

Effects of Onabotulinum Toxin A Intradetrusor Injections on Urinary Symptoms and Sexual Life in Women Affected by Multiple Sclerosis: A Prospective Controlled Study

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Abstract

Background: Voiding and sexual dysfunction in Multiple Sclerosis represent the most devastating dimensions of the disease. Pharmacological treatment of voiding dysfunction could improve sexual life in patients affected by the disease. We investigated the effects of Onabotulinum toxin A intradetrusor injections on urinary symptoms and sexual dysfunction, and on the psychological status of women affected by Multiple Sclerosis with refractory overactive bladder.

Methods: 41 patients underwent neurologic and urologic clinical evaluations and were administered the Female Sexual Function Index, the Incontinence-Quality of Life questionnaire, the Hamilton Anxiety Rating Scale and the Hamilton Depression Rating Scale, before and six months after Onabotulinum toxin A intradetrusor injection; 21 continent females affected by the disease acted as controls.

Results: At baseline, all patients were incontinent and 35/41 was sexually active, with low Female Sexual Function Index scores. Mild depression and anxiety were detected in all cases with a reduced quality of life. Six months after treatment, overactive bladder symptoms improved significantly in all patients. Arousal, lubrication, orgasm-related problems and desire alterations markedly improved, together with an improvement in anxiety, depression and quality of life. Scores of Female Sexual Function Index, Incontinence-Quality of Life questionnaire, Hamilton Anxiety Rating Scale and Hamilton Depression Rating Scale remained unchanged in controls.

Conclusion: Onabotulinum toxin A intradetrusor injections not only control overactive bladder symptoms in women affected by multiple sclerosis, but also significantly improve sexual life.

Keywords: Multiple sclerosis; Sexual dysfunction; Voiding dysfunction; Onabotulinum toxin A

Introduction

Multiple Sclerosis (MS) is a relatively frequent, inflammatory autoimmune illness of the central nervous system affecting about 2.5 million people around the world, representing the most common cause of neurological disability among young adults [1]. Among MS patients, 40 to 80% of women and 50 to 90% of men have sexual dysfunction (SD) [2]. In these patients, SD may represent the most devastating dimension of the disease, as it can damage the physical ability to touch, move and communicate during sexual intercourse and can affect urinary and bowel continence during sexual activity [3]. Nevertheless, sexual problems in MS patient often remain under-diagnosed and under-treated. MS-related SD can be divided into three main categories: primary SD, due to MS-related neurological deficits that directly affect sexual response; secondary SD, due to MS-related physical impairments and symptoms that indirectly affect sexual response (i.e., fatigue, spasticity and contractures, bowel and bladder dysfunction, cognitive impairment) and tertiary SD, due to the psychological, social and cultural concerns of having a chronic

disabling disease [2]. Lack of sexual interest and decreased libido, together with a reduced orgasmic ability represent the most frequent sexual alterations in women affected by the disease. Erectile dysfunction and lack of sexual desire are more often observed in MS men [4].

It is well known that a high proportion of MS patients during the course of the disease might also be affected by bladder dysfunction [4]. Recent studies have shown a relationship between SD and OAB in both sexes [5,6], thus it is possible to hypothesize that treatments for OAB symptoms could also improve patients' sexual life [7]. Indeed, in a previous study we demonstrated in a very short term follow up an improvement in MS patients' sexual life after Onabotulinum toxin A (Onabot/A) intradetrusor injections performed to improve OAB and urinary incontinence [8].

Herein we report, with a longer follow up, the results of a prospective study on the effects of Onabot/A intradetrusor treatment on urinary and sexual function in a group of women affected by MS. Changes in sexual function and psychological performance between patients and controls have also been investigated.

