

Increased risk of erectile dysfunction in men with multiple sclerosis: an Italian cross-sectional study

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Citation: Balsamo R, Arcaniolo D, Stizzo M. Increased risk of erectile dysfunction in men with multiple sclerosis: An Italian cross-sectional study. Cent European J Urol. 2017; 70: 289-295.

Article history

Submitted: April 12, 2017

Accepted: Aug. 4, 2017

Published online: Aug. 4, 2017

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Introduction Sexual dysfunctions (SDs) are common, but often underestimated symptoms in men with multiple sclerosis (MS). The most common sexual complaint in a multiple sclerosis male is erectile dysfunction (ED). The aim of this observational, cross-sectional study was to assess the prevalence of erectile dysfunction (ED) and its relationship with neurological disability, depression, urodynamic findings and lower urinary tract symptoms (LUTS) in these patients.

Material and methods From January 2014 to January 2016, there were 101 consecutive male patients with a diagnosis of Multiple Sclerosis according to the McDonald revised criteria and stable sexual relationships were included. Patients were evaluated with the International Index of Erectile Function (IIEF-15), Sexual Quality of Life Questionnaire-Male version (SQoL-M), International Prostate Symptom Score (I-PSS) and the Beck Depression Inventory-II (BDI-II). Neurological impairment was assessed using the Expanded Disability Status Scale (EDSS). The presence of Detrusor Overactivity (DO), Detrusor Underactivity (DU) and Detrusor Sphincter Dyssynergia (DSD), was defined by International Continence Society (ICS) criteria.

Results Erectile dysfunction (ED) defined according to the erectile function (EF)-subdomain score ≤ 25 was present in 75 patients (74.25%). Univariate regression analysis showed that Sexual Quality of Life Questionnaire-Male version ($P < 0.0001$), age ($P = 0.021$), Expanded Disability Status Scale score ($P = 0.001$), Beck Depression Inventory-II score ($P = 0.001$), International Prostate Symptom Score ($P = 0.001$), Detrusor Underactivity ($P = 0.002$), Multiple Sclerosis-Secondary Progressive ($P = 0.002$) was significantly associated with erectile dysfunction. All significant findings in univariate analysis were then entered into a multiple logistic regression model. The results indicated that the Beck Depression Inventory-II score ($P = 0.011$) and International Prostate Symptom Score ($P = 0.043$) were the only independent predictive factors of erectile dysfunction onset in these patients.

Conclusions Hence, in order to provide an effective approach and management for erectile dysfunction all the mentioned symptoms and clinical variables should be kept in mind.

Key Words: erectile dysfunction ↔ multiple sclerosis ↔ lower urinary tract symptoms ↔ urodynamic ↔ International Index of Erectile Function

INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system [1]. Multiple

sclerosis (MS), usually diagnosed between the age of 20 and 40 years [2], is one of the most frequent diseases of the central nervous system resulting in both somatomotor and autonomic disturbances [3].

Signs and symptoms can widely differ from patient to patient, depending on where the lesions are located. The main autonomic nervous system disorders include sweating abnormalities, lower urinary tract dysfunctions (LUTDs), gastrointestinal symptoms and sexual dysfunctions (SDs) [2]. Among these, sexual dysfunctions (SDs) are common, but often underestimated symptoms, even if their impact on the quality of life is remarkably high. The reported rate of sexual dysfunction (SD) in multiple sclerosis (MS) patients ranges from 50% to 90%, depending on the clinical characteristics of the studied population and the duration of follow-up [4, 5]. The most common sexual complaint in a multiple sclerosis (MS) male is erectile dysfunction (ED), that can be found in 23% to 91% of patients [6, 7]. Sexual dysfunctions (SDs) in multiple sclerosis (MS) are a complex set of conditions, associated with anatomic, physiologic, biologic, medical and psychological factors [8]. It is crucial for clinicians to identify and effectively manage erectile dysfunction (ED) and other sexual dysfunctions (SDs) in order to significantly improve the quality of life in subjects with multiple sclerosis (MS)

The aim of this observational, cross-sectional study were: to evaluate the prevalence of erectile dysfunction (ED) and its relationship with neurological disability, depression, lower urinary tract symptoms (LUTS) and urodynamic findings in a cohort of multiple sclerosis (MS) male patients to assess the sexual quality of life (SQoL) in this subset of patients.

