patients as well (OR: 34.94; CI95%=2.55-479.61; $p=0.008$).

Conclusions Anxiety was strongly associated with fatigue, depression, and secondary progressive disease form. These results emphasize the burden of psychiatric morbidity in pwMS.

Keywords Anxiety · Secondary progressive MS · Fatigue · STAI · Depression · Quality of life

Introduction

Multiple sclerosis (MS) is not a common disease with a prevalence of 101.8/100,000 in Hungary and an estimated number of 2.8 million patients worldwide [1, 2]. However, its impact goes beyond the mere prevalence data, as it is the most common neurological cause of disability among young people (20–45 years) after traumatic brain injury [3].

In recent years, several evaluations have concluded that regardless of the patients' physical condition, psychological symptoms seriously affect the patients' health-related quality of life (HRQoL) and are increasingly recognized as essential contributors to disability progression and increased health care utilization [4–7]. In fact, regarding several areas (such as the ability to work or drive), they appear to be even more important negative factors than physical symptoms, according to some studies [8–10]. Therefore, the emphasis was placed on identifying these disorders as soon as possible.

As compared to the other psychological aspects (cognition, depression, fatigue), anxiety is relatively less-well researched in MS, with nearly twice as many studies focusing on depression for example. According to prevalence

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data, it is widespread (20–45%) throughout the course of the disease and exceeds the lifetime prevalence of anxiety disorders in the general population (approximately 13%) [11, 12]. However, only a few evaluations assessed the risk factors relevant to anxiety in patients with MS (PwMS).

According to some studies, the occurrence of anxiety is more common around the time of diagnosis, yet it is not simply a one-time stress reaction. Based on epidemiological surveys, the closest correlation exists between the appearance of depression and anxiety, but other studies have also established female sex, disease duration, the relapsing-remitting course of the disease (RRMS), certain disease-modifying treatments (DMT), lower education, employment status, alcohol consumption, tobacco use, and certain personality types to also have a profound negative effect [13–18].

Some studies have also raised the adverse effects of cognitive functions and fatigue on anxiety [13]. Moreover, recent neuroimaging studies have shown a connection between network changes caused by frontal lobe atrophy, limbic system lesions, and anxiety development [19, 20]. Overall, it looks like anxiety is mainly caused by the pathology of MS itself, so it is often a symptom of the disease rather than a simple comorbidity. These findings make its recognition, treatment, and examination even more necessary.

In this assessment, our primary aims were to provide an overview of anxiety prevalence in PwMS in South-East Hungary and to investigate risk factors that are associated with anxiety development. As a secondary endpoint, we examined the effect of anxiety on the patients' HRQoL.

Patients and methods

Patients

We performed a cross-sectional study including 260 PwMS treated in the MS Outpatient Unit of the Department of Neurology of the University of Szeged, Hungary from September 2022 to December 2023. Inclusion criteria were:

1. Informed consent
2. ≥ 18 years of age,
3. Diagnosis of MS based on the original or the 2005, 2010 or 2017 revised McDonald criteria as applicable [21–24],
4. First language had to be Hungarian,
5. EDSS scores between 0 and 6.5 points.
6. They were in remission and did not receive steroid therapy for at least 30 days during the evaluation.

Exclusion criteria were:

1. Absence of informed consent,
2. EDSS scores > 6.5 points.
3. If they were undergoing acute infection or an acute relapse.
4. If they had a history of chronic alcoholism and/or had a history of drug abuse or dependence.

All sociodemographic and clinical data on the patients (including sex, educational state, age, age at disease onset, disease duration, EDSS score, clinical course, clinical disease activity and data on disease-modifying therapy [DMT]) were obtained and updated from the Multiple Sclerosis Register of Szeged [25]. The clinical course was determined based on the phenotypic classification of Lublin et al. from 2014 and the definition of secondary progressive MS (SPMS) by Lorscheider et al. from 2016 [26, 27].

Methods

The original Spielberger State-Trait Anxiety Inventory (STAI) has been specifically developed to evaluate state (STAIS) and trait (STAIT) anxiety and consists of 20–20 questions each. During everyday clinical practice however, the scales need to be shortened to make them more feasible as screening tools for rapid assessments or multiple admissions. Zsido et al. validated an abbreviated, 5-question long Hungarian version of the STAI (STAI5), which we utilized in our survey [28]. Per the original validation, anxiety was diagnosed with a score of ≥ 10 on the STAIS-5 and ≥ 14 points on the STAIT-5 [28].

