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Sexual Dysfunction in Patients with Multiple Sclerosis from Argentina: What are the Differences Between Women and Men?

Edgar Carnero Contentti[1] · **Juan Pablo Pettinicchi**[1] · **Alejandro Caride**[1] · **Pablo A. López**[1]

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Abstract
Sexual dysfunction (SD) has been reported in people with multiple sclerosis (pwMS). However, SD is commonly underdiagnosed in clinical practice. We aimed to assess SD frequency (primary, secondary and tertiary) in pwMS in both genders and to investigate possible associated risk factors. A cross-sectional study (pwMS = 202 and healthy volunteers (HV) = 200, matched for sex and age) based on self-administered questionnaires such as Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ-19), The Hospital Anxiety and Depression Scale, Fatigue Severity Scale and self-reported disability was performed in pwMS and controls. In addition, the Female Sexual Function Index (FSFI) and the International Index of Erectile Function (IIEF5-ED) were obtained in women and men, respectively. Factors associated with SD were analyzed in a multivariate model. The frequency of primary, secondary and tertiary SD in pwMS was 81%, 87.3% and 75.2%, respectively. Both erectile dysfunction (ED) and female SD were significantly higher in pwMS than in HV (89% vs. 26% and 54% vs. 21%, respectively). Only 45 (22.2%) pwMS had addressed sexual problems with their neurologist and 33 (16.3%) pwMS received counselling about their sexual problems. Higher MSISQ-19 total scores were significantly correlated with fatigue, anxiety, depression, self-reported disability and lower FSFI and IIEF5-ED scores. Furthermore, female SD was independently associated with primary SD, but no associated factors were found in male pwMS (multivariate analysis). In conclusion, SD is extremely common in pwMS from Argentina. The previously mentioned physical and neuropsychological factors have a negative impact on sexual function.

Keywords Multiple sclerosis · Sexual dysfunction · Neuropsychological factors · Physical factors · Latin America

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✉ Edgar Carnero Contentti
junior.carnero@hotmail.com; ecarnerocontentti@hospitalaleman.com

[1] Neuroimmunology Unit, Department of Neuroscience, Hospital Alemán, Av Pueyrredón 1640, C1118AAT Buenos Aires, Argentina

Introduction

Multiple sclerosis (MS) is a chronic and degenerative disease that mainly affects young adults (between 18 and 50 years) who may be sexually active, constituting an important cause not only of physical disability in several countries worldwide, but also of residual symptoms such as sexual dysfunction (SD) [1–5]. Symptoms of MS are varied and sensory as well as autonomic disorders, which affect quality of life (QoL) during follow-up, may also be reported [1–6]. In this line, different organic and neuropsychiatric conditions may cause SD [6–9]. According to the World Health Organization (WHO) [10], sexual health is a state of physical, emotional, mental and social well-being in relation to sexuality as a part of general health. SD is often unreported, underestimated, underdiagnosed, and therefore, undertreated [6–9].

Different prevalence of SD in people with MS (pwMS) has been reported in men (50–73%) and in women (45–70%) of Europe and North America, depending on the methods used [5, 9]. Zorzon et al. [5] reported that the incidence of SD was higher in pwMS (73%) than in general population (13%) or patients with other chronic diseases (39%). Moreover, men with MS have commonly been associated with decreased libido, erectile dysfunction (ED) and ejaculatory dysfunction compared to people with a different chronic disease or controls, while women with MS were more likely to report changes in vaginal sensation and anorgasmia than the other cohorts [5–9]. So far, data from Latin America have not been published yet. Although the etiology of SD in pwMS is still not entirely understood [11], SD related to MS has previously been grouped and conceptualized into three broad categories [9, 12–14] (developed to evaluate the perceived impact of MS symptoms on sexual health from a multidimensional perspective [14]) as follows: (1) *Primary SD* may be derived from MS-related neurologic (brain or spinal cord lesions) changes that directly impair sexual feelings or responses. This group includes changes in genital sensation, decreased libido, anorgasmia, decreased vaginal lubrication, ED among other symptoms; (2) *Secondary SD* plays a significant role in limiting sexual expression due to fatigue and physical limitations. This group includes chronic fatigue, spasticity, weakness, tremor and ataxia, sphincter dysfunction, pain, cognitive disorders among other symptoms; (3) *Tertiary SD* results from psychological, emotional, social and cultural aspects of MS that can interfere with sexual feelings and sexual response such as depression, alteration of body image or negative self-esteem.

A variety of factors, including MS activity and disability, fatigue, depression and anxiety may contribute to SD in pwMS [15]. Nevertheless, this problem is little discussed and treated by both patients and clinicians during the medical consultation [9]. Therefore, diagnosis, counseling and treatment of sexual problems should have a comprehensive, psychosexual and medical approach at initial stages (after MS diagnosis), since SD symptoms may begin even when there is a mild disability [9, 16].

We aimed to assess frequency of SD (primary, secondary and tertiary) in pwMS from Argentina and to evaluate their relationship with depression, anxiety, fatigue and disability. In addition, we evaluated possible associated factors for primary SD in women and men with MS, as well as female SD and male ED.

