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THE IMPACT FACTORS OF ERECTILE DYSFUNCTION IN MULTIPLE SCLEROSIS PATIENTS

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ABSTRACT. Sexual dysfunction (SD) is a common problem, but often underestimated in multiple sclerosis (MS) patients, having a major negative impact on quality of life in patients diagnosed with MS. The purpose of this study is to investigate the nature and prevalence of sexual dysfunction in patients with MS and the analysis of their relationship to various clinical and psychosocial variables. In 37 patients with relapsing remitting multiple sclerosis (41.63 ± 6.052 years), was assessed the ED using the short version of the of the International Index of erectile function (IIEF5). The assessment was made again after 12 months. The data obtained in the study was compared with data from a control group, which consisted of 30 people aged between 40 and 65 years (52.27 ± 8.35). The IIEF5 scores dropped to 16 [median; Q1-Q3 quartiles range (IQR) 12-20] in group 2, from 17 (median, IQR 13-21) in group 1, and are significantly lower compared to the control group (median 22.5 IIEF5; IQR 21-24; p <0.001). Analyzing the IIEF5 scores and EDSS scores in MS patients has shown a strong correlation between these two scores, both on admission (ρ = -0.874, p <0.001) and after 12 months (ρ = -0.879, p <0.001). Although ED is a frequent pathology at multiple sclerosis patients is often underestimated. The ED at MS patients can occur even in the absence of a marked physical disabilities.The sexual dysfunctions present in patients with MS are represented by a complex set of circumstances, associated with several anatomical, physiological, biological, and psychological factors
KEYWORDS: erectile dysfunction, IIEF5, multiple sclerosis, EDSS score, MSISQ-19

INTRODUCTION

Sexual dysfunction (SD) is a common problem, but often underestimated in multiple sclerosis (MS) patients, having a major negative impact on quality of life in patients diagnosed with MS [1]. In men, the rates of occurrence of symptoms ranges from 50% to 90%, depending on the clinical characteristics of the studied population and the elapsed time to re-assess the patients. A recent study showed that about 86% of men reported that MS determine an impaired sexual life. SD can occur at any stage of the disease, cases being reported in the early stages of the disease, but between 2 to 5 years of diagnosis, approximately 50% of men reported dissatisfaction with their sexual functioning [2,3].

Erectile dysfunction (ED) is present more frequently in MS patients than in patients with other chronic diseases or healthy subjects. ED in MS is associated with a significant reduction in quality of life, and also can compromise fertility being extremely complex and multifactorial. Due to this a multidisciplinary approach is needed for a correct diagnosis [4].

Sexual problems within MS may be caused by primary, secondary or tertiary sources. The primary causes are considered the direct physiological impairments caused by demyelinating lesions of the spinal cord and / or brain, the most common symptoms are numbness in the genitals, erectile dysfunction and ejaculatory dysfunction. Secondary causes refers to non-sexual physical changes that can affect the sexual response, such as spasticity, fatigue, bladder dysfunction, digestive dysfunctions, and pain. Tertiary causes include psychosocial and cultural issues that interfere with sexual satisfaction or performance, such as lack of self confidence , marked depression and interpersonal communication difficulties [5]. These organic and nonorganic factors can coexist, so to highlight all of the causes of ED in patients with MS, a detailed assessment is required.

The purpose of this study is to investigate the nature and prevalence of sexual dysfunction in patients with MS, the analysis of their relationship to various clinical and psychosocial variables, the impact of such factors on the severity of ED, and also to clarify the differences between patients with and without ED diagnosed with MS.

MATERIALS AND METHODS

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The study included 37 patients with relapsing remitting multiple sclerosis , aged 28 to 54 years (mean 41.63 ± 6.052), admitted to the Neurological Department of Arad County Hospital between February 2014 - March 2016 (group 1 preMS patients), patients to whom was assessed the ED using the short version of the of the International Index of erectile function (IIEF5). The assessment was made again after 12 months (group 2 postMS patients). The data obtained in the study was compared with data from a control group, which consisted of 30 people aged between 40 and 65 years (52.27 ± 8.35).

