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ARTICLE

Urodynamics in patients with multiple sclerosis: is it necessary? A randomized-controlled trial

Elie El Helou[a], Julien Sarkis[a], Georges Mjaess[b], Jad Zalaket[b], Christian Mouawad[b], Nicolas Sayegh[b], Souad Ghattas[b], Carine Azar[c], Jeanine El Helou[c], Halim Abboud[c], Salam Koussa[c] and Elie Nemr[a]

[a]Department of Urology, Faculty of Medicine, Saint Joseph University, Beirut, Lebanon; [b]Faculty of Medicine, Saint, Joseph University, Beirut, Lebanon; [c]Department of Neurology, Faculty of Medicine, Saint Joseph University, Beirut, Lebanon

ABSTRACT

Background: The need for complete urodynamic evaluation in Multiple Sclerosis (MS) patients with Lower Urinary Tract Symptoms (LUTS) is not fully established in the literature. The objective was to evaluate the effect of urodynamics in MS patients with LUTS on treatment outcomes.

Methods: MS patients with LUTS were recruited. On their first visit, urinary symptoms, symptom bother and urologic quality-of-life were evaluated using standardized questionnaires. On their second visit, patients were randomized into two groups: Group A underwent uroflowmetry, and Group B underwent a urodynamic study. Patients received treatment based on the whole evaluation and then were evaluated at 1, 3 and 6 months.

Results: Fifty MS patients with LUTS were randomized to 25 patients in each group. All scores decreased significantly after 6 months of treatment in both groups ($p < 0.05$). However, no differences were found between the two groups at baseline and at 1, 3 and 6 months of treatment ($p > 0.05$) concerning treatment outcomes.

Conclusion: A detailed clinical and non-invasive evaluation of MS patients with LUTS seems to be sufficient for prescribing an effective treatment. A urodynamic study does not influence the response to the prescribed treatment in terms of LUTS severity, bother or urologic quality-of-life.

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Multiple sclerosis; urodynamics; lower urinary tract symptoms; quality-of-life

Introduction

Multiple sclerosis (MS) is a frequent [1] and debilitating autoimmune neurological disease with various manifestations which often lead to major impairments in quality-of-life (QoL). Although the exact etiology of MS is unknown, it has been proven that it causes demyelination of the central nervous system, putting all neurologically controlled systems at risk [2]. The neuro-urological system is particularly affected, with lower urinary tract dysfunction (LUTD) causing lower urinary tract symptoms (LUTS) in 50–90% of MS patients during the course of the disease [3,4].

The effects of MS on the urinary tract are seldom life-threatening; however, they are considered a major health problem because of their disease-specific frequency and negative effect on a patient's urologic QoL [4]. Thus, it is crucial for a urologist to be involved in the multidisciplinary management of MS [3]. Due to the varying neurogenic bladder types in patients with MS, diagnosing the patient's urologic disorder is challenging [5]. While some urologists mainly rely on clinical evaluation and non-invasive testing (bladder diaries, ultrasonography, and uroflowmetry), others recommend an invasive urodynamic evaluation (uroflowmetry, cystomanometry, pressure/volume studies and electromyography) for symptomatic patients. Because of lack of evidence, a recent consensus statement declared that a urodynamic study should not be done routinely in the initial assessment of all MS patients reporting LUTS [6]. However, this is still recommended by several neuro-urology experts [7].

To our knowledge, there are no prospective randomized studies in the literature that evaluate the role of urodynamic testing in this category of patients. Therefore, the aim of this trial was to evaluate whether a urodynamic study has an added benefit for controlling LUTS and improving the urologic QoL of MS patients compared to a non-invasive approach.

Materials and methods

Study design

This is a prospective, single center, randomized controlled trial of MS patients with LUTS who were recruited from the registry of a national NGO. The study was approved by the Institutional Review Board (IRB) of our center (CEHDF908) and has been registered at ClinicalTrials.gov (NCT03336424). This clinical trial was conducted and reported in compliance with the consolidated standards of reporting trials (CONSORT) 2010 guidelines [8].