Methods

We conducted a cross-sectional study (n = 402) based on self-assessed questionnaires such as Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ-19) [14], The Hospital Anxiety and Depression Scale (HADS) [17, 18], Fatigue Severity Scale (FSS)

[19] and self-reported disability [20, 21] to evaluate SD and possible associated risk factors in pwMS and controls. In addition, we included the Female Sexual Function Index questionnaire (FSFI) [22, 23] to evaluate female SD and the International Index of Erectile Function (IIEF5-ED) [24, 25] to investigate ED in men. This study was carried out in an Argentinean population from February to April 2018. PwMS were invited to participate voluntarily in the web-based survey across the ALCEM (Asociación de Lucha Contra la Esclerosis Múltiple) or EMA (Esclerosis Múltiple Argentina) members and those who agreed were included in the study. This survey was developed independently of any ALCEM or EMA input. An online portal was designed to answer the survey and for data collection. People with remitting-relapsing MS (RRMS, n = 167) as well as primary progressive MS (PPMS, n = 17) or secondary progressive MS (SPMS, n = 18) forms previously diagnosed by current validated diagnosis criteria [3, 4] and 200 healthy volunteers (HV) matched for sex and age were included. HV were recruited between healthcare personnel, administrative personnel, or friends, none of them affected by MS. Demographic data, MS duration, age at survey, current employment status, marital status, sexual orientation, sexual performance, questions about sexual life (importance/relevance given to their sexual life, currently or previously to MS diagnosis) and discussion about sexual problems with physicians, friends or partners and use of either symptomatic or MS medication were evaluated. People with RRMS (100%) and SPMS (85%) were under treatment with disease-modifying drugs (DMTs). Exclusion criteria were: relapse 3 months prior to participating in the survey, age ≥ 65 years and self-reported disability ≥ 7 (unable to walk > 5 m even with aid [restricted to wheelchair]).

SD related to MS was defined as primary, secondary or tertiary according to the MSISQ-19 [14], based on 19 questions rating how various MS symptoms had interfered with his/her sexual activity (intimacy and satisfaction) over the previous 6 months; scoring: 1 = never, 2 = almost never, 3 = occasionally, 4 = almost always, 5 = always. Answers always or almost always (scored 4 or 5) were considered positive for SD. MSISQ-19 was adapted and translated in Spanish language by Reyes-Velarde [26], but it has not yet been validated in Argentina.

The FSFI questionnaire consisted of questions concerning the following aspects of sexuality: desire, arousal, orgasm, lubrication, satisfaction and pain; and scores ≤ 26.5 indicated female SD (only if all questions were answered) [22, 23]. Given that ED is the most frequent symptom in men with MS (it is also crucial for clinicians to identify and effectively manage ED in order to improve the QoL), we evaluated the IIEF5-ED scale. With respect to the IIEF5-ED questionnaire, scores ≤ 21 indicated ED [24, 25]. SD was quantified by a sexual functioning scale according to Szasz et al. [27]. Depression (HADS-D) and anxiety (HADS-A) were evaluated by the HADS [17]. HADS was validated for scores ≥ 8 in pwMS (score ≥ 8 indicates probable anxiety or depression in general population) on both subscales to indicate anxiety or depression [18]. Fatigue was evaluated by the FSS [19] and scores ≥ 45 indicated the presence of fatigue. Disability was measured by self-reported disability according to Kobelt et al. [20, 21]. Expanded Disability Status Scale (EDSS) is the most frequently used evaluation instrument in clinical practice to describe severity of neurological sequelae in pwMS [28]. Patients-reported disability scores range from 0 (without disability) to 9 (confined to bed), derived from the original EDSS [28] based on a standard neurological examination of different functional systems. Self-reported disability according to Kobelt et al. [21] was developed for clinical studies and a strong correlation (95% of feasibility and reliability) with a neurologist-scored EDSS [28] was observed, as previously published [20].

This study was approved by the Ethics Committee of the Hospital Alemán. All participants signed an electronic informed consent form before data collection.

Statistical Analysis

Results are presented as percentages, means with standard deviations (± SD) and median values. Categorical variables were assessed using Chi squared or Fisher's exact tests and Student T or Mann–Whitney U Tests were performed to compare continuous variables between groups, as appropriate. Kolmogorov–Smirnov test was used to evaluate normal distribution of variables. We applied multivariate logistic regression analysis to assess the impact of different risk factors potentially associated either to ED, female SD or primary SD in pwMS. All variables were included in multivariate regression if univariate analysis showed at least a trend ($p < 0.20$) towards association with ED, female SD or primary SD in pwMS. Based on the estimated prevalence of MS in Argentina [29], the total study sample size needed for a statistical power of 80% and a 95% confidence interval (CI) was calculated to be of at least 148 individuals for each study group (HV and MS). For all analyzes, p-values < 0.05 were considered statistically significant. Data analysis was performed using Graph-Pad Prism 6 software.