Patients who have experienced other neurological diseases, an EDSS score greater than 6.0 and also patients and people in the control group who used inhibitors of 5-phosphodiesterase (PDE5) were excluded from the current study. To confirm the diagnosis was used a computed tomography (General Electric Optima CT 520 Series SYS) or magnetic resonance imaging (General Electric 1.5 Tesla Optima 360) in the first 3 days after admission.

The state of depression in patients with MS was evaluated using the Hamilton depression scale through HAM-D questionnaire. This questionnaire consists of 17 questions, each question having a score between 0 and 4 points. The final results have a score between 0-50 points, and based on the scores depression can be classified as follows: between 0-7 points without depression, mild depression between 8-13 points, 14-18 points moderate depression, 19-22 points severe depression, and over 23 points very severe depression.

The multiple sclerosis severity was assessed using Kurtzke expanded disability scale (EDSS scale). Functional scores obtained using the EDSS scale varies between 0.0 and 10.0, and refers to pyramidal function, cerebellar, brainstem, sensory, visual, gastrointestinal and bladder, respectively mental function (mood and neurocognitive function). EDSS scores range from 1.0 to 4.5 refers to movable patients, and the EDSS score between 5 and 9.5 refers to patients with marked movement difficulty.

To better understand the impact of MS on sexuality and intimacy was used the MSISQ-19 questionnaire, a questionnaire composed of 19 questions in which are assessed various symptoms of MS having negative impact on activity and sexual satisfaction during the last 6 months. There is no right or wrong answers to the questions, for the primary sexual dysfunction the questions 12,16,17 and 19 are representative, for the secondary dysfunctions the questions 1,2,3,4,5,6,8,10 and 11, and for the tertiary dysfunctions the questions 7, 9, 13, 14, and 15.

Erectile dysfunction was assessed using the short version of the International Index of Erectile Function (IIEF5) which has 5 questions, each question with a score between 0 and 5 points and a maximum score of 25. Based on this questionnaire ED can be classified in: severe ED (between 1 and 7 points; grade 5), moderate ED (between 8 and 11 points; grade 4), mild to moderate ED (between 12 and 16 points; grade 3), mild ED(between 17 and 21 points; grade 2), and without erectile dysfunction (between 22 and 25 points; grade 1).

The research was conducted with the approval of the Ethics Committee of the Arad County Hospital in agreement with the Declaration of Helsinki (1989) of World Medical Association, and with the approval of the Ethics Committee of the "Vasile Goldis" Western University of Arad . All patients who participated in the study and the control group, received a consent form.

Each patient enrolled in the study completed a IIEF5 questionnaire, a HAM-D questionnaire and a MSISQ-19 questionnaire, at admission and at the regular checkup performed after 12 months. It was also rated the degree of disability of patients using the EDSS scale, confirming of the diagnosis being made based on clinical symptoms and imaging. The persons from the control group also completed IIEF5 and HAM-D questionnaires.

Statistical analysis

The IBM SPSS Statistics software for Windows, version 20.0, was used for statistical analysis of the data obtained. To test the normal distribution of data, was used the Shapiro-Wilk test, obtaining a mean plus / minus a standard deviation for normally distributed data and a median for data without normal distribution. To compare data from admission to those obtainde at the checkup control at 12 months was used t test for normally distributed data and Wilcoxon test for data without normal distribution. For comparisons between groups were used the t-test for normally distributed data, and the Mann-Whitney U test for the data without normal distribution, and the Chi-square test for the variables. The correlations between EDSS scores, IIEF5, HAM-D, MSISQ-19 and age were calculated using Spearman's correlation test for data without normal distribution and Pearson correlation test for normally distributed data. Values of p less than 0.05 were considered statistically significant.