CONTACT Elie El Helou elie.helou@usj.edu.lb Hotel-Dieu de France University Hospital, Faculty of Medicine, University of Saint Joseph, Beirut, Lebanon

Recruitment and participants

MS patients with LUTS were recruited between October 2017 and November 2019. We excluded patients with a history of any disease besides MS that could otherwise explain the presence of LUTS (benign prostatic hyperplasia, prostate cancer, bladder cancer and urethral stenosis), as well as those with other neurological conditions (spinal injury, cerebral infarct and demyelinating diseases other than MS). Patients with an active urinary tract infection were treated; those who had persistent LUTS were included in the study. Prior to study enrollment, written informed consent was obtained from all patients.

Interventions

Each patient visited our center twice. On the first visit, preliminary baseline demographics and disease characteristics were assessed in the following categories: age; sex; body mass index (BMI); type of MS as mentioned by the International Advisory Committee on Clinical Trials in MS (Primary Progressive Multiple Sclerosis (PPMS), Secondary Progressive Multiple Sclerosis (SPMS) and Relapsing Remitting Multiple Sclerosis (RRMS) [9,10]); previous urological follow-up; and prior medical (alpha-blockers or anti-muscarinics) or surgical treatment. The extent of MS disability was quantified using the established Kurtzek's Expanded Disability Status Scale (EDSS) [11].

Moreover, a baseline urologic evaluation was performed: the Overactive Bladder Symptom Scores (OABSS) [12] were used to assess filling symptoms while the voiding symptoms were evaluated using the voiding subscore of the International Prostate Symptom Score (IPSS-V) – a score validated for both genders [13,14]. Bother caused by symptoms was assessed using the Urinary Bothersome Questionnaire in Multiple Sclerosis for voiding (UBQMS-V) and filling (UBQMS-F) [15]. The urologic QoL was evaluated using the SF-Qualiveen questionnaire [16]. Patients also underwent a urinalysis with urine culture, plasmatic creatinine level and renal bladder ultrasound, and were asked to fill out a 24-hour bladder diary.

On the second visit, patients were randomized into two groups using a simple randomization: Group A underwent uroflowmetry and Group B underwent a urodynamic evaluation (uroflowmetry, cystomanometry, pressure flow study (PFS) and electromyography (EMG)). The urodynamic examination was conducted with a cystomanometer from Medtronic Medical Supplies (Dublin, Ireland); 6-Fr double-lumen bladder catheters were used for recording the intravesical pressure and a 12-Fr rectal balloon catheter was used for measuring abdominal pressure. The practice, quality control and interpretation followed the standards provided by the International Continence Society [17]. EMG recordings were obtained from perineal surface patches. PVR was evaluated by pelvic ultrasound directly following uroflowmetry in both groups.

The appropriate treatment was then initiated based on the entire evaluation: behavioral therapy, alpha-blockers, or clean intermittent catheterization for voiding symptoms; and anticholinergics for filling symptoms. The same physician (E.H.) was responsible for the interpretation of the urodynamic evaluation, the diagnosis, and the choice of treatment. The patients' urodynamic profiles are shown in Table 1.

Patients were then blindly contacted *via* phone on the first, third and sixth months following treatment in order to evaluate any change in their urinary symptoms (OABSS and IPSS-V), bother (UBQMS-V and UBQMS-F), urologic QoL (SF-Qualiveen) and adherence to treatment. No changes were made in the methods after trial commencement. The study CONSORT flow diagram of the trial steps is shown in Figure 1.

Outcomes

The primary endpoints were the change in symptom severity (OABSS and IPSS-V), bother (UBQMS-V and UBQMS-F), and QoL (SF-Qualiveen) in the first 6 months after the initiation of treatment. Secondary outcomes were the rate of precise pathophysiological diagnosis in each group, as well as the treatment they received and compliance to treatment.

Sample size estimate

The use of the Gpower® 3.1.9.2 software sample size calculation was based on the presumed use of an ANOVA model, with an effect size $f = 0.15$ (based conservatively on the expected increase in QoL measures), a type 1 error probability of 5%, power of 90%, a two-group design with four repeated measures, a correlation among repeated measures of 0.5, and a non-sphericity correction measure of 0.4. While

Table 1. Patient's urodynamics findings in both groups.