To measure cognition, all patients completed the validated Hungarian version of the "Brief International Cognitive Assessment for Multiple Sclerosis" (BICAMS), which comprises of 3 subtests: the Symbol Digit Modalities Test (SDMT), and the immediate recall tests of the Brief Visuospatial Memory Test Revised (BVMT-R) and the California Verbal Learning Test 2nd Edition (CVLT-II) [29]. In case of the SDMT, z-scores were calculated, while T-scores were utilized for the BVMT-R and CVLT-II as per the manual of the corresponding tests. In case of the SDMT, z-scores 1.5 SD below normal, while in case of BVMT-R and CVLT-II T-scores below 40 were considered impaired. Cognitive impairment (CI) was defined as impairment on ≥ 1 tests as was suggested by the BICAMS group in their recommendation paper. Since it is known from the literature that depression is closely related to anxiety, we evaluated the prevalence of depression with the Beck Depression Inventory (BDI-II) [30]. We considered patients showing relevant depressive symptoms, if they scored ≥ 13 points on the questionnaire. Due to the possible influence of fatigue on anxiety, all patients completed the Hungarian version of the Fatigue Impact Scale (FIS) [31]. Patients were considered to

have fatigue if their score was ≥40 points. To monitor the patient's quality of life, we used the MSQoL-54 questionnaire adapted to Hungarian native speakers [32]. All in all, 195 of the 260 patients filled out the questionnaire.

In addition, we also measured the physical condition of the patients. In addition to determining the Expanded Disability Status Scale (EDSS) score, we also measured the fine motor skills of the hand with the 9-hole peg test (9HPT), and the walking distance with the 25-foot walking test (T25FW). In case of the 9HPT test, z-scores were calculated based on previously published normative data: z-scores 1.5 SD above normal scores were considered impaired [33].

We also aimed to measure the possible effect of the number of T2 hyperintense lesions and "black-holes" on anxiety. The magnetic resonance imaging (MRI) scans of the brain were routinely conducted as part of the clinical follow-up procedure of the patients by the Department of Radiology. All brain MRI examinations were carried out on the same 3T Siemens MRI scanner, with standardized protocols specifically developed for MS diagnosis and follow-up. The number of lesions were always manually quantified by the same, experienced neuroradiologist. In line with the suggestion of the MAGNIMS, during routine follow-up scans, no contrast material is utilized, only in case of the first, diagnostic scan and an MRI conducted during acute relapse. As no included patient underwent testing within 30 days of an acute relapse, the included MRIs were conducted during the routine follow-up, thus no contrast material was used. Also, only approximately 40% of the patients had spinal MRI at some point, and as our center is referring center, a great number of these MRI scans were not conducted in our Department and was not quantified by our neuroradiologist, spinal lesions were also omitted from the analyses.

Table 1 Clinical and demographic data of the study population

Demographic and clinical data		Patients ($N=260$)
Clinical course	RRMS	236 (90.8%)
	PPMS	14 (5.4%)
	SPMS	10 (3.8%)
Sex	Male (%)	75 (28.8%)
	Female (%)	185 (71.2%)
Age at test (±SD)		42.78 ± 10.49
Age at the diagnosis (±SD)		30.71 ± 9.61
Disease duration (±SD)		12.05 ± 8.38
Education	12 years or less (%)	126 (48.5%)
	13 years or more (%)	133 (51.5%)
DMT type	None	10 (3.8%)
	Low efficacy	89 (34.2%)
	High efficacy	161 (61.9%)
Previous DMT escalation	Yes	99 (38.1%)
	No	161 (61.9%)
Median EDSS score (IQR)		1.5 (1.25)

RRMS, relapsing-remitting disease course; SPMS, secondary progressive disease course, PPMS, primary progressive disease course, DMT, disease modifying therapy, EDSS, Expanded Disability Status Scale; SD, standard deviation; IQR, interquartile range

Statistical analysis

Categorical variables are presented as the number of cases and the proportion of cases in each category. In case of continuous variables, data are presented using either the mean and standard deviation (SD) or the median and inter-quartile range (IQR). In our initial dataset, 27 probable clinical, demographic and MRI explanatory variables were present. To reduce these factors to a more manageable number, we conducted a model-free partial least squares (PLS) regression analysis with the raw STAI-T and STAI-S scores being the dependent variables. We only included parameters in the further analyses, if the variance importance of projection (VIP) score of the given factor was above 1. As the second step, we created clinically meaningful groups based on the identified influencing factors using the above specified criteria, and the specific thresholds of the given tests. Then two univariate multivariable logistic regression models were developed: one with trait and one with state anxiety as its dependent variable and the clinically relevant categories used as independent variables. To assess the differences between groups, Chi-square tests, Fischer-exact tests, one-way ANOVA and Mann-Whitney-U tests were utilized (as suitable).