RESULTS

1.The severity and prevalence of erectile dysfunction in the 3 groups of patients

After analyzing the IIEF5 scores, 30 patients in group 1 (81.08%), 32 patients (86.49%) in group 2 and 9 (30%) in the control group had various degrees of erectile dysfunction. Following the analysis of IIEF5 values using Tukey's Hinges test we observed that these values have dropped to 16 [median; Q1-Q3 quartiles range (IQR) 12-20] in group 2, from 17 (median, IQR 13-21) in group 1, and are significantly lower compared to the control group (median 22.5 IIEF5; IQR 21-24; $p < 0.001$).

Also, 14 patients from group 1 (37.84%), 10 patients from group 2 (27.03%) and 7 patients from the control group (23.33%) experienced mild ED. Mild

to moderate ED was recorded in 8 patients (21.62%) from group 1, 13 patients (35.14%) from group 2 and 1 patient (3.33%) from the control group. Moderate ED was recorded in 7 patients (18.92%) from group 1, 6 patients (16.22%) from group 2 and 1 patient (3.33%) from the control group and severe ED was registered in 1 patient (2.70%) from group 1, 3 patients (8.11%) from group 2 and 1 patient (3.33%) from the control group. (Table 1)

Table 1. The severity and percentage of erectile dysfunction at the 3 groups

	Group 1 patients preSM	Group 2 patients post SM	Control group	p values [1 vs 3]*	p Values [2 vs 3]*	p values [1 vs 2]**
No of patients	37	37	30			
Age Mean±SD Median (Q1-Q3)	 41.63±6.052 44 (40-47)	 44.65±6.052 45 (41-48)	 52.27±8.346 52 (45-60)	 <0.001	 0.001	 No sense
IIEF5 Mean±SD Median (Q1-Q3)	 16.89±5.015 17 (13-21)	 15.59±4.958 16 (12-20)	 21.83±3.312 22.5 (21-24)	 <0.001	 <0.001	 <0.001
Patients with ED **No (%)**	 30 (81.08%)	 32 (86.49%)	 9 (30%)	 <0.001	 <0.001	 <0.001
Severitz of ED(No (%)) **Mild** **Mild to moderate** **Moderate** **Severe**	 14 (37.84%) 8 (21.62%) 7 (18.92%) 1 (2.70%)	 10 (27.03%) 13 (35.14%) 6 (16.22%) 3 (8.11%)	 7 (23.33%) 1 (3.33%) 1 (3.33%) 0	 0.203 0.035* 0.050* >0.999*	 0.730 0.002* 0.120* 0.247*	 0.002* 0.001* <0.001* 0.081*

2. The association between erectile dysfunction and disability level of the patients with multiple sclerosis

The degree of disability in MS patients was assessed using the EDSS scale.Analyzing the obtained data, shows that a score of 1.0 on this scale was recorded at 3 patients from group 1 and at 1 patient from group 2, a score of 1.5 was recorded at 7 patients from group 1 and at 5 patients from group 2. A score of 2.0 was recorded at 4 patients from group 1 and 6 patients from group 2, a score of 2.5 was recorded at 5 patients from group 1 and 4 patients from group 2. A score of 3.0 was registered at 4 patients from group 1 and 6 patients from group 2, a score of 3.5 was recorded at 7 patients from group 1 and 6 patients from group 2, a score of 4.0 was recorded at 2 patients from group 1 and 3 patients from group 2, a score of 4.5 was recorded at 3 patients from group 1 and 4 patients from group 2, and a score of 5.0 was recorded at 2 patients from group 1 and 4 patients from group 2.

Analyzing the IIEF5 scores and EDSS scores in MS patients has shown a strong correlation between these two scores, both on admission (ρ = -0.874, p <0.001) and after 12 months (ρ = -0.879, p <0.001). Also there is a worsening of disability of patients from group 2 compared to group 1.