MATERIAL AND METHODS

From January 2014 to January 2016, consecutive male patients with multiple sclerosis (MS) in remission phase, who underwent urodynamic examination for the first time, were recruited from our neurological department. Criteria for inclusion were: men aged 18 years or older, diagnosis of multiple sclerosis (MS) according to the McDonald revised criteria [9], 'stable sexual relationship' (same partners for six or more consecutive months). Exclusion criteria were: treatment with antidepressant, anticonvulsant and anxiolytic, major psychiatric disease, previous pelvic surgery or radiotherapy, concomitant therapy with 5-alpha-reductase inhibitors, anti-cholinergics, alpha-blockers or any other drug for the treatment of erectile dysfunction, patients with catheter or with an episode of acute retention of urine in the last 4 weeks, poorly controlled diabetes and hypogonadism. The examination included urinalysis, ultrasonography and an urodynamic test according to the International Continence Society (ICS) – standard [10]. During the visit, patients filled out the International Index of Erectile Function-15 (IIEF-15)

[11], the Sexual Quality of life Questionnaire-Male version (SQoL-M) [12], the International Prostate Symptom Score (IPSS) [13] and the Beck Depression Inventory-II (BDI-II) [14]. An independent neurologist performed a neurological assessment using the Expanded Disability Status Scale (EDSS). A higher score means more severe neurological deficit according to Kurtzke [15]. All participants provided written informed consent before enrollment and the study was conducted in accordance with regulatory standards of Good Clinical Practice and the Declaration of Helsinki (1996).

Statistical analyses

Due to their asymmetric distribution, checked by the Shapiro-Wilk test, continuous variable differences between groups were tested by the Mann-Whitney test. The qualitative data was tested using the χ^2 test with Yate's continuity correction or Fisher's exact test. Multivariate logistic regression analyses were carried out to identify variables for erectile dysfunction (International Index of Erectile Function – Erectile Function ≤ 25) risk, incorporating as explanatory variables all the variables that showed a significant p-value in bivariate analysis. To avoid multicollinearity problems, predictors that were in strong correlation with other explanatory variables were dropped from the models. Goodness-of-fit of logistic regression models were checked using the Hosmer and Lemeshow test and the Odds ratios (ORs) with 95% confidence intervals were also calculated. Statistical analyses, were performed using IBM-SPSS® version 22.0 (IBM Corp., Armonk, NY, USA, 2013). A two-sided p-value < 0.05 was considered significant.

RESULTS

Study population

A total of 101 patients completed the study. Mean age was 41.2 ± 11.6 years and the mean duration of the disease was 11.5 ± 7.5 years. The course of multiple sclerosis (MS), urodynamic findings, Beck Depression Inventory-II (BDI-II), Expanded Disability Status Scale (EDSS) and International Prostate Symptom Score (IPSS) were reported in Table 1. The mean Beck Depression Inventory-II (BDI-II) score was 18.3 ± 14.7 and over half of patients (57.4%) fulfilled Beck Depression Inventory-II (BDI-II) criteria for depression. Mean Expanded Disability Status Scale (EDSS) score was 3.77 ± 2.01 , with no significant difference between the types of clinical course of the disease. Mean basal total testosterone (TT)

Table 1. Demographics, neurological, urological and sexual characteristics of patients

