



# Association Between the Neurogenic Bladder Symptom Score and Urodynamic Examination in Multiple Sclerosis Patients With Lower Urinary Tract Dysfunction

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**Purpose:** To determine the relationship between the neurogenic bladder symptoms score (NBSS) and urodynamic examination in patients affected by multiple sclerosis (MS) and related lower urinary tract dysfunction (LUTD).

**Methods:** We recruited 122 consecutive patients with MS in remission and LUTD from January 2011 to September 2013 who underwent their first urodynamic examination. Neurological impairment was assessed using the Expanded Disability Status Scale (EDSS) and bladder symptoms were studied with the NBSS.

**Results:** Median NBSS was 20.0 (interquartile range, 12.75–31.0). Neurogenic detrusor overactivity (NDO) was discovered in 69 patients (56.6%). The concordance between patients with NDO and maximum detrusor pressure during involuntary detrusor contraction (PdetmaxIDC)  $\geq 20.0$  cm H<sub>2</sub>O was 0.89 ( $\kappa$ -Cohen;  $P < 0.05$ ). Patients with EDSS scores of  $\geq 4.5$  had a greater NBSS (25.41 vs. 20.19,  $P < 0.05$ ), NBSS-incontinence (8.73 vs. 4.71,  $P < 0.05$ ), NBSS-consequence (4.51 vs. 3.13,  $P < 0.05$ ) and NBSS-quality of life (2.14 vs. 1.65,  $P < 0.05$ ). The NBSS was not associated with PdetmaxIDC  $\geq 20$  cm H<sub>2</sub>O ( $P = 0.77$ ) but with maximum cystometric capacity  $< 212$  mL (odds ratio, 0.95;  $P < 0.05$ ).

**Conclusions:** The NBSS cannot give adequate information the way urodynamic studies can, in patients with MS and LUTD.

**Keywords:** Multiple Sclerosis; Lower Urinary Tract Dysfunction; Urodynamics; Urinary Bladder, Overactive; Neurogenic Bladder Symptom Score

- **Research Ethics:** This study was conducted in accordance with the regulatory standards of Good Clinical Practice and the Declaration of Helsinki (1996). The study was approved by the Institutional Research Ethics Committee of the University of Catania.
- **Conflict of Interest:** No potential conflict of interest relevant to this article was reported.

## INTRODUCTION

Multiple sclerosis (MS) is a chronic neurological disorder characterized by disseminated demyelination of nerve fibers of the brain and spinal cord [1-3]. Lower urinary tract dysfunction

(LUTD) could be a common disorder in these patients. Approximately 75% of all MS patients will develop voiding dysfunction and LUTD during the course of the disease [4]. In fact, LUTD is secondary to several important changes in neurological control of the detrusor-sphincter function resulting in

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neurogenic detrusor overactivity (NDO), neurogenic detrusor underactivity (NDU) and/or detrusor-sphincter dyssynergia (DSD) [5].

Unfortunately, the global assessment of urological symptoms is very difficult to investigate and some patient-reported measures (PROMs) are not conclusive. Other PROMs have been cross-validated, such as the incontinence quality of life scale for spinal cord injury. However, because the items were not developed for patients with neurogenic bladder dysfunction, they may be incomplete or inappropriate.

With regards to valid PROMs, Welk et al. [6] have demonstrated that the neurogenic bladder symptom score (NBSS) could be used to evaluate neurogenic bladder dysfunction-related symptoms.

The aim of this study was to determine the relationship between the NBSS and urodynamic examination in a cohort of MS patients with LUTD and to investigate its relationship with other PROMs of sexual dysfunction and disability.

## MATERIALS AND METHODS

We enrolled 122 consecutive patients with MS in remission and LUTD who underwent their first urodynamic examination from January 2011 to September 2013. Criteria for inclusion were: diagnosis of MS according to the McDonald Revised criteria [7]. Indication for urodynamic examination was defined as following: frequency  $\geq 8$  micturition per day or  $\geq 1$  during the night, urgency and/or urinary incontinence. Exclusion criteria has been reported in a previous study [8,9] and included: history of hysterectomy, vaginal surgery, or stress urinary incontinence; history of antidepressant, anticonvulsant, and anxiolytic drug use; nitrite-positive urinary tract infection; previous surgical treatment for benign prostatic obstruction; or severe benign prostatic obstruction.