3. The association between depression and erectile dysfunction

The Hamilton Depression scores showed a very severe depression in 1 patient (2.7%) from group 1. Severe depression was recorded at 5 patients (13.51%) from group 1, at 4 patients from group 2 and at 1 patient (3.33%) from the control group. Moderate depression was recorded at 7 patients (18.92%) from group 1, 11 patients (29.73%) from group 2 and at 3 patients (10%) from the control group and mild depression was recorded at 15 patients (40.54%) from group 1, 14 patients (37.84%) from group 2 and 7 patients (23.33%) from the control group . In table 2 we can observe the extent of the corresponding ED distribution, mentioning that 30 patients from group 1 (81.08%) presented ED, 32 patients (86.48%) from group 2 had DE, 9 persons (30%) from the control group.

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Table 2. The repartition of ED based on depression evaluated with Hamilton scale

ED grade at patients with MS at admission	Depression					Total
	Normal	Mild Depression	Moderate Depression	Severe Depression	Very severe Depression	
Grade 1 – Without ED	4 (10.08%)	3 (8.11%)	0	0	0	7 (18.92%)
Grade 2 – Mild ED	5 (13.51%)	8 (21.62%)	1 (2.70%)	0	0	14 (37.84%)
Grad 3 – Mild to moderat ED	0	4 (10.08%)	3 (8.11%)	1 (2.70%)	0	8 (21.62%)
Grad 4 – Moderate ED	0	0	2 (5.41%)	4 (10.08%)	1 (2.70%)	7 (18.92%)
Grad 5 – Severe ED	0	0	1 (2.70%)	0	0	1 (2.70%)
Total	9 (24.32%)	15 (40.54%)	7 (18.92%)	5 (13.51%)	1 (2.70%)	37 (100%)
ED grade at patients with MS after 12 months	Depression					Total
	Normal	Mild Depression	Moderate Depression	Severe Depression	Very severe depression	
Grad3 1 – Without ED	4 (10.08%)	3 (8.11%)	0	0	0	7 (18.92%)
Grad 2 – Mild ED	5 (13.51%)	8 (21.62%)	1 (2.70%)	0	0	14 (37.84%)
Grad 3 – Moderate to mild ED	0	4 (10.08%)	3 (8.11%)	1 (2.70%)	0	8 (21.62%)
Grad 4 – Moderate ED	0	0	2 (5.41%)	4 (10.08%)	1 (2.70%)	7 (18.92%)
Grad 5 – Severe ED	0	0	1 (2.70%)	0	0	1 (2.70%)
Total	9 (24.32%)	15 (40.54%)	7 (18.92%)	5 (13.51%)	1 (2.70%)	37 (100%)

4. The association between erectile dysfunction and MSISQ-19 scores

The multiple sclerosis has a strong negative effect on sexuality and intimacy of the patients expressed by the MSISQ-19 score, a questionnaire in wich for the primary sexual dysfunction the questions 12,16,17 and 19are represenative, for the secondary dysfucntions questions 1,2,3,4, 5,6,8,10 and 11, and for the tertiary dysfunctions questions 7,9,13,14 and 15. The following figures illustrate the highly significant correlation between the IIEF5 scores and MSISQ-19 scores, at admission ($\rho = -0.794$, $p < 0.001$), and after 12 months ($\rho = -0.816$, $p < 0.001$). (figure 1 and 2)