No. of subjects	101 (100%)
Multiple sclerosis variants	
Relapsing remittant*	64 (63.3)
Primary progressive*	28 (27.7)
Secondary progressive*	9 (9.0)
Age (years)**	41.26 ±11.6
Expanded Disability Status Scale (EDSS) (score)**	3.77 ±2.01
Duration of disease (years)**	11.5 ±7.5
Beck Depression Inventory-II (BDI-II) (score)**	18.3 ±14.7
BDI-II (0-13)*	43 (42.5)
BDI-II (14-19)*	21 (20.7)
BDI-II (20-29)*	14 (13.8)
BDI-II (30-63)*	23 (22.7)
International Index of Erectile Function (IIEF)	
IIEF-15 (score)**	45 ±18.9
IIEF-Erectile Function (score)**	17.5 ±8.5
IIEF-Intercourse Satisfaction (score)**	8.6 ±4.2
IIEF-Orgasmic Function (score)**	6.3 ±3.2
IIEF-Sexual desire (score)**	6.6 ±2.4
IIEF-Overall Satisfaction (score)**	5.8 ±2.4
Male sexual dysfunction (IIEF-15 <60)*	75 (74.2)
Erectile Dysfunction (IIEF-ED <26)*	75 (74.2)
Testosterone (ng/dL)**	457.74 ±132.95
Diabetes*	9 (8.9)
Duration of lower urinary tract symptoms (LUTS) (years)**	8.24 ±7.58
International Prostate Symptom Score (IPSS)	
IPSS (score)**	14.46 ±9.1
IPSS (0-7)*	29 (28.7)
IPSS (8-19)*	44 (43.5)
IPSS (20-35)*	28 (27.7)
Urodynamics findings	
Detrusor overactivity*	43 (42.5)
Detrusor underactivity*	20 (19.8)
Detrusor sphincter dyssynergia*	10 (9.9)
Normal*	28 (27.7)

* number (%)

** mean±SD

Table 2. Overall sexual dysfunction and erectile dysfunction

No. of subjects	101
International Index of Erectile Function (IIEF)	
IIEF-15 (60-75)*	26 (25.7)
IIEF-15 (44-59)*	41 (40.6)
IIEF-15 (5-43)*	34 (33.6)
Male sexual dysfunction (IIEF-15 <60)*	75 (74.2)
Erectile Dysfunction (IIEF-ED <26)*	75 (74.2)
IIEF-Erectile Function (17-25)*	32 (42.7)
IIEF-Erectile Function (12-16)*	16 (21.3)
IIEF-Erectile Function (8-11)*	13 (12.7)
IIEF-Erectile Function (0-7)*	14 (18.7)

* number (%)

Table 3. Sexual quality of life (SQoL)

No. of subjects	101
Sexual Quality of Life Questionnaire-Male version (SQoL-M)**	40.6 ±26.3
SQoL-M (0-10)*	8 (7.9)
SQoL-M (11-20)*	23 (22.7)
SQoL-M (21-50)*	42 (41.5)
SQoL-M (51-89)*	22 (21.7)
SQoL-M (90-100)*	6 (5.9)
Erectile dysfunction (ED)-SQoL-M**	29.3 ±16.6
No ED-SQoL-M**	73.1 ±21.5

* number (%)

** mean ±SD

level was 457.74 ± 132.95 ng/dl. Nearly all men (99%) were heterosexual.

Overall sexual dysfunction and erectile dysfunction data on sexual function was shown in Table 2. There were 75 patients (74.25%) who met the criteria for male sexual dysfunction (International Index of Erectile Function -15 <60). Erectile dysfunction (ED) defined according to the erectile function (EF) subdomain score ≤ 25 was present in 75 patients (74.25%): 32 (42.7%) showed mild, 16 (21.3%) mild to moderate, 13 (17.3%) moderate and 14 (18.7%) severe erectile dysfunction (ED) (Table 2).

Data on the sexual quality of life was reported in Table 3. The mean Sexual Quality of Life Questionnaire-Male version (SQoL-M) score was 40.6 ± 26.3 . The mean Sexual Quality of Life Questionnaire-Male version (SQoL-M) score in patients with erectile dysfunction was 29.3 ± 16.6 , while in patients without erectile dysfunction was 73.1 ± 21.5 ($P < 0.0001$) (Table 4).