Results

Overall Population

General characteristics of the studied population (MS vs. HV) are summarized in Table 1. In addition, general features of sexual life in pwMS and HV are shown in Table 2. The frequency of primary, secondary and tertiary SD in pwMS was 81%, 87.3% and 75.2%, respectively. These frequencies were similar in the three forms of MS (RRMS: 80.5%, 86.6% and 80%, PPMS: 86.6%, 80% and 80% and SPMS: 80%, 73.3% and 80%, respectively). In this line, we did not find significant differences in the frequency of SD between men and women with MS, as illustrated in Table 3. Nevertheless, female pwMS with primary SD experienced a lower sexual desire than men (53.3% vs. 21.4%, $p = 0.0004$).

Female Population

One hundred and thirty-seven women with MS and 138 HV were included. As shown in Table 4, female SD was observed in 54.2% of pwMS compared to 21.8% in controls ($p < 0.0001$). Interestingly, 14.6% of women with MS had not had sexual activity during the last month compared to 6.5% in the control group ($p = 0.03$). When we evaluated the subdomains of the FSFI scale (lower score, higher female SD), we observed that female pwMS scored significantly lower in all the subscales compared to controls (from $p = 0.03$ to $p < 0.0001$). As shown in supplementary Table S1, MSISQ-19 total score as well as primary, secondary and tertiary SD correlated significantly (Spearman's correlation) with a higher score of self-reported disability, anxiety, depression, fatigue and lower FSFI total score, present female SD (FSFI ≤ 26.55) as well as a lower score on sub-scales for desire, excitement, lubrication, orgasm, satisfaction and pain. However, when we evaluated the different domains of the FSFI scale we found that higher self-reported disability score

Table 1 Comparison of demographics and clinical features among people with multiple sclerosis (MS) and controls (HV)

General characteristics	Female-MS	Male-MS	*p*-value	Overall MS	HV	*p*-value
N no	137	65		202	200	
Mean age at interview y, (±SD)	49.1 (±10.2)	42.6 (±9.7)	0.49	39.4 (±8.7)	38.2 (±8.3)	0.14
Female no (%)	–	–		137 (67.1)	138 (68.5)	0.83
MS duration, y mean (±SD)	7.5 (±0.5)	7.5 (±0.6)	0.97	7.5 (5.7)	–	
MS course						
RRMS	112 (81.7)	55 (84.6)	0.69	167 (81.8)	–	
PPMS	9 (6.7)	9 (13.8)	0.11	18 (8.8)	–	
SPMS	18 (13.4)	1 (1.5)	0.008	19 (9.1)		
Self-reported disability means (±SD)	2.4 (±0.1)	3.2 (±0.3)	0.007	2.6 (±2.1)	–	
Last relapse n (%)						
Clinically isolated syndrome	14 (10.2)	9 (13.8)	0.48	25 (13.2)	–	
<6 months	19 (13.8)	7 (10.7)	0.65	26 (12.7)	–	
6–12 months	26 (18.9)	13 (20.1)	0.85	39 (19.1)	–	
≥13 months	78 (56.9)	36 (55.3)	0.87	114 (55.8)	–	
Education (%)						
≤12 years	70 (51.7)	52 (80.7)	<0.0001	122 (60.7)	178 (89)	<0.0001
>12 years	67 (49.3)	13 (19.3)		80 (39.3)	22 (11)	
Employment n (%)						
Employed (full-time)	54 (39.4)	35 (53.8)	0.06	89 (44.6)	159 (79.5)	<0.0001
Employed (part-time)	37 (27.0)	10 (15.8)	0.07	47 (23.0)	28 (14)	0.02
Unemployed (looking for a job)	6 (4.3)	10 (15.3)	0.01	16 (7.8)	5 (2.5)	0.02
Unemployed (not looking for a job)	6 (4.3)	7 (10.7)	0.12	13 (6.3)	4 (2)	0.04
Housewife	34 (24.8)	3 (4.6)	0.0003	37 (16.5)	4 (2)	<0.0001
Marital status, n (%)						
Single	52 (37.9)	27 (41.5)	0.64	79 (39.2)	97 (48.5)	0.07
Married	66 (48.1)	30 (46.1)	0.88	96 (47.5)	85 (42.5)	0.31
Divorced	16 (11.6)	8 (12.3)	1	24 (11.7)	18 (9.0)	0.41

Table 1 (continued)

General characteristics	Female-MS	Male-MS	*p*-value	Overall MS	HV	*p*-value
Widowed	3 (2.1)	0	0.55	3 (1.6)	0	0.24
Hospital anxiety and depression scale						
Depression						
≥8	54 (39.4)	24 (36.4)	0.75	78 (38.2)	19 (9.5)	<0.0001
Mean (±SD)	6.5 (±0.3)	6.1 (±0.3)	0.45	6.4 (±3.8)	3.1 (±3.0)	<0.0001
Anxiety						
≥8	85 (62.0)	35 (53.8)	0.28	120 (58.8)	66 (33)	<0.0001
Mean (±SD)	9.1 (±0.3)	7.4 (±0.4)	0.006	8.6 (±4.1)	6.4 (±3.4)	<0.0001
Fatigue severity scale						
≥45	73 (53.2)	32 (49.2)	0.65	105 (51.4)	31 (15.5)	<0.0001
Mean (±SD)	43.01 (±1.2)	39.47 (±2.2)	0.14	42.03 (±15.3)	28.15 (±12.6)	<0.0001
Use of medications no (%)						
Antidepressants[a]	58 (42.3)	7 (10.7)	<0.0001	65 (31.8)	–	
Amantadine/modafinil (for fatigue)	25 (18.2)	12 (18.4)	1	37 (18.1)	–	
Antispasticity medications[b]	7 (5.1)	10 (15.3)	0.02	17 (8.3)	–	
Anticonvulsant[c]	8 (5.8)	5 (7.6)	0.75	13 (6.3)	–	
Opiates/marijuana	5 (3.6)	3 (4.6)	0.71	8 (3.9)	–	
None	34 (24.8)	28 (43.0)	0.01	62 (31.6)		
Use of medications no (%)						
Injectables	52 (37.9)	17 (26.1)	0.11	69 (34.8)	–	
Oral						
Fingolimod	46 (33.5)	12 (18.4)	0.03	58 (28.4)	–	
Teriflunomide	11 (8.3)	6 (9.2)	0.78	17 (8.3)	–	
Dimetil fumarate	12 (8.6)	4 (6.1)	0.78	16 (7.8)	–	