Figure 1. correlation between ED and MSISQ-19 at admission

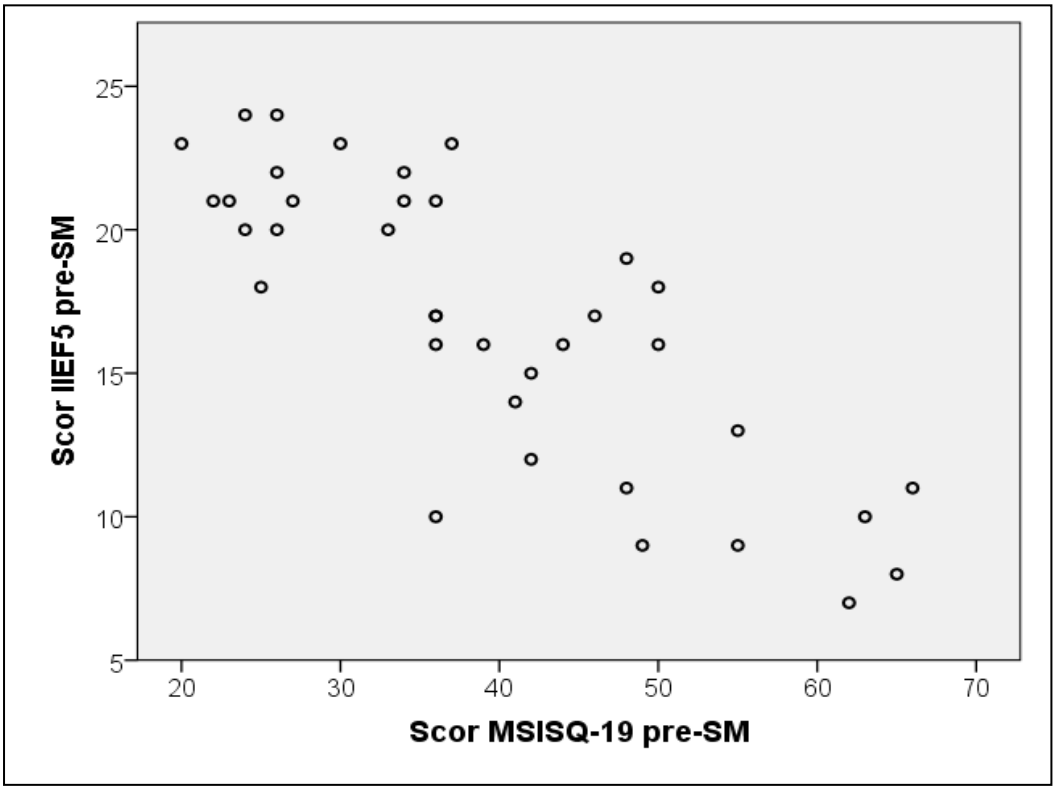
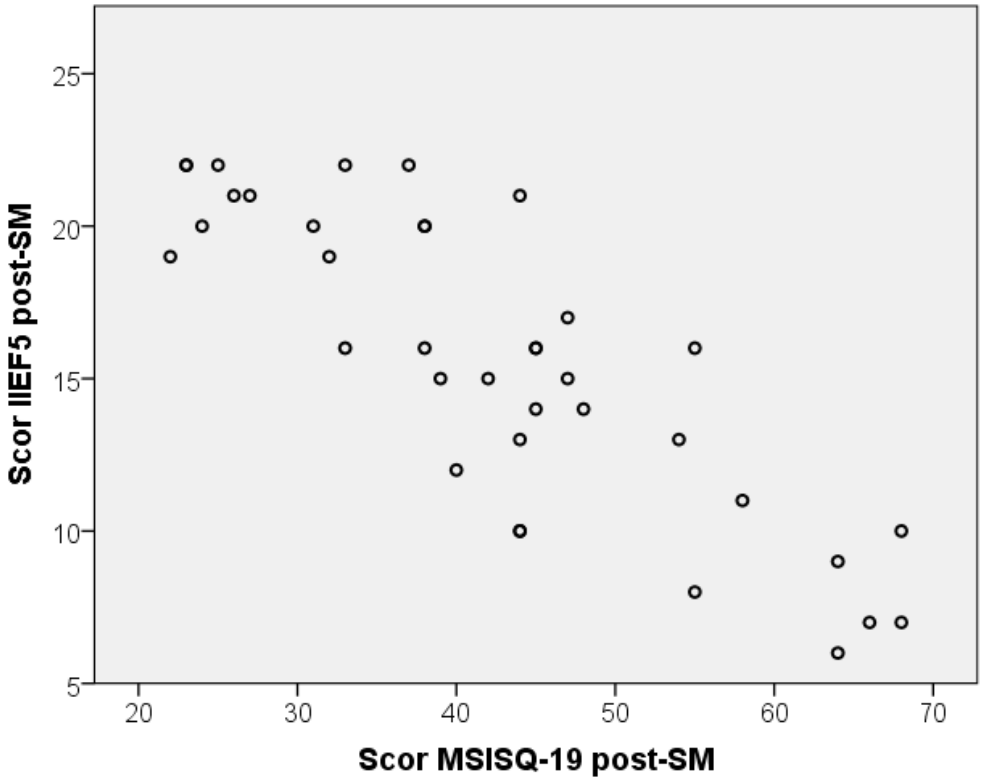