	Uroflowmetry Group ($n = 25$)	Invasive Urodynamics Group ($n = 25$)
Patients on MS treatment, *n*	23	20
Neurologically stable patients, *n*	24	23
Previous urodynamic evaluation, *n*	3	1
Uroflowmetry staccato curve, *n*	1	3 on uroflowmetry 2 on PFS Total : 5
High post-void residual, *n*	7	7
Low compliance, *n*	N/A	5
High BOOI (bladder outlet obstruction index), *n*	N/A	5
DSD (Detrusor sphincter dyssynergia), *n*	N/A	7

PFS, Pressure Flow Studies; N/A, Not Available.
Note: The two patients with upper tract dilatation on ultrasound were in the BUD group, one had only a low Qmax of 14 mL/min, the other was already on CIC with high PVR and low compliance.

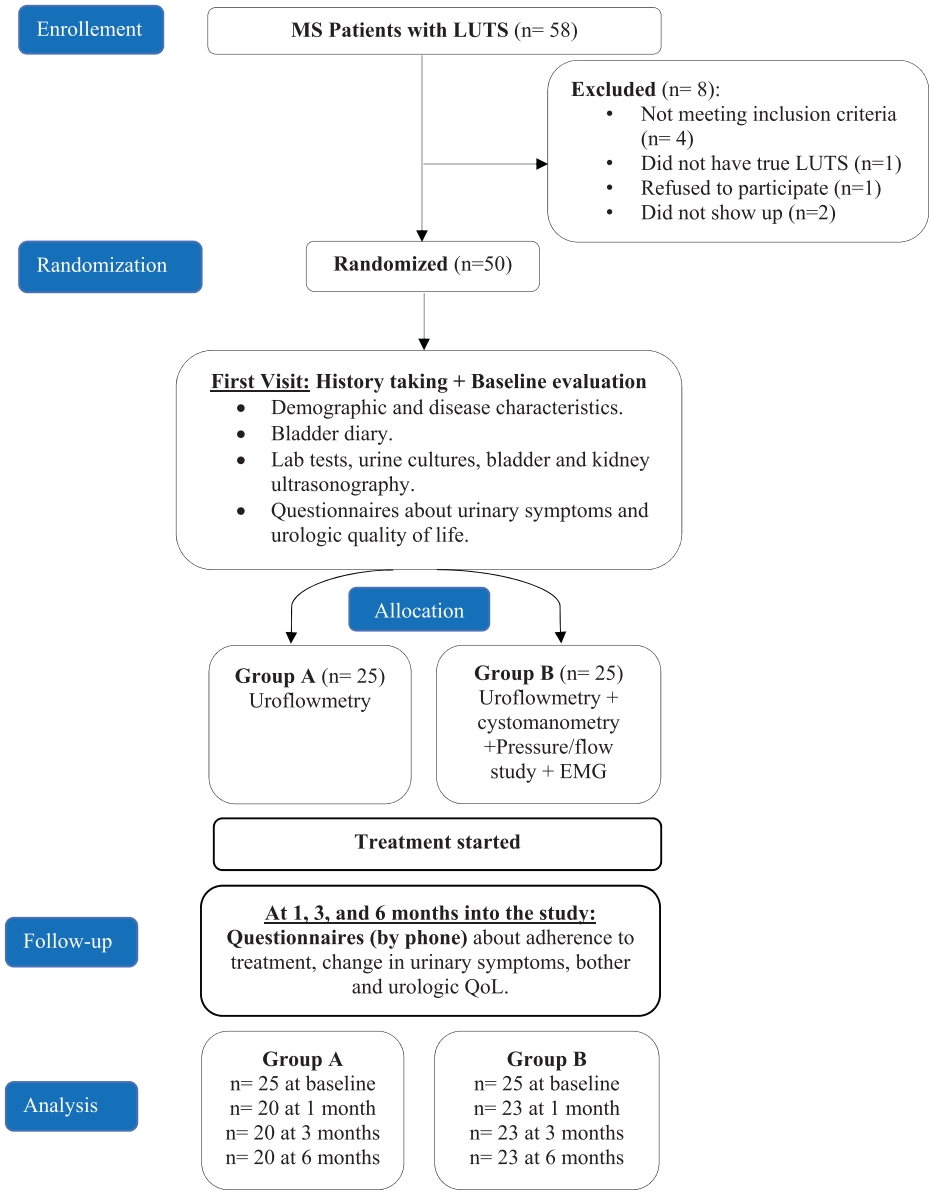

Figure 1. Study flow diagram.

per protocol calculations yielded 62 patients, 50 patients were included during the timeframe of the study.