Table 1 (continued)

General characteristics	Female-MS	Male-MS	*p*-value	Overall MS	HV	*p*-value
Intravenous						
Natalizumab	7 (5.1)	6 (9.2)	0.35	13 (6.3)	–	
Alentuzumab	1 (0.7)	1 (1.5)	0.54	2 (0.9)	–	
Ocrelizumab	3 (2.1)	3 (4.6)	0.38	6 (2.6)	–	
None	5 (3.6)	16 (24.6)	<0.0001	21 (10.2)	–	

[a]Amitriptiline and SSRIs

[b]Diazepam, tizanidine and baclofen

[c]Carbamazepine, pregabaline and gabapentin

Table 2 General characteristics of sexual life in people with MS and controls

General characteristics	Female-MS (n = 137)	Male-MS (n = 65)	*p*-value	Overall MS (n = 202)	HV (n = 200)	*p*-value
Importance of sexual problems in present life n (%)						
Great	63 (45.9)	38 (58.4)	0.13	101 (50.4)	143 (71.5)	< 0.0001
Little	70 (51.0)	22 (33.8)	0.02	92 (45.1)	48 (24)	< 0.0001
Uncertain	4 (2.9)	5 (7.6)	0.15	9 (4.4)	9 (4.5)	1
Sexual orientation n (%)						
Heterosexual	136 (99.1)	61 (93.8)	0.03	197 (97.5)	185 (92.5)	0.02
Gay/lesbian	1 (0.7)	3 (4.6)	0.09	4 (1.9)	11 (5.5)	0.06
Bisexual	0	1 (1.5)	0.32	1 (0.4)	4 (2.0)	0.21
Present sexual life compared to before MS disease n (%)						
More active	11 (8.0)	3 (4.6)	0.55	14 (6.8)	–	
Less active	74 (54.0)	41 (63.0)	0.28	115 (56.3)	–	
Unchanged	41 (29.9)	19 (29.2)	1	60 (29.4)	–	
Uncertain	11 (8.0)	2 (3.0)	0.23	13 (7.3)	–	
Masturbation n (%)						
More active	11 (8.0)	5 (7.6)	1	16 (7.8)	–	
Less active	35 (25.5)	28 (43.0)	0.01	63 (30.8)	–	
Unchanged	27 (19.7)	21 (32.3)	0.05	48 (24.0)	–	
No masturbation	60 (43.8)	10 (15.3)	< 0.0001	70 (34.8)	–	
Uncertain	4 (2.9)	1 (1.5)	1	5 (2.4)	–	
Discussion about sexual problems with physicians on the last year						
Yes n (%)	18 (13.1)	27 (41.5)	< 0.0001	45 (22.0)	35 (17.5)	0.26
Discussion about sexual problems with friends on the last year						
Yes n (%)	70 (51.0)	15 (23.0)	0.0002	85 (42.2)	163 (81.5)	< 0.0001
Discussion about sexual problems with partners on the last year						
Yes n (%)	37 (27.0)	5 (7.6)	0.001	42 (20.9)	81 (40.5)	0.002
Counselling about sexual issues on the last year						
Yes n (%)	12 (8.7)	18 (27.6)	0.001	30 (15.4)	26 (13.0)	0.39

Table 2 (continued)

General characteristics	Female-MS (n = 137)	Male-MS (n = 65)	*p*-value	Overall MS (n = 202)	HV (n = 200)	*p*-value
Sexual frequency						
At least 1 every 7 days	65 (47.4)	20 (30.7)	0.03	85 (41.6)	120 (60)	0.0002
1 every 15 days	29 (21.1)	12 (18.4)	0.71	41 (20.0)	36 (18.0)	0.61
Once a month	7 (5.1)	10 (15.3)	0.02	17 (8.8)	21 (10.5)	0.68
Once on the last 6 months	11 (8.0)	7 (10.7)	0.59	18 (9.3)	9 (4.5)	0.07
Once on the last 12 months	5 (3.6)	6 (9.2)	0.18	11 (5.3)	3 (1.5)	0.053
Lack of sexual activity on the last 12 months	18 (13.1)	10 (15.3)	0.66	28 (14.7)	11 (5.5)	0.002