Results

Clinical and demographic characteristics of the cohort

The demographic and clinical characteristics of the cohort are presented in Table 1. The mean age of the patients was approximately 43 years, their mean age at diagnosis was ~31 years, their mean disease duration was approximately 12 years. The cohort's overall median EDSS score was relatively low with a median EDSS score of 1.5 (1.25) points. More than 2/3rd of the patients were women (185 patients, 71.2%, female-to-male ratio 2.47:1); while the educational levels were balanced with 51.5% (133 patients) having some type of higher education than secondary school degree. The majority of the patients had the relapsing-remitting (RRMS) disease course (236 patients; 90.8%), received highly efficacious disease modifying treatments (HeDMT; 161 patients, 61.9%): natalizumab, alemtuzumab, ocrelizumab, cladribine, fingolimod or siponimod; and more than 1/3 (99 patients, 38.1%) of the patients have undergone therapy escalation to HeDMT. Only 14 patients (5.4%) had clinical relapse in the past year before testing, and 17 patients (6.5%)

received corticosteroid treatment in the past year - but ≥30 days - before testing (due to relaps and/or during the premedication procedure of alemtuzumab administration).

Anxiety scores and prevalence

The mean scores of the cohort on the STAIT-5 and the STAIS-5 questionnaires were 8.69 ± 3.38 and 7.14 ± 2.84 points respectively. Based on the scores of the questionnaires, we identified 23.1% (60 patients) with some level and form of anxiety. Trait anxiety was present in 12.7% (33 patients), while state anxiety could be identified in 18.1% (47 patients).

Influencing factors of anxiety

We evaluated the effect of several baseline demographic, clinical and MRI parameters which may have influenced the STAI-S and STAI-T scores. We examined the possible effect on these parameters of 27 independent variables (clinical and demographic data; pathopsychological test scores; limb function scores and MRI lesion numbers). Table 2 summarizes the raw scores on the psychological questionnaires, the 9HPT and T25FW scores and MRI parameters.

Table 2 The mean scores on the different psychological screens, functional tests and the mean number of MRI lesions of the cohort

Measures and MRI lesions	Mean ± SD
BDI-II.	7.12 ± 7.50
FIS	37.5 ± 36.05
SDMT	55.89 ± 12.47
BVMT-R	30.00 ± 5.96
CVLT-II.	64.43 ± 11.78
9HPT dominant hand 1. trial	24.07 ± 9.77
9HPT dominant hand 2. trial	22.21 ± 8.52
9HPT non-dominant hand 1. trial	25.25 ± 17.39
9HPT non-dominant hand 2. trial	22.97 ± 6.13
T25FW 1. trial	6.90 ± 5.41
T25FW 2. trial	6.85 ± 5.49
Total number of T2 hyperintense lesions	20.17 ± 16.33
Periventricular lesions	10.53 ± 7.98
(Juxta)cortical lesions	3.72 ± 5.20
Infratentorial lesions	1.64 ± 1.99
Non-periventricular, non-juxtacortical deep white matter lesions	4.01 ± 5.53
Black holes	3.95 ± 5.30

BDI-II., Beck's Depression Inventory; FIS, Fatigue Impact Scale; SDMT, Symbol Digit Modalities Test; BVMT-R Brief Visuospatial Memory Test Revised; CVLT-II., California Verbal Learning Test Second Edition; 9HPT, 9-hole peg test; T25FW, Timed 25-feet walk test; SD, standard deviation

PLS analysis for factor reduction

As the first step, we conducted an exploratory PLS analysis with STAI-T and STAI-S raw scores being the dependent variables. For this assessment, we utilized the raw scores of BICAMS (SDMT, BVMT-R, CVLT-II), BDI-II and FIS tests. Variables with a VIP score of ≥1 were considered as possible influencing factors.

Based on the PLS analysis, the following factors were considered as possible influencing factors on STAI5 scores, thus eligible for further assessment (Figs. 1 and 2):

A. STAI-S scores: clinical course, number of infratentorial lesions, EDSS score, SDMT score, BDI score, FIS score.
B. STAI-T: education, clinical course, 9HPT score with the non-dominant hand, BDI score, FIS score.