Baseline examination included urinalysis, ultrasonography of the upper urinary tract, postvoid ultrasonography, and a full urodynamic study according to the 2002 International Continence Society (ICS) [10]. NDO, DSD, or NDU were defined according to the 2002 ICS Standardization Report on terminology of lower urinary tract function [11-13].

Depression and anxiety were evaluated by the Hamilton Depression Scale (HAM-D) [14] and the Hamilton Anxiety Scale (HAM-A) [15], while neurological impairment was assessed using the Expanded Disability Status Scale (EDSS) [16]. Sexual function was assessed with the Italian Female Sexual Function

Index (FSFI) [17] and the International Index of Erectile Function-15 (IIEF-15) [18]. Sexual function was categorized by the summary score and estimated as “good” (60–75), “fair” (44–59), and “poor” (5–43) [19].

Bladder symptoms were investigated with the NBSS as reported by Welk et al. [6]. The NBSS contains 22 questions, which focus on incontinence, storage and voiding symptoms, and urinary complications associated with neurogenic bladder dysfunction. Two additional questions address bladder management and urinary specific QoL. Items use an adjectival scale with 4 or 5 ordinal responses. An adjectival scale is a symptom scale, which attempts to capture objective signs and symptoms, in contrast to a QoL instrument, which measures subjective responses related to social, emotional, and physical functioning.

The original English version of the NBSS was translated into Italian by two native Italian-speaking, independent, professional translators. Several physicians and a native English-speaking translator examined this “translation-back-translation” process, until all participants agreed that the original and back translated versions were equivalent. All participants provided written informed consent before enrollment and the study was conducted in accordance with the regulatory standards of Good Clinical Practice and the Declaration of Helsinki (1996). The study was approved by the Institutional Research Ethics Committee of the University of Catania.

Continuous variables, presented as mean  $\pm$  standard deviations and differences between groups, were tested by Student t-test or Mann-Whitney test, according to their normal or non-normal distribution, respectively (normality of variables’ distribution was tested by Kolmogorov-Smirnov test). The qualitative data was tested using the chi-square test or Fisher exact test, as appropriate.

The reliability of the NBSS was calculated using Cronbach alpha test. Multivariate logistic regression analyses were carried out to identify variables for predicting detrusor overactivity (DO), maximum cystometric capacity (MCC), and bladder compliance. The cutoff of maximum detrusor pressure during involuntary detrusor contraction ( $P_{detmaxIDC}$ )  $\geq 20$  cm H<sub>2</sub>O, MCC  $< 212$  mL, NBSS  $\geq 20$  and bladder compliance  $\leq 3$  (mL/cm H<sub>2</sub>O) were based on the median of the cohort and included in the multivariate logistic regression analysis. The cutoff of EDSS  $\geq 4.5$  was based on a previous report [20]. Predictive accuracy of the model was assessed in terms of the area under the receiver operating characteristics curve value, incorporating all independent predictors. One thousand bootstrap resamples

were used to reduce over fit bias. Bootstrapping is a general approach to statistical inference based on building a sampling distribution for a statistic by resampling from the data at hand.

All tests were completed using IBM SPSS Statistics ver. 19.0 (IBM Co., Armonk, NY, USA) and for all statistical comparisons significance was considered as  $P < 0.05$ .

## RESULTS

Table 1 lists the baseline characteristics of patients included. Seventy-two subjects (59.0%) were female and 50 (41.0%) were male. Median age was 46.0 years (interquartile range [IQR], 41.5–53.5), median NBSS was 20.0 (IQR, 12.75–31.0). NDO was diagnosed in 69 patients (56.6%) after urodynamic test. The  $\kappa$ -Cohen test demonstrated a concordance of 0.89 between patients with NDO and  $P_{detmax} \geq 20.0$  cm H<sub>2</sub>O ( $P < 0.05$ ).

The Cronbach alpha coefficients for total and domain score were sufficiently high, ranging from 0.89 to 0.95 for the total sample. The test-retest procedure revealed that the concordance correlation coefficient was very high for both NBSS total score (Pearson  $P = 0.91$ ) and for each domain (Pearson  $P$  always  $> 0.90$ ).