Patients and Methods

41 MS women, who were followed up and treated at the MS centre of the Departments of Neurology and Urology at the University Hospital, were screened for participation in the study. The inclusion criteria were: female gender, age ≥ 18 years and a definitive diagnosis of MS. Included patients had to be affected by OAB symptoms and detrusor overactivity (DO) refractory to conventional anti-muscarinics, willing to undergo an intravesical treatment with Onabot/A injections. Exclusion criteria were: male gender, OAB symptoms owing to bladder outlet obstruction due to high-grade urogenital prolapse, recurrent urinary tract infections, cognitive impairment (as assessed by a Mini Mental State Examination score >28) [9], pregnancy, anticoagulant therapy (in view of Onabot/A injections), psychoactive agents modulating bladder function (venlafaxine, amitriptyline) or other drugs believed to interfere with bladder function, and a relapse in the 6 months preceding enrolment. 21 MS continent females with similar clinical neurological features acted as controls. The experimental procedures were carried out in accordance with the Declaration of Helsinki and approved by the institutional review board (CEAS No. 2319/14). Patients gave their informed written consent. They were also informed about the possible need for intermittent catheterization after Onabot/A treatment.

Clinical evaluation

Information was collected regarding age, disease symptom onset, comorbidities and concomitant medications, as well as history of depression and, if present, how it had been treated. Schooling, civil status and work were investigated in all the patients. The diagnosis of MS had been made according to the modified McDonald criteria [10]. All the patients displayed periventricular, juxtacortical, infratentorial and spinal lesions at the MRI scans. The neurological evaluation was performed using the Expanded Disability Status Scale (EDSS). The EDSS is the most frequently used scale for the assessment and quantification of symptom severity and physical functioning of patients with MS. The final score may range from 0 to 10, where 0 stands for "normal functioning without any neurological deficits" and 10 represents "death due to MS" [11].

Urologic assessment

Patients underwent history, physical examination, serum chemistry, urinalyses and culture and urodynamics. A 3 day voiding diary was used to record daytime and night-time urinary frequencies and daily episodes of urinary incontinence. On urodynamics, the first volume and maximum pressure of uninhibited detrusor contractions (UDC-first volume and UDC-pmax) and maximum cystometric capacity (MCC) were recorded. Oral anticholinergics were discontinued one month before commencing the study. Patients maintained their disease-modifying and skeletal muscle antispastic therapy throughout the study.

Sexual functioning, quality of life and psychological status

For the assessment of female sexual function, the Female Sexual Function Index (FSFI) was used [12]. The FSFI is a widely used, multidimensional, self-report instrument consisting of 19-items covering six domains: sexual desire (2 items), arousal (4 items), lubrication (4 items), orgasm (3 items), satisfaction (3 items) and pain

(3 items). A score ≤ 26.55 is classified as female sexual dysfunction. The International-Quality of Life (I-QoL) questionnaire was used to investigate patients' QoL [13]. In order to assess the presence of anxiety and depression in these patients, the Hamilton Anxiety Scale (HAM-A) and the Hamilton Depression Scale (HAM-D) were used [14,15]. HAM-A is a standardized instrument with 14 items, each of which is evaluated on a 5-point scale ("absent," "light," "moderate," "severe" and "very severe"). The resulting score can vary from 0 to 56, though a total score of 18 is considered pathological. Factors of somatic anxiety (items 7-13) and psychic anxiety (items 1-6 and 14) and the total score were investigated. HAM-D consists of 21 graduated items, some to 3 levels of severity (0-2), others to 4 (0-3) and yet others to 5 (0-4). The severity cut off is as follows: ≥ 25 severe depression, 18-24 moderate depression, 8-17 light depression, ≤ 7 absence of depression. The factors most often used are: anxiety/somatization, weight, cognitive disorders, diurnal variations, deceleration, slowing down and sleeping disorders. Patients in the control group did not complain of urinary symptoms. They were asked to complete the FSFI and the I-QoL questionnaires, and the HAM-A and HAM-D scales at baseline and at the six month follow up.

Onabot/A detrusor injection

After the preliminary clinical and urodynamic assessment patients underwent Onabot/A 100 U (Botox; Allergan Inc., Irvine CA, USA) diluted in 10 ml NaCl, injected into the detrusor muscle at 20 sites, under cystoscopic control [16]. Patients were followed up for at least 6 months. At this time point, they repeated the clinical and urodynamic investigations, QoL assessment, anxiety, depression and sexual function evaluation using the above-mentioned questionnaires. The primary outcomes of the study were changes from baseline in sexual function and QoL after treatment. Secondary outcomes were changes from baseline in urinary symptoms, urodynamic dysfunction, anxiety and depression after Onabot/A intradetrusor injections.