Influencing factors of the prevalence of anxiety

After identifying the possible influencing factors, these raw scores were converted into clinically more informative and meaningful categories: we identified patients with cognitive impairment, fatigue and depression based on the z- and T-scores of the BICAMS battery and the specific thresholds on the FIS and BDI scores. We found that 16.2% (42 patients) showed signs of depression; 40.0% (104 patients) had fatigue and 20.0% (52 patients) had cognitive impairment. We created two groups by the EDSS scores at the threshold of 3 points (clinically meaning moderate disability, a usual threshold utilized in clinical trials and epidemiological surveys): 223 patients (85.8%) had an EDSS score 0–3.0 points, while 37 patients (14.2%) had an EDSS score ≥3.5 points. We also divided the patients into 3 categories based on their infratentorial lesion numbers. Based on clinical experience of relevance, three groups were created: patients who had no infratentorial lesions ($N=84$, 32.3%), patients with 1 infratentorial lesion ($N=61$, 23.5%) and patients with at ≥1 infratentorial lesions ($N=115$, 44.2%). Lastly, we created two groups based on the patients 9HPT performance with the non-dominant hand: based on the z-scores, 147 patients (56.5%) on the first trial, while 116 (44.6%) on the second trial could be considered impaired.

As the third step, we utilized two univariate multivariable logistic regression models. In the first case, the presence of trait anxiety, in the second case, the presence of state anxiety was the dependent variable, while in both cases, the above mentioned, converted, clinically relevant parameters (higher/lower education, the three clinical courses, the presence of cognitive impairment, the presence of fatigue, the presence of depression, the presence of

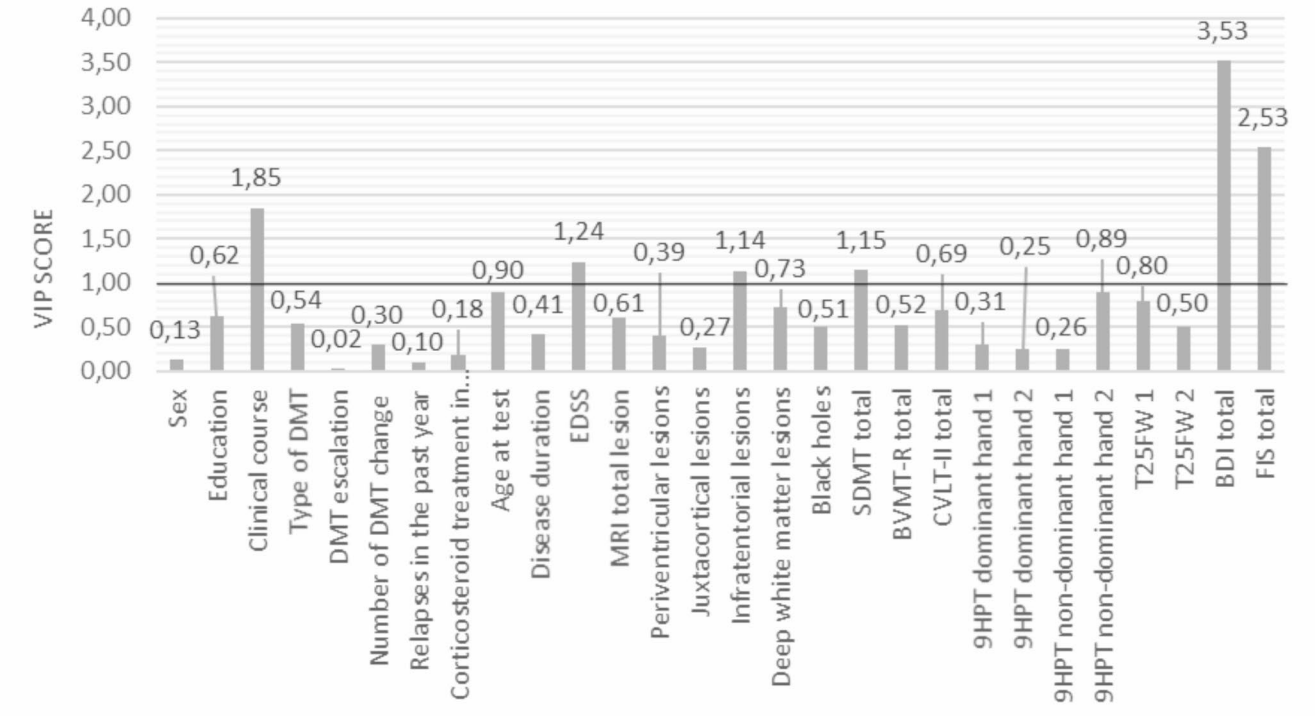

Fig. 1 Variable importance in projection (VIP) scores of the different factors contributing to STAI-S scores in the PLS analysis