Ninety-five (77.9%) had bladder management with spontaneous voiding while 27 (22.1%) used clean intermittent catheterization. Patients with  $EDSS \geq 4.5$  (more serious impairment) had greater (worse) mean NBSS (25.41 vs. 20.19,  $P < 0.05$ ), NBSS-incontinence (8.73 vs. 4.71,  $P < 0.05$ ), NBSS-consequence (4.51 vs. 3.13,  $P < 0.05$ ) and NBSS-QoL (2.14 vs. 1.65,  $P < 0.05$ ).

Table 2 lists the clinical and urodynamic findings according to NBSS cutoff. Patients with  $NBSS \geq 20$  had reduced values of MCC (131.0 mL vs. 212 mL,  $P < 0.01$ ).

A positive association was found between the NBSS and EDSS, HAM-A, and HAM-D and negative between NBSS and IIEF-15 and FSFI (Table 3). Significant associations were found on linear regression analysis between NBSS-QoL and MCC ( $r = -0.18$ ,  $P < 0.05$ ) and compliance ( $r = -0.19$ ,  $P < 0.05$ ) but not with  $P_{detmaxIDC}$  ( $r = 0.15$ ,  $P = 0.09$ ). The NBSS was not demonstrated to independently predict  $P_{detmaxIDC} \geq 20$  cm H<sub>2</sub>O ( $P = 0.77$ ) while it weakly predicted  $MCC < 212$  mL (odds ratio [OR], 0.95; 95% confidence interval, 0.91–0.99;  $P < 0.05$ ).

The accuracy of the base model for predicting  $P_{detmaxIDC} \geq 20$  cm H<sub>2</sub>O was 0.80 without significant gaining in accuracy when adding the NBSS. On the contrary, the base models for predicting  $MCC < 212$  mL were improved from 0.77 to 0.79 when adding NBSS, but without statistical significance.

**Table 1.** Demographics, neurological, sexual, and urodynamic characteristics of patients included in the study

Characteristic	Value
Sex	
Male	50 (41.0)
Female	72 (59.0)
Multiple sclerosis variants	
Relapsing remittent	85 (69.7)
Primary progressive	15 (12.3)
Secondary progressive	22 (18.0)
Age (yr)	46.0 (41.5–53.5)
EDSS	4.5 (2.9–6.0)
Duration of disease (mo)	156.0 (60.0–231.0)
HAM-A	12.0 (8.0–16.2)
HAM-D	13.0 (9.0–19.5)
NBSS total score	20.0 (12.75–31.0)
Incontinence subscale	0 (0.0–11.0)
Storage + voiding subscale	10.0 (7.75–13.0)
Consequences subscale	4.0 (1.0–6.0)
QoL item	2.0 (1.0–3.0)
NBSS $\geq 20$	63 (51.6)
IIEF-15	41.5 (22.0–57.0)
IIEF-EF	16.0 (7.7–24.0)
IIEF-IS	7.0 (4.0–10.2)
IIEF-OF	7.0 (2.0–10.0)
IIEF-SD	7.0 (4.0–8.0)
IIEF-OS	4.0 (2.0–8.0)
Male sexual dysfunction (IIEF-15 $< 60$ )	40 (80.0)
FSFI	16.0 (2.0–25.5)
FSFI-Desire	3.0 (1.2–4.8)
FSFI-Arousal	2.1 (0.0–4.1)
FSFI-Lubrication	2.1 (0.0–4.5)
FSFI-Orgasm	1.2 (0.0–2.4)
FSFI-Satisfaction	1.6 (0.0–4.0)
FSFI-Pain	1.4 (0.0–6.0)
Female sexual dysfunction (FSFI $< 26.55$ )	48 (66.6)
Neurogenic detrusor overactivity	69 (56.6)
Detrusor underactivity	24 (17.8)
Detrusor sphincter dyssynergia	70 (51.9)
AOFC (cm H <sub>2</sub> O)	28.5 (21.4–44.5)
MCC (mL)	153.5 (125.0–220.3)
$P_{detmaxIDC}$ (cm H <sub>2</sub> O)	34.7 (6.8–55.2)
$V_{pmaxIDC}$ (mL)	136.0 (99.0–170.0)
Compliance (mL/cm H <sub>2</sub> O)	10.2 (4.0–37.7)