Predictors of erectile dysfunction

Univariate analysis showed that Sexual Quality of Life Questionnaire-Male version (SQoL-M) ($P < 0.0001$), age ($P = 0.021$), Expanded Disability Status Scale score (EDSS) ($P = 0.001$), Beck Depression Inventory-II score (BDI-II) ($P = 0.001$), International Prostate Symptom Score (IPSS) ($P = 0.001$), Detrusor Underactivity (DU) ($P = 0.002$), Multiple Sclerosis-Secondary Progressive ($P = 0.002$) were significantly different according to the presence/absence of erectile dysfunction (Table 4). All these variable were included into a multiple logistic regression model, Sexual Quality of Life Questionnaire-Male (SQoL-M) version that showed multicollinearity problems was dropped from the model. The results indicated that Beck Depression Inventory-II score

Table 4. Comparison of Demographics, Depression, Neurological Impairment, International Prostate Symptom Score (IPSS) and the urodynamic findings according to the presence of erectile dysfunction (IIEF-ED <26)

	Erectile Dysfunction	No Erectile Dysfunction	p-value
No. of subjects*	75 (74.3)	26 (25.7)	–
Multiple sclerosis variants			
Relapsing remittant*	40 (53.3)	24 (92.4)	0.002
Primary progressive*	27 (36.0)	1 (3.8)	
Secondary progressive*	8 (10.7)	1 (3.8)	
Age (years)**	42.6 ±11.8	37.5 ±10.6	0.021
Expanded Disability Status Scale (EDSS) (score)**	4.2 ±1.9	2.5 ±1.5	0.001
Duration of disease (years)**	11.4 ±7.9	11.9 ±6.5	0.367
Testosterone (ng/dL) **	439.60±94.9	475.88±125.19	0.105
Diabetes*	7 (10%)	2 (8%)	0.880
Beck Depression Inventory-II (BDI-II) (score)**	23.0 ±14.3	5.0 ±3.5	0.001
BDI-II (0–13)*	18 (24.0)	25 (96.2)	0.0001
BDI-II (14–19)*	20 (26.7)	1 (3.8)	
BDI-II (20–29)*	14 (18.6)	0 (0)	
BDI-II (30–63)*	23 (30.7)	0 (0)	
International Prostate Symptom Score (IPSS) (score)**	17.1 ±8.4	6.8 ±6.5	0.001
IPSS (0–7)*	13 (17.3)	16 (61.6)	0.0001
IPSS (8–19)*	35 (46.7)	9 (34.6)	
IPSS (20–35)*	27 (36.0)	1 (3.8)	
Sexual Quality of Life (SQoL) (score)**	29.3 ±16.6	73.1 ±21.5	0.0001
Urodynamics findings			
Detrusor overactivity*	39 (52.9)	4 (15.4)	0.002
Detrusor underactivity*	14 (18.7)	6 (23.4)	
Detrusor sphincter dyssynergia*	8 (10.7)	2 (7.7)	
Normal*	14 (18.7)	14 (53.8)	

* number (%)

** mean ±SD

(BDI-II) (OR = 2.315, P = 0.011) and International Prostate Symptom Score (IPSS) (OR = 1.605, P = 0.043) were the only independent predictive factors of erectile dysfunction (ED) onset in these patients (Table 5).

DISCUSSION

Sexual dysfunctions (SDs) are common and are very distressing symptoms of multiple sclerosis (MS). It has been shown that the proportion of sexual dysfunctions (SDs) in multiple sclerosis (MS) is greater than in other neurological diseases, and almost five times higher than in the general population [16]. We provided our contribution to this under-investigated topic, analyzing the prevalence of sexual