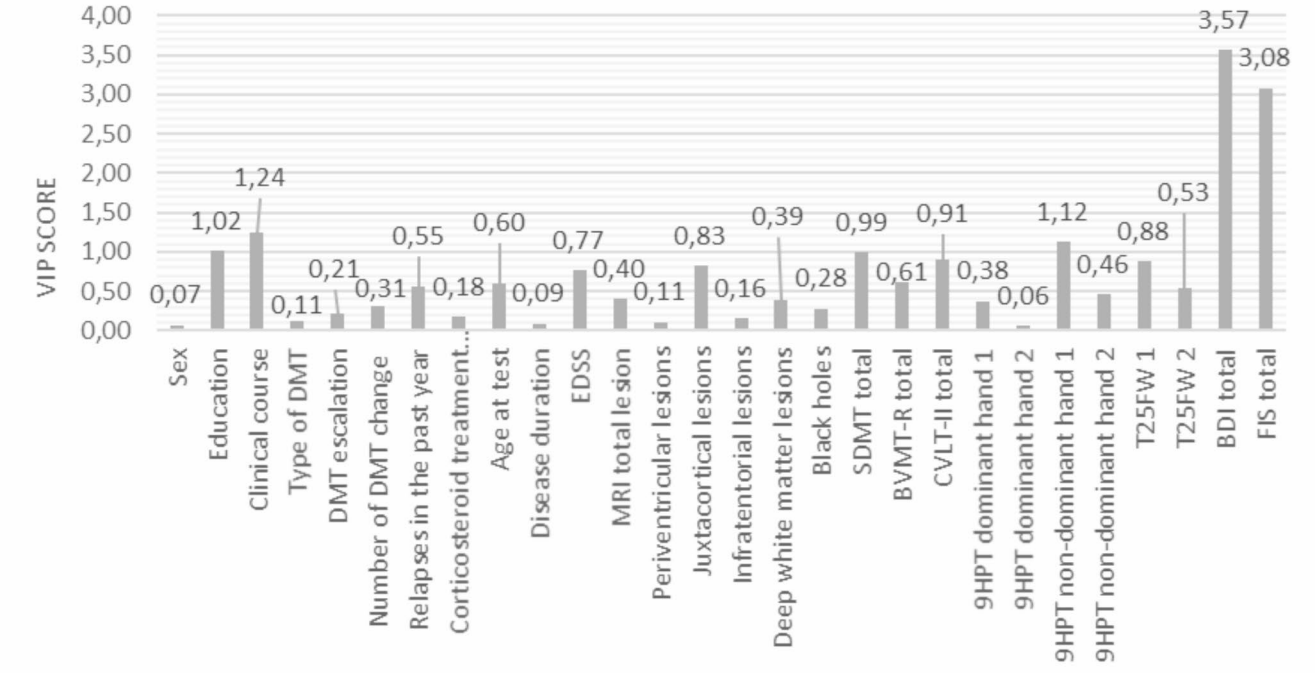

Fig. 2 Variable importance in projection (VIP) scores of the different factors contributing to STAI-T scores in the PLS analysis

impairment on the 9HPT, different number of infratentorial lesions and EDSS scores 0–3 points or ≥ 3.5 points) were the independent variables. These analyses revealed that the level of education, EDSS scores, the impairment on the 9HPT, the number of infratentorial lesions and the presence of cognitive impairment had no significant effect on the prevalence of neither state nor trait anxiety. On the other hand, we found that fatigue and depression had a significant

Table 3 The difference between the prevalence of trait anxiety among the patients based on depression and fatigue

Trait anxiety		No	Yes	*p*-value
Depression	Not present	201 (93.1%)	15 (6.9%)	< 0.001
	Present	24 (57.1%)	18 (42.9%)	
Fatigue	Not present	150 (96.2%)	6 (3.8%)	< 0.001
	Present	77 (74.0%)	27 (26.0%)	

Table 4 The difference between the prevalence of state anxiety among the patients based on depression, fatigue and the clinical courses

State Anxiety		No	Yes	*p*-value
Depression	Not present	192 (88.9%)	24 (11.1%)	< 0.001
	Present	19 (45.2%)	23 (54.8%)	
Fatigue	Not present	143 (91.7%)	13 (8.3%)	< 0.001
	Present	70 (67.3%)	34 (32.7%)	
Clinical course	RRMS	196 (83.1%)	40 (16.9%)	0.001
	PPMS	13 (92.9%)	1 (7.1%)	
	SPMS	4 (40.0%)	6 (60.0%)	