Table 3 Comparison among female and male MS patients and SD according to MSISQ-19

Characteristics of patients with MS and SD (scored 4–5)[a]	Female	Male	*p*-value	Total
N no	119	55		174[b]
Primary sexual dysfunction n (%)[a]	99 (83.1)	42 (77.7)	0.30	141 (81.0)
Less feeling or numbness in my genitals	27 (27.2)	10 (23.8)	0.83	37 (26.2)
Lack of sexual interest or desire	53 (53.5)	9 (21.4)	0.0004	62 (43.9)
Less intense or pleasurable orgasms or climaxes	42 (42.4)	22 (52.3)	0.35	64 (45.4)
Takes too long to orgasm or climax	55 (55.5)	20 (47.6)	0.46	65 (46.0)
Inadequate lubrication (women)/erection (men)	44 (44.4)	27 (64.2)	0.04	71 (50.3)
Secondary sexual dysfunction n (%)[a]	103 (86.5)	49 (89.0)	0.80	152 (87.3)
Muscle tightness or spasms in my arms, legs, or body	33 (32.0)	27 (55.1)	0.007	60 (39.4)
Bladder or urinary symptoms	32 (31.0)	16 (32.6)	0.85	48 (31.5)
Bowel symptoms	6 (5.8)	5 (10.2)	0.33	11 (7.2)
Feelings of dependency because of MS	28 (27.1)	11 (22.4)	0.69	39 (26.5)
Tremors or shaking in my hands or body	40 (38.8)	17 (34.6)	0.72	57 (33.5)
Pain, burning, or discomfort in my body	50 (48.5)	20 (40.8)	0.38	70 (46.0)
Problems moving my body the way I want during Sx activity	35 (33.9)	18 (36.7)	0.85	53 (34.8)
Problems with concentration, memory, or thinking	49 (47.5)	17 (34.6)	0.16	66 (43.4)
Exacerbation or significant worsening of my MS	41 (39.8)	13 (26.5)	0.14	54 (35.5)
Tertiary sexual dysfunction n (%)[a]	88 (73.9)	43 (78.1)	0.57	131 (75.2)
Feeling that my body is less attractive	51 (57.9)	22 (51.1)	0.56	73 (55.7)
Feeling less masculine or feminine due to MS	35 (39.7)	15 (34.8)	0.70	50 (38.1)
Fear of being rejected sexually because of MS	22 (25.0)	15 (34.9)	0.30	37 (28.2)
Worries about sexually satisfying my partner	56 (63.6)	30 (69.7)	0.43	86 (65.6)
Feeling less confident about my sexuality due to MS	37 (42.0)	16 (37.2)	0.70	53 (40.4)

[a]Primary SD items = 12, 16, 17, 18, 19; secondary SD items = 1, 2, 3, 4, 5, 6, 8, 10, 11; tertiary SD items = 7, 9, 13, 14, 15 according to MSISQ-19

[b]Lack of sexual activity during the last year is an exclusion criterion for MSISQ-19 use[15]

correlated significantly with lower general FSFI score, excitation, orgasm, and pain (supplementary Table S2). The rest of the variables evaluated were not significant.

On the other hand, multivariate analysis indicated that primary and secondary SD were independently associated with FSFI, and female SD was independently associated with primary SD, as illustrated in Tables 5 and 6.

Male Population

A total of 65 men with MS and 63 controls were included. As shown in Table 4, ED was associated with male pwMS compared to controls (89% vs. 26.2%, $p < 0.0001$). As illustrated in supplementary Table S3, we observed that male pwMS with higher MSISQ-19 total score as well as primary, secondary and tertiary SD correlated significantly with higher self-reported disability score, anxiety, depression, fatigue and lower IIEF5-ED total score and presence of ED (FSFI ≤ 21). Likewise, men with MS and anxiety, depression, fatigue, lower IIEF5-ED total score and presence of ED were correlated significantly with primary SD. The rest of the correlations among clinical aspects and MSISQ-19 in men with MS are summarized in supplementary Table S3.

Table 4 Female SD and erectile dysfunction occurrence of people with MS and controls (HV)