Statistical analysis

SPSS software (SPSS Inc., USA) was used for the statistical analyses. Wilcoxon matched paired test was used to analyze any change in urodynamic values and the questionnaire scores following the Onabot/A injections. Spearman's correlation coefficient was used to evaluate possible correlations between changes in urodynamic and questionnaire values at the baseline and 6-month follow up assessment. Holm's correction for multiple comparisons was applied to disclose false significance. All values are expressed as mean \pm SD. $p \leq 0.05$ indicates statistical significance.

Results

All the 41 patients were naïve to Onabot/A treatment and all completed the study. No local or systemic side effects were noted in any patient either during or after Onabot/A intravesical treatment. Four patients presented with urinary tract infection during the observation period. Patients' demographics, disease duration, MS clinical features and EDSS are shown in Table 1. The 21 patients in the control group showed clinical characteristics similar to those of treated patients, in terms of age, disease duration, MS clinical features and neurological disability. They all completed the questionnaires at the beginning of the study; 19 of them completed the questionnaires at the 6-mos follow up.

	No. of patients	Age (years) (mean ± SD)	Disease duration (years) (mean ± SD)	RR-MS	PP-MS	SP-MS	EDSS (mean ± SD)
				No. of pt.s (mean ± SD)	No. of pt.s (mean ± SD)	No. of pts (mean ± SD)	
Patients	41	44.5 ± 13.7	16.2 ± 4.5	24	4	5	4.5 ± 2.9
Control patients	21	43.2 ± 10.6	15.2 ± 3.4	17	4	4	3.4 ± 1.8

Table 1: Patients' demographics.

Clinical and urodynamic results

At baseline, all the patients complained of increased daytime and night-time urinary frequencies and all were affected by daily urinary incontinence episodes. Five patients presented with coital incontinence (Table 2). On urodynamics, all the patients suffered from DO, with detrusor external sphincter dyssynergia in 16 cases (Table 3). Five patients performed intermittent self-catheterization. At the 6-month follow-up after the Onabot/A injection, OAB symptoms and daily urinary incontinence episodes decreased significantly (Table 2). DO disappear in 25 of the 41 patients (60.9%) who also achieved a complete urinary continence. In the remaining 16 patients, some episodes of urinary incontinence (2.3 ± 2.6 episodes/day in the 3 day voiding diary) persisted at the 6-month follow-up. Urodynamic parameters at 6 months follow up are showed in Table 3. Post-void

residual urine increased and six additional patients needed to perform intermittent catheterization.

Clinical parameters	Baseline	6-mos follow up	p
Daytime urinary frequency	11.4 ± 4.4	6.9 ± 2.4	<0.001*
Night-time urinary frequency	3.6 ± 1.7	1.8 ± 0.2	<0.001*
Urge urinary incontinence episodes/day	4.2 ± 2.6	1.03 ± 0.7*	<0.001*

Table 2: Clinical results in 41 females affected by OAB symptoms due to Multiple Sclerosis before and 6 mos after Onabotulinum toxin A intraderusor injections.

	Baseline	6-month follow-up	p value
UDC-first volume (ml)	132.8 ± 98.7	291.4 ± 131.6	<0.001
UDC p-max (cm H2O)	41.5 ± 23.9	22.3 ± 12.7	<0.01
Maximum cystometric capacity (ml)	232.7 ± 106.4	370 ± 113.6	<0.0001
pDetQmax (cm H2O)	32.9 ± 9.7	20.7 ± 8.1	<0.001
Qmax (ml)	22.7 ± 11.6	14.9 ± 7.9	<0.001
Detrusor external sphincter dyssynergia (No. of patients)	16	16	-
Post-void residual volume (ml)	54 ± 52.3	94.3 ± 78.4	<0.02

Table 3: Urodynamic parameters in 41 females affected by multiple sclerosis before and 6 months after intraderusor injections of Onabotulinum toxin A.