Figure 2. Correlation between ED and MSISQ-19 after 12 months



DISCUSSION

Erectile dysfunction is one of the most common sexual dysfunction in patients with multiple sclerosis, while ejaculatory disorders and low libido had a lower prevalence [6,7]. Similar to the results obtained by Redelman in a study from 2009 in which about 50% of patients included in the study presented ED, in our current study 30 of the 37 enrolled patients (81.08%) presented ED, respectively 32 patients (86.48%) reported ED at the 12 months evaluation.

The ED present in MS patients is largely due to the impairment of spinal cord pathways that have somatic involvement in the sacral segments (reflexogen erection), and also due to the demyelination located in the pons Varolii [8]. A correlation between the location of demyelinations and ED is one of our future goals of a new study in which we will determine also the serum levels of testosterone, given that at MS patients the hypothalamic-pituitary-thyroid function can be altered [9]. However, the male patients may still have nocturnal tumescence and morning erections, indicating that their problem is not psychiatric in nature, as previously considered [10,11].

Also in thecategory of primary sexual dysfunction are the ejaculatory disorders which can be be present in various forms, including premature ejaculation, retrograde ejaculation, or delayed ejaculation. The ejaculatory dysfunction and ED are often related to one another, about a third of those with ED presenting some type of ejaculatory disorder [12].

The prevalence of secondary and tertiary disorders are slightly more difficult to estimate. Urinary incontinence, pyramidal signs of the lower limbs, and age at the onset of symptoms are commonly associated with ED, and fatigue can negatively affect sexual activity [13]. In our study, using MSISQ-19 questionnaire, were evaluated these primary, secondary and tertiary sexual dysfunction, being found significant correlations between prevalence and severity of ED and the scores the questionnaire.

The correlation between physical disability and ED is still controversial, while several studies have found a significant relationship between levels of disability of MS patients and DE [2.14], others did not [15]. The data recorded in our study have demonstrated a significant correlation between IIEF5 scores and disability scores assessed with EDSS scale. Also significant associations were observed between ED and depression [16,17], depression being a frequent symptom in patients with MS determining a prevalence increase.

In addition to symptoms related to MS, many symptomatic treatments currently used in clinical practice, such as antispasmodics, antidepressants or anticonvulsants, may have the potential to cause ED and other sexual dysfunction [16]. In particular,

delayed ejaculation and orgasm can be common side effects of selective serotonin reuptake inhibitors, while sexual desire (libido) and arousal difficulties are also frequently reported [18]. The baclofen injection may compromise also erection with a dose-dependent effect [19].

Based on our study, we attempted to calculate a multiple logistic regression. The multiple logistic regression through we try to estimate the dependent variable Erectile Dysfunction post-MS (which gives us the actual diagnosis of the patient to have or not ED, which is a variation of binary form presence / absence of the disease) is based on independent predictor variables: age pre-MS, HAM-D scores pre-MM, EDSS scores, and MSISQ-19 scores. The multiple linear regression is considered only for MS patients (patients from group 1 and 2)using Forward method based on the Wald statistical test. The final model is obtained in 3 steps, details of SPSS model can be found in the following tables:

Case Processing Summary

Unweighted Cases[a]		N	Percent
Selected Cases	Included in Analysis	37	100.0
	Missing Cases	0	.0
	Total	37	100.0
Unselected Cases		0	.0
Total		37	100.0

a. If weight is in effect, see classification table for the total number of cases.