	Female		*p*-value	Male		*p*-value
	MS	HV		HV	MS	
N no	137	138		65	63	
Mean age at survey y, (±SD)	38.8 (±9.2)	39.1 (±9.0)	0.76	40.0 (±8.0)	36.8 (±6.0)	0.01
MS duration, y m (±SD)	7.51 (±5.9)	–		7.09 (±5.1)	–	
Education no (%) > 12 años	90 (65.2)	118 (86.1)	< 0.0001	28 (50.1)	60 (95.2)	< 0.0001
Self-reported disability, m (±SD)	2.4 (±1.9)	–		3.2 (±2.3)	–	
Female Sexual Function Index (FSFI)						
DS present, FSFI ≤ 26.55 (%)	64 (54.2)	28 (21.88)	< 0.0001			
Lack of sexual activity during the past month (%)*	20 (14.6)	9 (6.5)	0.03			
Total score, m (±SD)	23.7 (±9.1)	28.9 (±7.7)	< 0.0001			
Domains						
Desire, m (±SD)	3.6 (±1.4)	4.2 (±1.0)	< 0.0001			
Arousal, m (±SD)	3.8 (±1.7)	4.7 (±1.5)	< 0.0001			
Lubrication, m (±SD)	4.0 (±1.5)	4.9 (±1.9)	< 0.0001			
Orgasm, m (±SD)	3.8 (±1.8)	5.0 (±1.5)	< 0.0001			
Satisfaction, m (±SD)	4.1 (±1.6)	4.9 (±1.5)	< 0.0001			
Pain, m (±SD)	4.2 (±2.0)	5.0 (±1.6)	0.001			
The International Index of Erectile Function (IIEF5-ED)						
Total score, m (±SD)				16.1 (±4.7)	22.7 (±2.6)	< 0.0001
Erectil dysfunction (ED)						
ED present (IIEF5-ED ≤ 21)				49 (89.0)	16 (26.2)	< 0.0001
Mild (IIEF5-ED 17-21)				21 (42.8)	13 (81.2)	0.003
Mild to moderate (IIEF5-ED 12-16)				19 (38.7)	3 (18.7)	< 0.0001
Moderate (IIEF5-ED 8-11)				7 (12.7)	0 (0)	0.33
Severe (IIEF5-ED 0-7)				2 (3.6)	0 (0)	1

On the other hand, factors independently associated with primary SD or ED in men with MS were not found in multivariate analysis, as shown in Tables 5 and 6.

Discussion

This is the first study conducted in Argentina that determined the frequency of SD in a cohort of pwMS and tried to confirm whether there are factors associated with the development of this problem, which negatively affects QoL in both genders.

In the present study, we observed that SD was highly common in pwMS. Similar frequencies of SD between both genders were also found. However, we observed that decreased libido (symptom of primary SD [9–14, 30]) was more frequent in women than in men (53.5% vs. 21.4%, $p < 0.001$). In contrast, a study observed that male with MS reported symptoms of SD more commonly than female with MS ($p = 0.002$) [5]. Moreover,

Table 5 Multivariate analysis via logistic regression including potential variables associated to both erectile dysfunction (IIEF5-ED ≤ 21) and female SD (FSFI ≤ 26.55) in people with MS

Potential variables associated to erectile dysfunction and female SD	Erectile dysfunction (IIEF5-ED ≤ 21)				Female SD (FSFI ≤ 26.55)			
	Univariate model OR (95%CI)	*p*-value	Multivariate model* OR (95%CI)	*p*-value	Univariate model OR (95%CI)	*p*-value	Multivariate model* OR (95%CI)	*p*-value
Age at survey y, m (± SD)	1.06 (0.95–1.18)	0.28			1.02 (0.98–1.07)	0.22		
MS duration y, m (± SD)	1.13 (0.90–1.42)	0.26			1.02 (0.96–1.10)	0.38		
Self-reported disability m (± SD)	1.75 (1.03–2.96)	0.03	2.04 (0.84–4.95)	0.11	1.16 (0.94–1.41)	0.14	0.95 (0.72–1.24)	0.72
HAD scale								
Depression								
Total score	2.0 (1.10–3.61)	0.02	1.76 (0.84–3.66)	0.12	1.07 (0.97–1.18)	0.17	0.87 (0.73–1.02)	0.10
Anxiety								
Total score	1.12 (0.84–1.50)	0.40			1.04 (0.95–1.14)	0.29		
Fatigue severity scale								
Total score	1.06 (1.0–1.13)	0.03	0.88 (0.71–1.08)	0.24	1.02 (0.99–1.05)	0.07	0.97 (0.93–1.01)	0.24
MSISQ-19 total score	1.19 (1.04–1.35)	0.007			1.13 (1.08–1.19)	< 0.0001		
MSISQ-19 primary SD subscale score								
Total score	1.26 (0.99–1.92)	0.056	0.97 (0.60–1.56)	0.92	1.45 (1.26–1.67)	< 0.0001	1.46 (1.24–1.74)	< 0.0001
MSISQ-19 secondary SD subscale score								
Total score	1.37 (1.07–1.77)	0.01	1.48 (0.91–2.39)	0.10	1.13 (1.06–1.21)	0.0002	1.13 (1.02–1.24)	< 0.01
MSISQ-19 tertiary SD subscale score								
Total score	1.42 (1.06–1.90)	0.01	1.37 (0.70–2.66)	0.35	1.17 (1.07–1.27)	0.0002	1.11 (0.98–1.25)	0.09

*The variables included on multivariate regression were selected from the results of univariate analysis using $p < 0.20$

Table 6 Results of logistic regression (multivariate) analysis including potential variables associated to primary sexual dysfunction in people with MS for both genders