Sexual and psychological functioning and quality of life

At baseline, 35/41 patients were sexually active, with low scores in all the FSFI domains. The domains impaired most were arousal and lubrication, followed by orgasm-related problems and desire alterations (Table 4). In these patients, no significant relationship was found between age, disease duration, EDSS and impaired sexual function. After Onabot/A treatment, a significant improvement was observed in all the considered domains; only "pain" remained substantially unchanged (Table 4). FSFI domains appeared to be significantly improved in continent patients. In addition, a significant amelioration in FSFI scores was detected in patients without DO as compared to those with persisting DO (mean ± SD FSFI: 4.4 ± 0.9 vs. 2.7 ± 3.08, respectively; p<0.01). At baseline, I-QoL scores revealed a reduced QoL in all patients (Table 5). Moreover, the evaluation of anxiety at baseline, as assessed by the HAM-A scale, yielded a mean ±

SD total score of 17.66 ± 15.31 which is very close to that of pathological anxiety. In these patients both psychic and somatic anxieties were affected (Table 6). All the considered domains improved at the 6-month follow-up. Particularly, patients who became continent presented with a higher improvement in HAM-A total scores as compared to incontinent patients (Table 5). Particularly, scores of question 1 related to anxiety, question 6 related to depressed mood, question 7 related to somatoform symptoms and question 12 related to genito-urinary symptoms were improved. With regard to the baseline HAM-D evaluation, the mean ± SD total score (17.8 ± 9.3) revealed a mild depression, with all the domains being affected. The HAM-D scores also improved after Onabot/A treatment (Table 5). The mean ± SD of HAM-D total score was better in continent patients as compared to that in patients with persisting incontinence, although it did not reach statistical significance (Table 5). Worth of noting, QoL

significantly improved in both continent and incontinent patients at the 6-month follow-up (Table 5).

Control group. In control MS women, the FSFI scores indicated a good sexual function both at baseline and at 6 mos follow up (Table 6).

In these patients, the I-QoL, HAM-A and HAM-D scores were significantly better than those observed in treated patients and remained unchanged along the whole follow up.

FSFI domains	Baseline	6 mos follow up		6 mos follow up
	35 patients	All patients	Continent pt.s (20)	Incontinent pt.s (13)
	(mean ± SD)	(mean ± SD)	(mean ± SD)	(mean ± SD)
Desire	3.3 ± 1.1	4.3 ± 1.2*	4.7 ± 1.2*	3.3 ± 0.6
Arousal	2.9 ± 2.1	4.1 ± 1.3**	4.8 ± 0.8**	2.6 ± 0.7
Lubrication	2.9 ± 2.4	4.4 ± 1.5*	5.2 ± 0.4*	2.6 ± 1.5
Orgasm	2.7 ± 2.5	3.4 ± 2.4*	3.5 ± 2.7*	3.0 ± 2.8
Satisfaction	3.8 ± 2.0	4.2 ± 2.0 §	5.1 ± 1.3§	2.9 ± 0.7
Pain	3.7 ± 2.7	3.9 ± 2.6	4.0 ± 2.6	3.9 ± 2.2

Table 4: FSFI scores in 41 females affected by OAB symptoms due to multiple sclerosis before and 6 months after Onabotulinum toxin A intradetrusor injections. Comparison between continent and incontinent patients after treatment (*: p<0.005; **: p<0.0005; §: p<0.004).

	All patients	Controls	All patients	Controls	p	Continent patients	Incontinent patients
	(mean ± SD)	(mean ± SD)	(mean ± SD)	(mean ± SD)		(mean ± SD)	(mean ± SD)
	Baseline	Baseline	6 mos f-up	6 mos f-up		6 mos f-up	6 mos f-up
I-QoL scores	45.39 ± 16.31	76.5 ± 15.9	69.9 ± 20.2	74.1 ± 14.2		70.5 ± 17.2	68.4 ± 22.3
HAM-A total score	17.66 ± 15.31	9.02 ± 7.2	10.3 ± 9.2	8.79 ± 7.5	0.001	9.8 ± 4.6	10.8 ± 9.5
HAM-D total score	17.8 ± 9.3	8.6 ± 8.1	10.21 ± 8.3	9.02 ± 5.8	0.0002	9.73 ± 6.4	10.03 ± 7.7

Table 5: Changes in I-QoL, HAM-A and HAM-D scores before and 6 months after Onabotulinum toxin A intradetrusor injections in 41 females affected by OAB symptoms; comparison with 21 untreated MS female patients.