Random sequence generation and allocation concealment

The patients were randomly assigned to the different groups (ratio 1:1) using simple randomization by an independent researcher who was not responsible for the intervention or the data analysis of the study. The allocated group was noted on a sheet of paper next to each participant's name. E.H., who was in charge of the intervention, assigned each patient to a group and proceeded with the intervention accordingly.

Blinding

Both the patient and the practitioner were not blinded. However, the physician responsible for the follow-up and the statistician were both blinded.

Statistical analysis

Continuous data were presented as mean ± standard deviation (SD), while categorical data were presented as number (*n*) and percentage (%). Statistical analyses were performed according to the intention-to-treat principal.

Clinical outcomes were evaluated at recruitment (baseline) and at 1, 3 and 6 months after the initiation of treatment. Intergroup comparison using the Mann–Whitney U-test was used for continuous data and the Chi-square test or the Fisher's exact test for categorical data. The Wilcoxon signed rank test was used for intra-group comparison. The Shapiro-Wilk test was applied to test the normality of continuous variables. The normally distributed variables are presented as the mean ± SD and compared using a student's *t*-test. A *p*-value < 0.05 is considered statistically significant. All statistical analyses were performed with 2-sided tests using IBM SPSS(R) Statistics.

Table 2. Baseline characteristics.

Baseline characteristics	Uroflowmetry group ($n = 25$)	Invasive urodynamics group ($n = 25$)
Age in years, mean ± SD	40 ± 10	42 ± 12
BMI in Kg/m^2, mean ± SD	25.61 ± 4.68	24.54 ± 4.01
Sex, *n* (%)		
Female	16 (64%)	15 (60%)
Male	9 (36%)	10 (40%)
MS duration in years, median (Q1;Q3)	9 (4;19)	6 (5;16)
Urinary symptoms duration in years, median (Q1;Q3)	3 (2;9)	5 (3;7)
EDSS score, mean ± SD	3.5 ± 2.2	3.5 ± 2.1
Disease course, *n* (%)		
PPMS	5 (20%)	7 (28%)
SPMS	4 (16%)	4 (16%)
RRMS	16 (64%)	14 (56%)
Previous urologic treatment, *n* (%)		
Alpha-blocker	4 (16%)	3 (12%)
Anti-muscarinic	3 (12%)	5 (20%)
None	18 (72%)	17 (68%)
Previous urologic surgery, *n* (%)		
Yes	0	1 (4%)
No	25 (100%)	24 (96%)

SD, Standard Deviation; Q1, Lower Quartile; Q3, Upper Quartile; BMI, Body Mass Index; EDSS, Expanded Disability Status Scale; CIS, Clinically Isolated Syndrome; PPMS, Primary Progressive Multiple Sclerosis; SPMS, Secondary Progressive Multiple Sclerosis; RRMS, Relapsing Remitting Multiple Sclerosis.
Note that no differences between groups were statistically significant.

Results

Baseline characteristics

A total of 50 patients were included in the study. Twenty-five patients each were assigned at random to the uroflowmetry group (Group A) and the invasive urodynamics group (Group B). The mean (SD) participant age was 40 (10) in Group A and 42 (12) in Group B. The majority of patients were women (64% in Group A, 60% in Group B). The baseline characteristics discussed in Table 2 were similar: no significant inter-group differences ($p > 0.05$) were found for age, sex ratio, BMI, mean EDSS score, type of MS, duration of MS, duration of urinary symptoms, previous urological follow-up and anterior urological treatment. In addition, no significant differences were found between the two groups for all baseline values on primary outcome measures (Table 3), with comparable baseline OABSS score ($p = 0.792$), IPSS-V score ($p = 0.763$), UBQMS-F questionnaire ($p = 0.506$), UBQMS-V questionnaire ($p = 0.680$) and SF-Q score ($p = 0.641$).

Primary outcomes

Both groups showed a significant decrease in their OABSS score at 6 months when compared to baseline: the median (Q1;Q3) OABSS score decreased from 7 (4;9) to 2 (1;5) in Group A ($p < 0.001$), and from 7 (4;9) to 2 (0;4) in Group B ($p < 0.001$). However, no statistical difference was found between the two groups after 1, 3 and 6 months of treatment.

Similarly, IPSS-V decreased significantly in Group A (7 vs. 4, $p < 0.001$) and in Group B (8 vs. 2, $p < 0.001$), with no statistical difference between the two groups after 1, 3 and 6 months of treatment.