Potential variables associated to primary SD	Female-MS				Male-MS			
	Univariate model OR (95%CI)	*p*-value	Multivariate model * OR (95%CI)	*p*-value	Univariate model OR (95%CI)	*p*-value	Multivariate model * OR (95%CI)	*p*-value
Age at survey y, m (±SD)	1.05 (0.99–1.11)	0.08	1.04 (0.96–1.11)	0.27	1.00 (0.92–1.08)	0.92		
MS duration y, m (±SD)	1.02 (0.93–1.11)	0.64			0.96 (0.86–1.08)	0.58		
Self-reported disability m (±SD)	1.26 (0.94–1.69)	0.11	1.01 (0.71–1.43)	0.93	0.99 (0.76–1.29)	0.96		
HAD scale								
Depression								
Total score	1.15 (0.99–1.33)	0.05	1.04 (0.96–1.11)	0.20	1.30 (1.03–1.63)	0.02	1.19 (0.87–1.63)	0.25
Anxiety								
Total score	1.17 (1.02–1.33)	0.01	1.14 (0.94–1.36)	0.15	1.18 (0.72–9.34)	0.14	1.08 (0.82–1.41)	0.56
Fatigue severity scale								
Total score	1.03 (1.00–1.07)	0.02	1.02 (0.98–1.07)	0.23	1.03 (0.99–1.07)	0.12	0.99 (0.94–1.05)	0.89
FSFI (total score)	0.90 (0.83–0.97)	0.008	0.91 (0.84–0.98)	0.01	–	–	–	–
Desire	0.38 (0.23–0.62)	0.0001			–	–	–	–
Arousal	0.68 (0.49–0.94)	0.002			–	–	–	–
Lubrication	0.68 (0.50–0.93)	0.01			–	–	–	–
Orgasm	0.60 (0.41–0.86)	0.006			–	–	–	–
Satisfaction	0.73 (0.54–0.98)	0.03			–	–	–	–
Pain	0.74 (0.55–0.99)	0.004			–	–	–	–
Erectil dysfunction (total score)	–	–	–	–	0.82 (0.69–0.97)	0.02	0.89 (0.74–1.08)	0.52
Mild (IIEF5-ED 17–21)	–	–	–	–	0.28 (0.07–1.02)	0.054		
Mild to noderate (IIEF5-ED 12–16)	–	–	–	–	3.74 (0.73–19.0)	0.11		
Moderate (IIEF5-ED 8–11)	–	–	–	–	2.00 (0.21–18.2)	0.53		
Severe (IIEF5-ED 0–7)	–	–	–	–	264,625 (0.00–1^{12})	0.97		

*The variables included on multivariate regression were selected from the results of univariate analysis using $p < 0.20$. Primary SD may be derived from MS-related neurologic (brain or spinal cord lesions) changes that directly impair sexual feelings or responses. This group includes changes in genital sensation, decreased libido, anorgasmia, decreased vaginal lubrication, ED, etc.[9]

a review including 455 women and 326 men with MS reported that the prevalence of SD in women was 33–75% and in men 47–75% [31]. Likewise, other reports informed an estimated prevalence of SD of 40–80% in women and 50–90% in men [32, 33], in line with our results. In this cohort, we found that 30% of pwMS had a poor sexual performance compared to 11.5% on the HV group. Consistent with other studies [5, 34], participants reported that their sexual life and sexual problems have little importance for them and neither these issues are communicated nor discussed with their families, friends or clinicians (Table 2). A recently published study evaluated factors associated with patients' sex-related communications with their MS clinicians (n = 73), and the authors observed that more than half of pwMS had SD, but only one-third of them addressed their sexual concerns with their clinicians [15, 34]. Thus, the frequency of communication about sexual concerns was associated with satisfaction and clinician variables, whereas self-efficacy for these interactions was associated with emotional health variables [34]. These results suggest that we should consider interventions to increase the confidence and communication of pwMS on their sexuality. Some differences in relation to data from Europe are probably due to cultural reasons, and even to talk about sexual life or sexuality may be a "taboo" for some people in Argentina.

The normal male sexual response cycle may be divided into five inter-related events: libido, erection, ejaculation, orgasm and detumescence, while the female sexual response cycle has four main elements: libido, arousal, orgasm and satisfaction [35–37]. In addition, emotional (neuropsychological aspects) and partner components are intimately related to his or her satisfaction's sexuality and therefore should also be assessed during the diagnosis and treatment of SD [15]. ED was the most frequent symptom (23–91%) reported in men with MS [38, 39], in line with our results (89%). ED in pwMS was associated with both spinal cord and pons lesions as the most relevant causes [40, 41]. In this cohort, patients with ED correlated significantly with primary, secondary and tertiary SD. When we evaluated the symptoms of primary SD, we also observed that men with MS had a less intense orgasm (52%) with a longer time to reach climax (48%) and a decreased libido (22%). Other studies reported that ED (50–75%), ejaculatory dysfunction and/or orgasmic dysfunction (50%), decreased libido (39%) and anorgasmia (37%) were the most frequent symptoms in men with MS [9, 41–44]. In addition, we also found a significant association between ED and higher disability score, depression, fatigue and SD. However, we did not find risk factors associated with ED in our multivariate model. ED is classified as a primary SD symptom, but only secondary and tertiary SD were associated with ED (univariate analysis). These results are probably due to a high association with fatigue, anxiety and depression that led to a significant impact on secondary and tertiary SD and overall sexuality [9, 15–17, 45]. A recently published study (n = 101) found that depression was the only predictor of ED in pwMS (OR = 2.3, $p = 0.01$) [46]. Most cross-sectional studies observed significant associations between SD and these neuropsychological aspects, but a few cross-sectional studies were published in relation to these specific topics [15]. Different cohorts observed that both women and men with MS had a significant association between depression and distinct subscales of SD (e.g. erectile and ejaculatory function, orgasm, desire) in men, and in women according to the FSFI questionnaire [16, 47, 48]. Nevertheless, this was not reproduced by Dupont et al. [49]. who did not find a clear association between depression and SD (n = 116) in pwMS. In other study [50] (n = 538) that assessed SD related to depression, fatigue and physical function in pwMS, a direct association was not observed. In addition to mood disorders, a few studies assessed the relation between SD and anxiety [15]. Only three cross-sectional studies observed an association between SD and anxiety in both genders [16, 47, 51]. In this context, the side effects of