Values are presented as number (%) or median (interquartile range). EDSS, Expanded Disability Status Scale; HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Depression Scale; NBSS, neurogenic bladder symptoms score; IIEF-15, International Index of Erectile Function; IIEF-EF, IIEF-erectile function; IIEF-IS, IIEF-intercourse satisfaction; IIEF-OF, IIEF-orgasmic function; IIEF-SD, IIEF-sexual desire; IIEF-OS, IIEF-overall satisfaction; FSFI, Female Sexual Function Index; AOFC, amplitude of the first overactive contraction; MCC, maximum cystometric capacity;  $P_{detmaxIDC}$ , maximum detrusor pressure during involuntary detrusor contraction (IDC);  $V_{pmaxIDC}$ , volume at first IDC.

**Table 2.** Clinical and urodynamic findings according to NBSS cutoff

Variable	NBSS < 20 (n = 59)	NBSS ≥ 20 (n = 63)	P-value
Age (yr)	47.5 (42.0–56.50)	46.0 (37.0–55.0)	0.578
Duration of disease (mo)	90.0 (60.0–165.0)	168.0 (36.0–216.0)	<0.01
EDSS	4.0 (2.0–5.0)	4.0 (3.5–7.5)	0.430
HAM-A	12.0 (8.25–23.0)	11.0 (8.0–23.0)	0.320
HAM-D	10.0 (8.50–19.0)	16.0 (9.0–22.0)	<0.01
IIEF-EF	18.0 (8.5–24.7)	11.0 (5.0–17.0)	0.372
IIEF-IS	9.0 (4.5–11.7)	7.0 (3.0–9.0)	0.350
IIEF-OF	8.0 (2.0–10.0)	6.0 (2.0–9.0)	0.592
IIEF-SD	6.5 (4.5–8.0)	7.0 (6.0–8.0)	0.092
IIEF-OS	5.0 (2.0–8.0)	4.0 (2.0–4.0)	0.479
MCC (mL)	212.0 (130.0–357.0)	131.0 (117.0–225.0)	<0.01
NDO, n (%)	26 (44.1)	37 (58.7)	0.620
PdetmaxIDC (cm H <sub>2</sub> O)	39.9 (6.2–76.2)	85.9 (63.6–104.0)	0.121
Compliance	10.8 (2.4–41.8)	3.3 (1.2–6.2)	0.357
FSFI	14.6 (1.5–27.3)	16.0 (2.0–25.7)	0.829
FSFI-Desire	3.3 (1.2–5.7)	3.0 (1.2–4.6)	0.167
FSFI-Arousal	2.1 (0.3–4.8)	3.0 (0–4.1)	0.328
FSFI-Lubrication,	2.4 (0–4.8)	3.4 (0–4.5)	0.021
FSFI-Orgasm	1.2 (0–2.3)	2.2 (0–3.5)	<0.01
FSFI-Satisfaction	2.4 (0–4.6)	2.0 (0.2–3.9)	0.680
FSFI-Pain	1.4 (0–6.0)	1.6 (0–5.9)	0.467

Values are presented as median (interquartile range) unless otherwise indicated.

NBSS, neurogenic bladder symptoms score; EDSS, Expanded Disability Status Scale; HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Depression Scale; IIEF, International Index of Erectile Function; IIEF-EF, IIEF-erectile function; IIEF-IS, IIEF-intercourse satisfaction; IIEF-OF, IIEF-organic function; IIEF-SD, IIEF-sexual desire; IIEF-OS, IIEF-overall satisfaction; MCC, maximum cystometric capacity; NDO, neurogenic detrusor overactivity; PdetmaxIDC, maximum detrusor pressure during involuntary detrusor contraction; FSFI, Female Sexual Function Index.