dysfunctions (SDs) in multiple sclerosis (MS) male patients and their influence on the sexual quality of life. According to a review article by Schmidt et al. [4], sexual dysfunctions (SDs) are estimated to occur in between 64% and 91% of men with multiple sclerosis (MS), erectile dysfunction (ED) being the most commonly reported (19–62%). In our series the high prevalence of erectile dysfunction (ED) (74.2%) is consistent with these published data. It is generally known that multiple sclerosis substantially determines a generalized demyelination process that interrupts the continuity of the neural pathways and alters the neural function that is essential for normal erection function (EF) [2, 3]. The relationships of sexual dysfunctions (SDs) with age has previously been assessed by other authors with contrasting results [17–20]. In our study although age was a significant factor associated to erectile dysfunction (ED) in univariate analysis, it was not confirmed in multiple logistic regression analysis. This observation might be related to the small sample size of the study. In our study according to Mattson et al. [20] none of the multiple sclerosis (MS) patterns can be considered an independent predictive factor of sexual dysfunctions (SDs) and erectile dysfunction (ED), although in some studies more severe sexual dysfunctions (SDs) were attributed to the primary [21] and secondary progressive types [18], while sexual dysfunctions (SDs) were less frequently associated to the relapsing–remitting type [22].

Our study showed a significant relationship between depression and sexual disorders, with more than a half of the patients (57.4%) having fulfilled the Beck Depression Inventory-II (BDI-II) criteria for depression. Depression is the most common psychiatric disorder in multiple sclerosis (MS) patients and is more prevalent than other chronic diseases [23]. In multiple sclerosis (MS) patients, many factors can trigger depression such as localization of brain lesions, psychosocial factors, drugs used for treatment, and disabilities of patients [24]. The prevalence of depressive symptoms was high in men with multiple sclerosis and consistent with other studies. Marie et al. found depression to be the most common mental comorbidity, with a rate of 46% in a sample of 8983 multiple sclerosis patients [25]. A recent systematic review confirmed for the first time a bidirectional association between depression and sexual dysfunctions (SDs). Patients with multiple sclerosis (MS) who are depressed might not search for sexual intimacy, and, conversely, patients with multiple sclerosis related sexual dysfunctions might experience reactive depression [26]. Our study confirms the negative correlation of depressive symp-

Table 5. Results of binary logistic multiple regression analyses including potential risk factors for erectile dysfunction based on erectile function subdomain <26 points

Variables in the equation	OR	95% C.I. for OR		p-value
		Lower	Upper	
Age	0.977	0.867	1.101	0.704
Expanded Disability Status Scale (EDSS)	4.336	0.739	25.429	0.104
International Prostate Symptom Score (IPSS)	1.605	1.015	2.538	0.043
Beck Depression Inventory-II (BDI-II)	2.315	1.209	4.432	0.011
Multiple sclerosispattern (Relapsing-remitting)	1.000	Reference		
Multiple sclerosispattern (Secondary progressive)	1.736	0.007	422.141	0.844
Multiple sclerosispattern (Primary progressive)	0.379	0.002	59.979	0.707
Urodynamics (normal)	1.000	Reference		
Urodynamics (Detrusor Overactivity)	0.071	0.000	10.248	0.297
Urodynamics (Detrusor Sphincter Dyssynergia)	0.012	0.000	3.828	0.133
Urodynamics (Detrusor Underactivity)	0.000	0.000	14.914	0.112

toms with erectile function (EF) and Sexual Quality of Life Questionnaire in men with multiple sclerosis. Data from our neurology department suggest that depression is often missed by neurologists or under treated with medication when detected. At the time of the study, only 20% of patients was being treated with antidepressants and this data are consistent although lower compared to other studies [27]. Moreover, the treatment of depression itself may result in iatrogenic erectile dysfunction (ED), as dopamine is known to enhance libido and sexual arousal while serotonin has a clear inhibitory effect on sexuality [26]. Thus, in an effort to avoid confounding factors, we excluded from the analysis patients that were being treated for depression.

Neurological disability has been associated with sexual dysfunctions (SDs), in particular in women affected by multiple sclerosis (MS) [17, 21, 28], while less data have been provided in male patients. In our study although Expanded Disability Status Scale (EDSS) score was a significant factor in univariate analysis, its effect was diminished in multivariate analysis.