RRMS, relapsing-remitting disease course; SPMS, secondary progressive disease course, PPMS, primary progressive disease course

association with both state and trait anxiety. When fatigue is not present, the odds of trait anxiety are 82% lower (OR: 0.18; 95% CI95%: 0.06–0.53; $p = 0.002$). The prevalence of depression has a similarly strong association as in the case of pwMS without depression, the chance of trait anxiety is reduced by 81% compared to those with depression (OR: 0.19; CI95%=0.07–0.51, $p = 0.001$). A very similarly strong association with the absence of fatigue (OR: 0.33; CI95%= 0.13–0.85, $p = 0.021$) and depression (OR: 0.14; CI95%=0.06–0.35; $p < 0.001$ could be identified in case of state anxiety too. Importantly, a higher chance for state anxiety was found based on the clinical courses of the disease: SPSM patients showed an elevated likelihood for anxiety (OR: 34.94; CI95%=2.55-479.61; $p = 0.008$), while such influence was not found in case of trait anxiety.

Based on the results of the regression analysis, we compared the presence of trait and state anxiety in patients with and without depression and fatigue, while also compared the prevalence of state anxiety in the different clinical courses. We found that 42.9% of depressed patients had trait and 54.8% state anxiety, while if depression was not present, trait anxiety occurred in only 6.9% and state anxiety in 11.1% of the patients (both differences are significant on the level of $p < 0.001$). When fatigue was present, trait anxiety was present in 26.0%; when there was no fatigue, then only in 3.8% (also both differences are significant on the level of $p < 0.001$). During the state anxiety assessment, if fatigue was present, 32.7% had anxiety; while only 8.3% had anxiety in patients with no fatigue ($p < 0.001$). Based on the clinical course, 60.0% of SPMS patients showed anxiety, while only 16.9% in case of RRSM and only 7.1% in case of PPMS patients ($p = 0.001$). The results are summarized in Tables 3 and 4.

Table 5 The difference between the scores of patients with and without trait anxiety on the subscales of MSQoL-54 questionnaires

MSQoL-54 subscale	Patients without anxiety		Patients with anxiety		*p*-value
	Mean ± SD	*N*	Mean ± SD	*N*	
Physical health	78.34 ± 27.28	169	60.58 ± 28.99	26	< 0.001
Role limitations due to physical problems	75.74 ± 38.13	169	56.73 ± 39.72	26	< 0.001
Emotional well-being	69.30 ± 15.55	169	43.69 ± 15.13	26	< 0.001
Role limitations due to emotional problems	83.63 ± 33.95	169	53.85 ± 42.24	26	< 0.001
Pain	81.52 ± 23.69	169	56.60 ± 22.49	26	< 0.001
Energy	58.41 ± 20.05	169	34.00 ± 13.82	26	< 0.001
Health perceptions	65.74 ± 23.21	169	39.81 ± 19.82	26	< 0.001
Social function	83.19 ± 20.78	169	63.78 ± 25.16	26	< 0.001
Cognitive function	76.33 ± 19.64	169	56.92 ± 21.82	26	< 0.001
Sexual function	81.82 ± 27.38	169	67.33 ± 30.80	26	0.006
Satisfaction with sexual function	68.79 ± 33.72	169	49.03 ± 34.99	26	0.008
Health distress	73.79 ± 22.17	169	48.46 ± 23.65	26	< 0.001
Change in health	50.15 ± 23.22	169	42.31 ± 24.26	26	0.165
Overall quality of life	73.34 ± 17.80	169	52.50 ± 17.69	26	< 0.001

SD, standard deviation

Quality of life

Patients with both trait and state anxiety reported worse HRQoL than their non-anxious counterparts according to MSQOL-54 assessment. In case of state anxiety, they exhibited lower scores in each specific subscale of the questionnaire, while in case of trait anxiety, only 1 out of the 14 subscales did not show significant difference (change in health, $p = 0.165$). Tables 5 and 6 summarizes the respective differences between the groups.

Discussion

It has been shown for more than 20 years that pwMS have a higher prevalence of anxiety than healthy subjects or patients with other neurological disorders [34]. However, the measured prevalence data showed high variability, with rates ranging between 4 and 57% [35]. Earlier systematic reviews and meta-analyses demonstrated the pooled prevalence to be approximately 22%; while a current systematic review found that the average prevalence of anxiety in MS

Table 6 The difference between the scores of patients with and without state anxiety on the subscales of MSQoL-54 questionnaires