**Table 3.** Spearman correlation between variables

NBSS	Spearman rho								
	MCC	Pdetmax	PdetmaxIDC	Compliance	HAM-A	HAM-D	EDSS	FSFI	IIEF-15
Total score	-0.213*	-0.401**	-0.005	-0.086	0.447**	0.389**	0.278**	-0.228*	-0.194*
Incontinence	-0.154	-0.472**	-0.050	0.009	0.326**	0.302**	0.332**	-0.149	-0.219
Storage + voiding	-0.097	-0.200*	0.033	-0.127	0.369**	0.312**	0.121	-0.206	-0.186
Consequence	-0.197*	-0.197*	-0.028	-0.060	0.379**	0.384**	0.254**	-0.446**	-0.102
QoL	-0.291**	-0.229*	0.076	-0.229*	0.474**	0.408**	0.398**	-0.329**	-0.457**

NBSS, neurogenic bladder symptoms score; MCC, maximum cystometric capacity; Pdetmax, maximum detrusor pressure; PdetmaxIDC, Pdetmax during involuntary detrusor contraction; HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Depression Scale; EDSS, Expanded Disability Status Scale; FSFI, Female Sexual Function Index; IIEF, International Index of Erectile Function; QoL, quality of life.

\*P < 0.05. \*\*P < 0.01.

## DISCUSSION

The findings of this study suggest that the NBSS was initially related to anxiety, depression, and disability. After urodynamic examination, the NBSS was independently related to MCC, but not to NDO.

It is generally known that MS substantially determines a generalized demyelination process that interrupts the continuity of the neural pathways and alters the neural function that is essential for normal sexual activity and urinary function [21].

LUTD is very common in MS and can occur in different urodynamic form, like NDO in 34%–99% of cases, NDU in 0%–40% of cases, or DSD in 5%–83% of cases [22]. Although the epidemiology of DO may consistently differ on the basis of the definitions used in literature, a recent meta-analysis showed a prevalence ranging from 27% to 91% [23]. The pathology of neurogenic bladder is often associated with alterations of the electromechanical properties of the detrusor smooth muscle, including increased detrusor excitability [24].

In this context, several PROMs have been introduced in order to identify possible patterns of LUTD and to try to investigate patient responses to medical therapy.

Very recently, NBSS has been designed specifically to assess signs and symptoms related to neurogenic bladder dysfunction. Previous studies generally focused on incontinence, but the three NBSS domains better represent the spectrum of neurogenic bladder dysfunction and the associated complications [6].

We have also recently showed that sexual QoL assessed through the MS Intimacy and Sexuality Questionnaire, as well as IIEF-15 and FSFI was significantly impaired by neurological disability (EDSS), suggesting the needs of a global assessment in MS patients, including sexual function and QoL.

However, one could argue that this PROMs should be also related with urodynamic findings due to the alterations of neurological pathways in MS that could influence sexual function as well as bladder function.

Precisely to this regard, we have demonstrated in patients with neurogenic bladder dysfunction the level of PdetmaxIDC  $\geq$  20 cm H<sub>2</sub>O, MCC < 135 mL and compliance  $\leq$  3 mL/cm H<sub>2</sub>O were predictors of moderate-severe erectile dysfunction, strengthening the hypothesis of a common link between bladder and erectile dysfunction.

Unfortunately, one of the most important challenges is the true relationship between PROMs of LUTD and the objective evaluation of bladder dysfunction after urodynamic examination.

Herein, we showed that NBSS did not independently predict PdetmaxIDC  $\geq$  20 cm H<sub>2</sub>O ( $P=0.77$ ) but weakly predicted MCC < 212 mL (OR, 0.95;  $P<0.05$ ) with no statistical significance in gaining accuracy when compared to the base model.

Not surprisingly, the NBSS-QoL subscores were related to MCC and compliance. It should be noticed that many reports demonstrated a negative impact between QoL and MS alterations, secondary to severe neurological disability, depression, and other psychiatric disorder that can arise during the course of MS [25].

After external validation, NBSS is a valuable tool that can investigate QoL and different aspects of bladder dysfunction, but it cannot replace urodynamic examination in MS patients with LUTD.

However, this study had some limitations. It was a cross-sectional study and we obtained our sample from an outpatient setting. Second, we did not assess bowel function and several studies have reported a relationship between sexual and bladder dysfunction and bowel function. Finally, the NBSS questionnaire was translated in Italian by a native English-speaking translator; however, it has been not statistically tested.

On the contrary, one possible strength of this study is the evaluation of the relationship between urodynamic findings and NBSS in an external cohort of MS patients with LUTD. The current study demonstrated that NBSS was related to neurological disability expressed as EDSS, but was weakly correlated with some urodynamic variables.

In fact, the urodynamic exam is still the most useful determinant for the assessment of bladder function and cannot be replaced by PROMs, such as the NBSS.

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