High percentage (75%) of multiple sclerosis (MS) patients experience lower urinary tract symptoms (LUTS) [19]. In our series, the prevalence of lower urinary tract symptoms (LUTS) was 61.3% and this observation is consistent with Araki et al. [29]. In particular, the International Prostate Symptom Score (IPSS) was an independent predictive factor of erectile dysfunction (ED) onset with a risk

of erectile dysfunction that increases by 1.6 times for each International Prostate Symptom Score (IPSS) point increment (OR = 1.60; P = 0.043). An association between sphincteric dysfunction and sexual dysfunctions (SDs) was documented in some studies [20, 30], independently of age and others comorbidities [31], probably due to sharing the same autonomic segment [30]. Lower urinary tract symptoms is sustained by a complex alteration of the neurological control of the detrusor-sphincter function, resulting in Detrusor Overactivity (DO) (34–91%), Detrusor Underactivity (DU) (0–40%) and /or Detrusor Sphincter Dyssynergia (DSD) (5–83%) [32]. We found that none of this three urodynamic findings were independently correlated with erectile dysfunction. There has been a large body of evidence linking lower urinary tract symptoms (LUTS) with depression. Some studies have documented not only a significant impact of lower urinary tract symptoms (LUTS) on the psychosocial wellbeing, but also showed a strong negative effect of depression on perception, development and prolongation of lower urinary tract symptoms [33]. However, we did not evaluate such interactions.

In other studies, it has been demonstrated that multiple sclerosis (MS) patients presented low testosterone levels in the blood [34, 35], so we decided to exclude men affected by hypogonadism. In the present study, erectile dysfunction (ED) patients presented a mean lower testosterone levels compared to non-erectile dysfunction (ED) patients (Table 4), but this difference is not significant.

Our findings confirm the idea of a multifactorial etiology of erectile dysfunction (ED) in multiple sclerosis (MS). Therefore, in clinical practice, each patient needs an individualized evaluation of factors that could contribute to his sexual problems, but unfortunately the majority of physicians may lack the adequate training to discuss it with their patients [36]. Particularly diagnosing sexual dysfunctions (SDs) in multiple sclerosis (MS) men seems to be increasingly important, as effective methods to treat these conditions are available. In fact, Chao et al. found that intracavernosal therapy with trimix could be effective for neurogenic erectile dysfunction (ED), including in multiple sclerosis (MS) patients [37]. More recently, studies on the promising efficacy of sildenafil and tadalafil have been published [38, 39]. An appropriate discussion with patients on these issues could produce some clear benefits: (1) the knowledge that erectile dysfunction is a common problem in multiple sclerosis and in other chronic illnesses can alleviate the feeling of stigma in the patient; (2) talking openly of sexual problems can be helpful for the patients;

(3) the doctor – patient relationship can be reinforced; and (4) the patient will be more likely to be referred to or independently seek professional help that could result in improvement in his sexual functioning [40].

This study had some limitations. It was a cross-sectional study and we obtained our sample from an outpatient clinic. Our study only provided an association between erectile dysfunction (ED), Beck Depression Inventory-II (BDI-II) score, International Prostate Symptom Score (IPSS) and did not establish a cause-result relationship. Therefore, further large-scale randomized clinical trials are required to determine potentially predictive factors of erectile dysfunction (ED) in multiple sclerosis (MS) male patients. In addition, data analysis was performed using as a dependent variable only erectile dysfunction (ED) and a sub-analysis of other sexual dysfunction (SD) has not been performed due to the lack of recognized cut-off. Thus, the results from this study must be interpreted with caution. Finally, we know that some of the medications that patients received in the course of their treatment could have

affected sexual functions. However, we did not evaluate such interactions.

CONCLUSIONS

Erectile dysfunction (ED) is highly prevalent, but commonly overlooked in multiple sclerosis (MS) patients and has a significant impact on their sexual quality of life (SQo-L). The prevalence of erectile dysfunction (ED) is much higher in men with multiple sclerosis (MS) when compared with the general population. Depressive and urinary symptoms are very common and have a great impact on patients' sexual function and their sexual quality of life (SQo-L). Hence, in order to provide an effective approach and management for erectile dysfunction (ED), all the mentioned symptoms and clinical variables should be kept in mind. More focus on erectile dysfunction (ED) and the use of appropriate screening tools in clinical practice with multiple sclerosis (MS) patients are recommended.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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