MSQoL-54 subscale	Patients without anxiety		Patients with anxiety		*p*-value
	Mean ± SD	*N*	Mean ± SD	*N*	
Physical health	80.09 ± 26.15	161	56.47 ± 29.17	34	< 0.001
Role limitations due to physical problems	78.43 ± 36.60	161	48.53 ± 39.86	34	< 0.001
Emotional well-being	70.41 ± 14.72	161	44.47 ± 15.15	34	< 0.001
Role limitations due to emotional problems	86.54 ± 29.67	161	47.06 ± 47.22	34	< 0.001
Pain	83.20 ± 21.60	161	54.51 ± 26.51	34	< 0.001
Energy	59.16 ± 19.30	161	36.24 ± 18.55	34	< 0.001
Health perceptions	66.71 ± 23.01	161	41.32 ± 19.60	34	< 0.001
Social function	84.78 ± 18.86	161	60.78 ± 26.87	34	< 0.001
Cognitive function	76.96 ± 19.36	161	58.53 ± 21.80	34	< 0.001
Sexual function	83.35 ± 26.52	161	63.64 ± 30.61	34	< 0.001
Satisfaction with sexual function	69.56 ± 34.20	161	50.00 ± 31.28	34	0.001
Health distress	74.94 ± 21.72	161	48.97 ± 22.42	34	0.001
Change in health	51.55 ± 21.95	161	37.50 ± 27.00	34	< 0.001
Overall quality of life	74.49 ± 16.61	161	51.96 ± 19.42	34	< 0.001

SD, standard deviation

to be 36% (based on 32 studies) [5, 13, 36]. However, all these examinations highlighted that there is a significant difference in sample size, the measurement tool, and the sociodemographic composition is quite heterogeneous in each study group, possibly explaining the heterogeneity in the results. Also, most data on psychiatric disorders in MS originates from North American or Western European population, while there is scarce information on the frequency of anxiety and its association with different clinical-demographic factors in Middle Eastern Europe [13, 36]. During our examination, we identified 23.1% (60 patients) with some level and form of anxiety among pwMS in Hungary, which is in line with earlier results in the literature.

Aside from the prevalence data, associated factors of anxiety among pwMS were another objective in our examination. Other psychological symptoms and co-morbidities (depression, CI and fatigue), clinical (EDSS score, clinical course of the disease) and demographic factors (age, sex etc.) have all been reported as possible associated with anxiety in pwMS.

The co-occurrence of depression and anxiety is a well-established phenomenon: a great number of previous evaluations found a strong bidirectional relationship between depression and anxiety in both the general population and MS patients as well [35]. Prevalence rates of anxiety among patients with depression are much higher than in non-depressed patients (up to 90%) in the general population and among pwMS as well [37, 38]. In our study, we also determined a similarly strong relationship between the mood disorders, with prevalence rates of 42.9% for trait and 54.8% for state anxiety among depressed patients.

The relationship between fatigue and anxiety is less-well established than with depression, however it tends to show a positive association. A recent paper from the UK reported register-based data on fatigue and its association with clinical factors on a very large cohort (approximately 20000 patients) and found that anxiety is a significant predictive factor for fatigue [39]. Positive associations were reported from Norway, the Netherlands, Canada and Saudi-Arabia as well in the past couple years [40–43]. Our findings are in line with these recent results, establishing that beside depression, fatigue seems to be the strongest associated factor with anxiety in pwMS.

Several studies have shown that cognitive impairment is significantly associated with increased anxiety [44]. Anxiety was also negatively correlated with self-perception of cognitive impairment [45]. A prospective study showed that anxiety was a significant predictor of cognitive change over time [46]. In our survey however, we were unable to demonstrate any effect of CI on anxiety. If we look at the results however, it might be less surprising: the relationship between anxiety and cognition is less bidirectional as with depression, and mainly anxiety effects cognitive performance, not the other way around. It should also be noted that the prevalence of CI in our present cohort was lower compared to our previous report (20.0 vs. 57.1%) [47]. We think that the low CI prevalence is explained by the fact that the patients in the study did not fill the BICAMS assessment for the first time, and as our previous follow-up study showed, there is an improvement in CI in the long term [48]. This low level of cognitive dysfunction might also play some role in the absence of association.

In the literature, age and sex are the most commonly discussed risk factors [13]. Surveys indicated that the age-sex pattern for anxiety in the general population was only observed during fertile periods, while the risk for new cases became similar for both sexes after menopause [49]. In our study however, we did not find a significant association between anxiety and sex or age. The reason behind this is unclear, however if we look at the mean age of our patients (42.78 ± 10.49 years), we find a generally middle-ages population, with a relatively higher number of older patients. This may have resulted in a not-significant age-sex pattern.