According to the UBQMS questionnaire, 40% of patients in both groups were initially enormously bothered by their filling symptoms. At 6 months, only 13% ($p < 0.001$) were still enormously bothered in the invasive urodynamics group, and none were in the uroflowmetry group ($p < 0.001$). No statistical difference was found between the two groups after 1, 3 and 6 months of treatment. Similar results were found for UBQMS-V.

SF-Q decreased significantly in Group A (1.75 vs. 0.50, $p < 0.001$) and in Group B (2.00 vs. 0.75, $p < 0.001$), again with no statistical difference between the two groups, after 1, 3 and 6 months of treatment.

The results are shown in Table 3 and Figure 2.

Secondary outcomes (*Table 4*)

During their first visit, patients in the invasive urodynamics group received a more precise pathophysiological explanation for their urologic symptoms (96% of patients) compared to those in the uroflowmetry group (28% of patients) ($p < 0.001$). Both groups received comparable treatment for their symptoms ($p = 0.506$), with anticholinergics being the most common therapy (59.1% in Group A and 33% in Group B).

Finally, 70% of patients were adherent to their treatment plan in Group A, compared to 87% of patients in Group B ($p = 0.263$). Only two patients had their anticholinergics changed because of drug side-effects.

Discussion

Although LUTD affects up to 90% of MS patients during the course of their disease [3,4], it remains rarely morbid, with a low incidence of reported upper tract abnormalities [18]. However, the altered quality-of-life it causes is of extreme importance [4]. The urologist has a challenging role in establishing the correct diagnosis for LUTS [5]. To assist physicians in their diagnostic approach, Amarenco et al. [19] developed the First-Line Urological Evaluation in MS (FLUE-MS) algorithm in 2013, which is based on a non-invasive evaluation followed by a referral of the patient to a neuro-urology unit in case of potential issues. However, the FLUE-MS algorithm

Table 3. Primary outcome measures at baseline, 1 month, 3 months and 6 months.

	Group A: Uroflowmetry group ($n = 25$)				Group B: Invasive urodynamics group (n = 25)				p^* (Intergroup comparison between Group A and Group B)			
		Postintervention, at:				Postintervention, at:				Postintervention, at:		
Variable	Baseline	1 month	3 months	6 months	Baseline	1 month	3 months	6 months	Baseline	1 month	3 months	6 months
OABSS, median (Q1;Q3)	7 (4;9)	4 (1;7)	2 (1;6)	2 (1;5)	7 (4;9)	3 (1;5)	3 (1;4)	2 (0;4)	0.792	0.759	0.787	0.824
		$p^{**} < 0.001$				$p^{**} < 0.001$						
IPSS-V, median (Q1;Q3)	7 (5;11)	5 (2;10)	4 (1;7)	4 (1;7)	8 (4;11)	4 (2;7)	2 (0;4)	2 (0;4)	0.763	0.358	0.252	0.164
		$p^{**} < 0.001$				$p^{**} < 0.001$						
UBQMS-F, *n* (%)									0.506	0.173	0.208	0.245
0	2 (8%)	4 (20%)	6 (30%)	7 (35%)	2 (8%)	9 (39.1%)	12 (52.2%)	13 (56.5%)				
1	4 (16%)	9 (45%)	8 (40%)	7 (35%)	9 (36%)	10 (43.5%)	7 (30.4%)	6 (26.1%)				
2	9 (36%)	6 (30%)	5 (25%)	6 (30%)	4 (16%)	1 (4.3%)	1 (4.3%)	1 (4.3%)				
3	10 (40%)	1 (5%)	1 (5%)	0	10 (40%)	3 (13%)	2 (8.7%)	3 (13%)				
		$p^{**} < 0.001$				$p^{**} < 0.001$						
UBQMS-V, *n* (%)									0.680	0.306	0.770	0.710
0	5 (20%)	6 (30%)	9 (45%)	11 (55%)	4 (16%)	8 (34.8%)	12 (52.2%)	14 (60.9%)				
1	6 (24%	7 (35%)	8 (40%)	6 (30%)	9 (36%)	11 (47.8%)	7 (30.4%)	6 (26.1%)				
2	6 (24%)	5 (25%)	3 (15%)	3 (15%)	6 (24%)	4 (17.4%)	4 (17.4%)	3 (13.0%)				
3	8 (32%)	2 (10%)	0	0	6 (24%)	0	0	0				
		$p^{**} < 0.001$				$p^{**} < 0.001$						
SF-Q, median (Q1;Q3)	1.750 (1.250;2.250)	0.625 (0.438;1.438)	0.500 (0.250;1.125)	0.500 (0.125;1.063)	2.000 (1.250;2.500)	1.125 (0.625;1.875)	0.750 (0.250;1.500)	0.750 (0.250;1.375)	0.641	0.180	0.525	0.378
		$p^{**} < 0.001$				$p^{**} < 0.001$						