FSFI domains	Baseline	6 mos follow up	p level
	21	19	
Control patients (untreated)	(mean ± SD)	(mean ± SD)	
Desire	4.4 ± 2.1	4.5 ± 1.8	ns
Arousal	5.1 ± 2.4	4.9 ± 2.2	ns
Lubrication	5.7 ± 1.9	5.5 ± 2.0	ns
Orgasm	5.0 ± 2.2	4.8 ± 1.7	ns
Satisfaction	5.2 ± 1.7	5.0 ± 1.3	ns
Pain	4.1 ± 1.1	4.0 ± 1.4	ns

Table 6: FSFI scores in 21 untreated multiple sclerosis female patients (controls) at baseline and at 6 month follow up.

Discussion

The results of the present study show that in all the female MS patients who have been treated with intradetrusor Onabot/A

injections, the neurotoxin not only induced a significant improvement in urinary symptoms, urodynamic dysfunction and QoL, but also in sexual functioning and psychological performance. Only one previous study demonstrated, in a very short term follow up, an improvement in MS patients' sexual life after Onabot/A treatment [8]. In that study, however, a control group represented by continent patients was not included, and an adequate comparison on changes in sexual function and psychological performance between control patients and cases was not performed.

It has been retained that SD in MS patients may have a multifactorial nature, which could be partly related to depressive symptoms, as no strict correlations between MS duration, lesional burden, disability and SD have been found [17]. This observation is in keeping with our results. Unfortunately, very few studies investigated the relationships between urinary symptoms and sexual functioning in MS patients. In a cross-sectional study the determinants of sexual impairment in MS patients have been investigated [18]. The Authors observed that bladder dysfunction in MS might be a significant proxy of SD in men and women. These results indicate a relationship between urinary disturbances and SD, although the absence of urological symptoms does not exclude the presence of sexual problems. Conversely, a number of studies in patients with idiopathic OAB

showed that treatments designed to control OAB symptoms also lead to an improvement in sexual life [19-24]. In one recent review, 91% of 152 females affected by OAB symptoms and other dysfunction presented with a FSFI total score <26 [25]. Most of MS patients in the present study showed a low disability and a non-progressive disease course, and all were affected by SD. Reduced sexual desire and arousal as well as altered vaginal lubrication and orgasm-related problems were observed in these patients, together with OAB and urge urinary incontinence. The baseline assessment also revealed a mild degree of depression and anxiety and a poor QoL. Six months after the neurotoxin injection, all the FSFI domains improved significantly in continent patients. Particularly, desire, arousal and lubrication better improved. Simultaneously, patients reported a significant improvement in QoL and in their psychological status. We believe that the beneficial effect on SD in our patients may be attributed to an indirect consequence of the overall urologic clinical improvement on sexual function at both psychological and emotional levels. The positive effect obtained also on anxiety and depression suggests that urinary symptoms have a negative impact on patient's psychological performance. In the present study, the observation that MRI did not reveal any lesion in the spinal cord at the S2-S4 level and the finding that Onabot/A improved sexual function further suggest that sexual problems in these patients were not due to structural lesions in the pathways mediating sexual function, but were secondary to bladder and emotional features. Although in the present study we could not account for any placebo effect due to the administration of a new medication, adding a control group of continent patients allowed us to strengthen the obtained results. The lack of a significant improvement in sexual function in patients who improved but did not reach a complete urinary continence furthermore made more significant these results.

Conclusion

Urinary disturbances and sexual problems affect QoL and psychological status in patients with a low disabling MS. Onabot/A intradetrusorial injections not only control urinary symptoms in MS patients, but also induce a significant improvement in their sexual life.

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Authors contribution

Protocol/project development: Giannantoni Antonella and Proietti Silvia.

Data collection or management: Gubbiotti Marlena, Rossi de Vermandois Jacopo A.

Data analysis: Salvini Eleonora.

Manuscript writing/editing: Giannantoni A, Di Stasi SM.

Manuscript writing/editing and language editing: Mearini E.

Conflict of Interest

Giannantoni Antonella is a scientific consultant for Allergan SpA, Irvine CA. Gubbiotti Marilena, Rossi de Vermandois Jacopo A, Salvini Eleonora, Proietti Silvia, Di Stasi SM and Ettore Mearini declare no conflict of interest.

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