Numerous studies reported a significant relationship between a high level of disability and a high level of anxiety [13]. We determined the physical disability not only with the EDSS score, but also the hand function with the 9HPT and limited mobility with the T25FW measures. Despite this, no significant association was found between physical parameters and anxiety. It is important to note however, that in our survey, the median EDSS was only 1.5 points, the T25FW and 9HPT also showed good hand and foot functions. The lack of association may very well lie in the overall very good physical condition of our cohort.

The possible exacerbating effect of relapses on anxiety is an important question and the information is conflicting as some earlier surveys reported positive associations between acute shubs and anxiety in pwMS, however a most recent meta-analysis on the predictors of anxiety reported no such connection [13, 50]. Also recently, two well-constructed studies from Italy were published: Menculini et al. found some connection between the two phenomenon while Sparaco et al. reported none [51, 52]. Our results reinforce the latter survey's outcome as we also found no association between the presence of relapses and anxiety. It is possible, the reason for this lies in the different methodologies of the evaluations. Menculini et al. found that recent hospitalization due to acute relapse exacerbated anxiety, while we excluded patients who underwent acute exacerbation in the past month [51]. All in all, further assessments are needed to get a clearer picture on the matter.

The disease course is another important question, however, results are conflicting in the literature. Some studies indicate a higher incidence among RRSM patients, given the unpredictable and fluctuating nature of RRMS, and the number of relapses over time could significantly increase anxiety levels [53, 54]. However, other studies show another possible association. A systematic review found that the prevalence of anxiety was different in clinical forms of MS, with higher rates in the progressive onset clinical course (21.4% RRMS; 24.1% PMS), however, the difference was not statistically significant [55]. In our study, the SPSM disease form represented an elevated probability for anxiety and we measured a much higher prevalence of anxiety than in other clinical courses. To our best knowledge, no other paper found this kind of association. The reason behind this might lie in SPMS itself. This clinical course by definition means a much worse physical and cognitive state and it is much harder to treat with much less DMTs available than RRMS. Patients usually have residual symptoms, sleep disturbances, urination problems, fear of falling, fatigue, and central neuropathic pain, all that can lead to a higher rate of anxiety [56]. Another factor could be the different definition of SPMS among the different studies. Based on the earlier classification criteria, SPMS and RRMS definitions overlapped much more than today, thus probably a portion of patients with higher EDSS scores considered to be RRMS patients at the time could be re-classified as SPMS today, which fact may influenced the outcome of these assessments [57]. However, it is also important to consider, that the number of SPMS patients in our cohort was very low, evidently biasing our analyses to a degree (e.g.: the very wide 95%CI), thus the observed connection (OR: 34.94) should be very carefully interpreted as the association is likely much less robust then appearing here. However, this result still reinforces the importance of considering that the conversion into a later, progressive phase of the disease not only affects the patients' physical state, but their psychological well-being as well. Thus, further analyses on large patient cohorts, directed at the difference between the clinical courses are needed to draw clear conclusions on the matter.

The impact of psychological symptoms on patients' HRQoL should not be overlooked. Several studies have investigated the relationship between HRQoL and depression, anxiety, stress and fatigue [58]. Some results even proposed, that cognitive and psychological symptoms affect HRQoL of pwMS more significantly than physical damage [9]. In line with these results, we found that patients with anxiety reported a significantly worse HRQoL on all measured areas of life than patients without anxiety.

We acknowledge there are significant limitations of our study. First, SPMS and PPMS was represented by only a small sample size in our cohort that may have reduced statistical power to detect possible associations. It is also important to take into account that we used self-report rating scales and a short-form anxiety measure, which might be less sensitive than longer measures and structured clinical interviews.

The strength of the article is the relatively high overall cohort size and that we evaluated a wide area of possible influencing factors, taking into account not only clinical and demographic parameters, but also psychological and MRI measures as well.

Conclusion

The results of our study add important data to the scarce literature in Middle-Eastern Europe regarding the relationship between anxiety and MS. We found that Hungarian MS outpatients presented an elevated prevalence of anxiety and had lower quality of life. The presence of depression and fatigue significantly raise the frequency of anxiety. It seems, that the secondary progressive form of the disease may represent a stronger association with anxiety than other courses. As anxiety is reported to significantly impair patients' quality

of life and increase the appearance of harmful addictions, further efforts are needed to understand how it develops in MS patients in order to treat it appropriately and avoid underdiagnosis.

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Data availability The research data used in this article are not publicly available on legal and ethical grounds.

Declarations

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the University of Szeged (Approval numbers: 207/2015-SZTE RKEB and 124/2013-SZTE RKEB).

Consent to participate Informed consent was obtained from all individual participants included in the study.

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