UBQMS-F, Urinary Bothersome Questionnaire in Multiple Sclerosis – Filling dysfunction assessment questionnaire; UBQMS-V, Urinary Bothersome Questionnaire in Multiple Sclerosis – Voiding dysfunction assessment questionnaire; SF-Q, SF-Qualiveen; OABSS, Overactive Bladder Symptom Score; IPSS-V, International Prostate Symptom Score- voiding subscore.
*p calculated using Mann-Whitney Test, considered significant if < 0.05. ** p calculated using Wilcoxon Signed Ranks Test, considered significant if < 0.05.

Table 4. Secondary outcome measures at 6 months.

Secondary Outcomes	Group A: Uroflowmetry group ($n = 25$)	Group B: Invasive urodynamics group ($n = 25$)	p^*
Received precise diagnosis, *n* (%)			
Yes	7 (28%)	1 (96%)	
No	18 (72%)	1 (4%)	<0.001
Treatment, *n* (%)			
Behavioral therapy	3 (13.6%)	6 (25%)	
Anticholinergic	13 (59.1%)	8 (33%)	
Alpha-blocker	1 (4.5%)	2 (8.3%)	
CIC	0	1 (4.2%)	
Alpha-blocker + anticholinergic	5 (22.7)	6 (25%)	
Alpha-blocker + CIC	0	1 (4.2%)	0.506
Compliance to treatment, *n* (%)			
Yes	14 (70%)	20 (87%)	
No	6 (30%)	3 (13%)	0.263

CIC, Clean intermittent catheterization.
* p was considered significative if < 0.05.

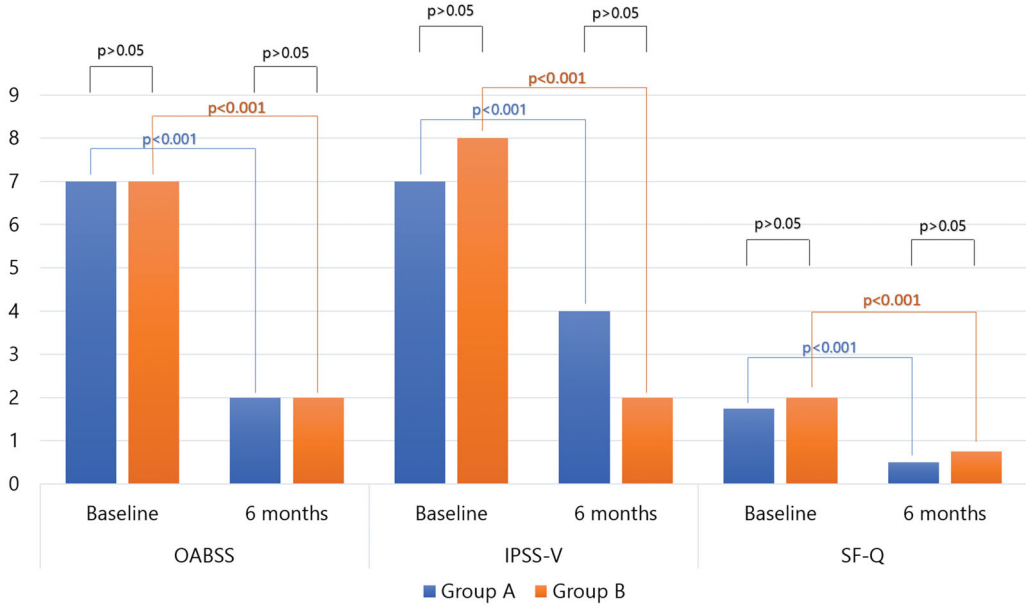

Figure 2. Primary outcomes comparison at baseline and 6 months. OABSS, Overactive Bladder Symptom Score; IPSS-V, International Prostate Symptom Score–voiding subscore; SF-Q, SF-Qualiveen. p was considered significant if < 0.05.

does not specify the next step that should be done by the neuro-urology unit, and it remains unclear whether a urodynamic study in MS patients should be conducted.