Dependent Variable Encoding

Original Value	Internal Value
Absenta DE post SM	0
Prezenta DE post SM	1

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	11.541	1	.001
	Block	11.541	1	.001
	Model	11.541	1	.001

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	17.765[a]	.268	.490

a. Estimation terminated at iteration number 8 because parameter estimates changed by less than .001.

Classification Table[a]

	Observed		Predicted		
			ED presence post_SM		Percentage Correct
			ED absence post SM	ED presence post SM	
Step 1	ED presence post_SM	ED absence post SM	2	3	40.0
		Ed presence post SM	1	31	96.9
	Overall Percentage				89.2

a. The cut value is .500

Classification Table[a]

	Observed		Predicted		
			Prezența_DE_post_SM		Percentage Correct
			Absența DE post SM	Prezența DE post SM	
Step 1	Prezența_DE_post_SM	Absența DE post SM	2	3	40.0
		Prezența DE post SM	1	31	96.9
	Overall Percentage				89.2

a. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	EDSS score pre_SM	2.688	1.310	4.211	1	.040	14.697	1.128	191.464
	Constant	-3.344	2.103	2.527	1	.112	.035		

a. Variable(s) entered on step 1: Scor_EDSS_pre_SM.

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The final significantly model obtained (p = 0.001) by which we determine whether a patient has or not ED using significant predictors is characterized in the table below (results in the table below are the essential results in the tables above, tables provided by software SPSS 20). Note that the model significant predictors pre-MS EDSS scores.

Variable	Coeficient (B)	Standard Error (SE)	Wald statistic	Grade of freedom	p-value	Exp (B)	95% IC pentru Exp (B)
EDSS score pre-SM	2.688	1.310	4.211	1	0.040	14.697	1.128– 191.464
Constant	-3.344	2.103	2.527	1	0.112	0.035	

The interpretation of the variables in the regression equation obtained for the diagnostic of ED for a patient with MS (patients like those in group 1 abd 2) is :

- EDSS score pre-MS: for an increase with a unit value of EDSS scores pre-MS , the chance of the patient to have post-MS ED is increased by a factor of Exp (2.688) = 14.697 (so the chances of having ED are the 14.697 higher). For an increase with K units of the EDSS scores pre-MS, the odds ratio increases and has a value Exp (k * B). Thus, for k = 3 (a value increase of 3 units EDSS score pre-MS), the chance of having ED post MS increases Exp (3 * 2.688) = Exp (8,064) = 3.177

The logistic regression equation obtained is:
Logit (ED) = -3.344 + 2.688*(EDSS score pre-MS).

How can we use this equation? We can predict the likelihood of post-MS ED for a patient for wich we know the EDSS score at admission. For example, if we consider an MS patient (patient like those from group 1 and 2) with EDSS score of 3.0 at admission, we obtain logit (DE) = -3.344 + 2.688 * 3 = 4.72, and transforming this value in probability we obtain Prob = exp (4.72) / (1 + exp (4.72)) = 0.9911636, so the probability that the patient with MS and EDSS score equal to 3.0 to be diagnosed with ED is 99.12%.

CONCLUSIONS

Although ED is a frequent pathology at multiple sclerosis patients is often underestimated. The ED at MS patients can occur even in the absence of a marked physical disabilities.

The sexual dysfunctions present in patients with MS are represented by a complex set of circumstances, associated with several anatomical, physiological, biological, and psychological factors, having a major role over quality of life in these patients. Treatment of sexual dysfunction in MS requires a multidisciplinary team and close cooperation between practitioners and patients. PDE-5 inhibitors are the first line of treatment for patients with MS. If their inefficienct, it may be tried the second-line treatments, such as intracavernosal injection or intraurethral injection of prostaglandin E1, or third-line therapy such as surgical implantation of a penile prosthesis.

The awareness of doctors and patients about this pathology may help in developing ideal medication management, improving the quality of life for these patients.

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Compliance with ethical standards

Conflict of interest None