antidepressants (ADs) on late orgasm or loss of response to orgasm should also be emphasized [52]. Approximately, 30–60% of patients treated with selective serotonin reuptake inhibitors may experience some type of SD [53]. In this cohort, 31.8% of pwMS used ADs, but we did not find a significant correlation between SD and ADs use in men with MS. Nevertheless, consistent with reports from Europe [54], ADs use correlated significantly with SD in women with MS, so it should be considered in clinical practice.

On the other hand, we observed an increased prevalence of female SD compared to a Polish cohort (54.2% vs. 27.7%) [54]. We also found that a low educational level, high disability, anxiety, depression, fatigue, low FSFI (total and the subdomains) score correlated significantly with SD in women with MS, consistent with prior reports [53–55]. In addition, women with a higher disability score correlated with a lower FSFI total score, arousal, orgasm and pain. In contrast, Hutler et al. [56] found that a lower disability score was correlated with negative sexual changes such as decreased lubrication or orgasmic capacity and sensations in a cohort of women with MS (n = 47). Likewise, Zorzon et al. [5] found that anorgasmia (37.1%), decreased vaginal lubrication (35.7%) and decreased libido (31.4%) were the most frequent symptoms in women with MS. Interestingly, we found that primary (OR = 1.46) and secondary SD (OR = 1.13) were significantly associated with female SD. In addition, female SD was the only risk factor significantly associated with primary SD.

A recently published review reported that two studies found a significant association between SD and fatigue [15]. One study found a significant impact only in female pwMS [57], whereas another author [16] observed this association in both genders. No differences between SD and fatigue in women with MS (n = 70) and controls (n = 72) were identified by Gumus et al. [58]. Another longitudinal study [59] reported that pwMS (n = 93) had increased symptoms of SD in both genders during a whole observation at period of 6 years. Higher follow-up, age, physical disability level, fatigue and depression were independently associated with deterioration of sexual functioning in pwMS. In the present study, satisfaction was the only FSFI subdomain score correlated with fatigue, in line with an European study [54].

We acknowledge several limitations in our study. One potential limitation may be that the data obtained for the diagnosis of SD and neuropsychological aspects were from self-reported questionnaires that were not subsequently confirmed by direct evaluation of a specialist; although there is growing evidence that patient-reported outcomes have an important role in measuring the effects of various symptoms such as SD and neuropsychological aspects. These questionnaires help to alleviate the common barriers that are reported around sexual issues [47]. However, these studies may have self-report biases (individuals may have felt more comfortable scoring their problems on their own). Conversely, many clinicians choose not to evaluate SD for a variety of reasons (e.g., visit time limits, perceiving patient discomfort, and perceiving lack of competence in the area) [15]. Moreover, variables such as cognitive disorders, QoL, brain and spinal MRI (number and location of lesions to evaluate association with anatomical topography), and urological and gynecological examinations (anatomical, hormonal and sphincter dysfunction) were not evaluated and it is a strong limitation. On the other hand, although this sample is representative, the results may not demonstrate the whole pwMS of Argentina or Latin America. Despite these limitations, the results of this study have important clinical implications and data from Latin American populations is needed in order to be compared with data from European and North American populations, who would be expected to present differences in comparison with patients in these other regions.

To summarize, SD should be evaluated in pwMS in everyday clinical practice. We confirmed that SD is extremely common in pwMS in both genders. Physical and neuropsychological factors previously mentioned have a negative impact on sexual function and therefore should be screened, diagnosed and treated in order to improve patients' QoL. In addition, more studies are needed to evaluate the relative effects of current DMTs on SD and QoL.

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Compliance with Ethical Standards

Conflict of interest ECC has received professional travel accommodation stipends from Merck-Serono, TEVA, Genzyme, Biogen-Idec and Novartis. ECC has also received reimbursement for developing educational presentations from Merck, Genzyme, Biogen-Idec, Roche and Novartis as well as Grants for research from Novartis, Bayer and Merck. JPP has received professional travel accommodation stipends from Biogen-Idec, TEVA and Bayer as well as Grants for research from Biogen-Idec. AC has received honoraria for developing educational presentations as well as Grants for research from Genzyme and Biogen-Idec. PAA has received professional travel accommodation stipends from Merck-Serono, TEVA, Genzyme, Biogen-Idec and Roche. He has also received honoraria for developing educational presentations from Merck-Serono, Biogen-Idec and Roche as well as Grants for research from Novartis.

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