Our study found that conducting a whole urodynamic evaluation including cystomanometry, PFS, and EMG does not influence treatment choice or outcome. Both groups showed a clear improvement in terms of LUTS severity, bother, and urologic quality-of-life after 6 months of treatment initiation. This was demonstrated by a decrease in the OABSS, IPSS-V, UBQMS and SF-Qualiveen scores. However, no statistically significant differences were found in terms of outcome improvement between groups A and B after 1, 3 and 6 months of treatment ($p > 0.05$). This is despite the fact that an accurate diagnosis was established in a larger proportion of cases in Group B compared to Group A (96% versus 28%, $p < 0.001$). Taken together, this data would suggest that, even though a greater understanding of the LUTD is established using a urodynamic study, it does not necessarily translate into a better outcome.

On one hand, Wang et al. [20] have suggested in a retrospective non-comparative study of 126 MS patients with LUTD that a comprehensive urodynamic study is key to choosing the right therapy. Amarenco et al. [15] would also argue that in many MS patients with LUTS, urodynamic evaluation is necessary to better understand the LUTD. On the other hand, a 2014 review article by Dillon and Lemack [21] concluded that a clinical examination combined with non-invasive urologic studies is sufficient to treat most MS patients with LUTS. A urodynamic study may be needed in some specific cases, but should not necessarily be part of the initial approach.

Our results could be explained by the limited number of first-line therapeutic choices for neurogenic bladder: antimuscarinic drugs are usually the first-line treatment for filling LUTS, while alpha blockers are used initially in voiding LUTS. A thorough history-taking, clinical examination, urine analysis and culture, plasma creatinine test, and ultrasound with a simple uroflowmetry seem to be

sufficient for choosing the right first-line treatment for MS patients with LUTS.

Adherence to treatment did not differ between the two groups despite the fact that some clinicians might think that providing a more complex and extensive test to a patient could result in a better compliance to treatment. Instead, a urodynamic study seems to add a transient anxiety for patients whose quality-of-life has already deteriorated. This is implied by the fact that question 5 of the SF-Q, 'Do you feel worried about your bladder problems?', was the only item that differed significantly between the two groups on the questionnaire subanalysis, and only on the first visit ($p = 0.029$).

Since MS is a relapsing-remitting or a progressive disease, patients require a close follow-up to detect any change in the urinary function in order to adjust treatment. We consider the 6-month follow-up used in our study sufficient to provide the patient with the best possible outcome, especially in the non-invasive group, since this evaluation could easily be repeated if the urologist found it necessary. However, repeating invasive urodynamics regularly seems less feasible due to the complexity of the exam and its cost.

This study is not devoid of limitations. First, both the patient and the practitioner could not be blinded; this was technically impossible for the former, and the latter had to prescribe his treatment based on the results of the intervention. Second, our findings should not be extrapolated to the rare patients with upper tract dilation or renal failure since only two patients had dilation and no patients had renal failure in our study. However, we believe that our study provides useful insight for clinicians counseling a patient with multiple sclerosis and urinary symptoms. Additional trials with larger patient samples are necessary to add evidence-based practice and eventually determine if a certain subgroup of MS patients might benefit from a urodynamic study.

Conclusion

A detailed clinical and non-invasive evaluation (with uroflowmetry only) seems to be sufficient for MS patients presenting with LUTD in order to prescribe an effective treatment. Adding a complete urodynamic study can lead to a better understanding of the LUTD but does not seem to influence the choice and the response to the prescribed treatment in terms of LUTS severity, bother, and urologic quality-of-life.

Author contributions

Conceptualization EH. Methodology EH, JS, GM, JZ and CM. Formal analysis EH, JS, GM, JZ, CM, JH and EN Investigation EH, JZ, CM, NS, SA, and CA. Writing – Original draft EH, JS and GM. Writing – Review and editing JZ, CM, NS, SA, CA, JH, HA, SK, EN. Supervision EH and EN.

All authors have read and approved the final version of the manuscript and agree with the order of presentation of the authors.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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ORCID

Georges Mjaess http://orcid.org/0000-0002-8703-4611

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