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Research Article

Importance of Urodynamic Dysfunctions as Risk Factors for Recurrent Urinary Tract Infections in Patients with Multiple Sclerosis

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ABSTRACT

Objective: To analyses the role of urodynamic dysfunctions as risk factors for recurrent Urinary Tract Infections (rUTIs) in patients with Multiple Sclerosis (MS).

Material and methods: We carried out a prospective cohort study of 170 MS with lower urinary tract symptoms patients submitted to urodynamic study. Patients were followed for one year and 114 (84 women (74%) and 30 men (26%); mean age 49 years), completed the study. We recoded their clinical variables and urodynamic findings. The statistical tests used were Fisher´s exact test, chi square test, Student´s t-test and multivariate regression analysis.

Results: 37 patients (32%) had rUTIs, in univariate analysis. We found that patients with rUTIs had significant more symptom progression time, MS duration, Expanded Disability Status Scale score and greater frequency of Primary and Secondary Progressive MS types, lower maximum flow rate (Qmax), voided volume, bladder voiding efficiency, detrusor pressure at maximum flow, and bladder contractility index and greater frequency of Stress Urinary Incontinence (SUI). Multivariate analysis identified the urodynamic factors: Qmax Odds Ratio (OR)=0.90 and SUI (OR=2.95) as the independent predictors of rUTs.

Conclusion: Two urodynamic variables: Qmax and SUI are independent risk factors for rUTIs in MS patients. These two variables might be associated with Pelvic floor dysfunctions.

Keywords: Multiple sclerosis; Recurrent urinary tract infections; Urodynamics; Urinary bladder neurogenic; Pelvic floor

INTRODUCTION

Multiple Sclerosis (MS) is the first cause of nontraumatic spinal cord injury [1], which frequently leads to Neurogenic Lower Urinary Tract Dysfunction (NLUTD), urodynamic studies are essential for patients with NLUTD [2]. However, despite the great prevalence of LUTD guidelines on MS do not recommend urodynamic studies, unless there are urologic complications [3]. Among MS complications we found recurrent Urinary Tract Infections (rUTIs), which not only affects the health of this patient doubling their risk of mortality [4], but also promote MS relapse by triggering autoimmune processes [5]. In the general population, risk factors for UTIs are thought to include clinical intrinsic factors (e.g., older age, male sex) and extrinsic factors (e.g., prior antibiotic use, urinary catheters, disease severity) [6]. In patients with NLUTD, urodynamic alterations may promote UTIs [7]. Therefore, expert committees recommend performing urodynamic studies in MS patients with rUTIs [8,9], although up to now, there is not empirical data which support this recommendation. The aim of this study is to analyse which urodynamic findings can be risk factors for rUTIs controlling the clinical risk factors by a multivariate regression analysis.

MATERIALS AND METHODS

We carried out a prospective study between January 2017 and September 2018. The sample size was 170 patients with MS and Lower Urinary Tract Symptoms (LUTS) who were submitted to a

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urodynamic study. Inclusion criteria were: MS progression time of at least one year, and age ≥ 18 years. We excluded patients with congenital urinary tract alterations; urolithiasis, genitourinary tumours, and NLUTD not secondary to MS. Fourteen patients were excluded due to these criteria. A one-year follow up was made by the hospital's neurology department, and finally 114 patients (84 women (74%) and 30 men (26%); mean age 49 ± 10.0 years), completed the study. The study was approved for the by the Scientific Committee of our centre, and all patients signed an informe4d consent before the performance of urodynamic study. Sample size was calculated based on the data provided by Wiedemann et al [10], and Bemelmans et al [11]. Assuming an Expanded Disability Status Scale (EDSS) score difference of 1.5 points, a Standard Deviation (SD) of 2.36 points, an alpha level of 5%, and a statistical power of 80%, the minimum sample size was calculated at 37 patients per group. MS was diagnosed by the neurology department in accordance with the McDonald criteria. When the follow-up finished, we recorded data regarding demographic, neurological status (including level of disability, measured using the EDSS) [12], and the presence and type of LUTS and rUTIs diagnosed by the European Association of Urology criteria. Thirty-seven patients (32%) had rUTIs. We performed the urodynamic study according to the International Continence Society (ICS) specifications [13], except the defined issues and guidelines for good urodynamic practice [14], using a solar polygraph (MMS, Enschede, and the Netherlands). The study comprised a free uroflowmetry test, followed by a multichannel urodynamic study including cystometry, a pressure-flow study, and a perineal electromyography (EMG). Filling was performed using a 6 Fr double-lumen catheter with saline at ambient temperature and at a rate of 20 mL/min. Bladder pressure was measured using the urethral catheter. Abdominal pressure was measured using a rectal balloon catheter. Detrusor-External Sphincter Dyssynergia (DESD) was defined as increased EMG activity during involuntary detrusor contraction. Bladder Voiding Efficiency (BE) as percentage of post-void residual urine of total bladder capacity (post-void residual urine+voiding volume). Detrusor Contractility was measured according to Bladder Contractility Index (BCI) and bladder outflow resistance according to Bladder Outlet Obstruction Index (BOOOI) Results were stored electronically; the SPSS statistics software (version 20) was used for statistical analysis. All values are expressed as means ± SD. The Fisher exact test and the chi-square test were used for qualitative variables; the t-test was used to compare the means of parametric data. Quantitative data were tested for normal distribution using the Kolmogorov-Smirnov test. Stepwise logistic regression was used to determine the contributing factors for recurrent urinary tract infection. A value of $p<0.05$ was considered to be statistically significant.

RESULTS

Descriptive statistics

Mean MS progression time was 17 ± 8.3 months. Sixty-nine patients (61%) were classified as having Relapsing-Remitting MS (RRMS), 13 (11%) as Progressive MS (PPMS), 31 (27%) as Secondary Progressive MS (SPMS), and one (1%) as tumefactive MS. Thirty-three patients (29%) were receiving no treatment. Forty-four patients (39%) were being treated with first line drugs: glatiramer acetate 8 (7%), interferon beta-1a 7 (6%), interferon beta-1b 7 (6%), peginterferon beta-1a one patient (1%), dimethyl fumarate 5 (4%), and teriflunomide 16 (14%). Thirty-seven patients (32%) were being treated with second line drugs: natalizumab one patient (1%), fingolimod, 11 (10%) and alemtuzumab, 7 (6%). Mean EDSS score was 4.7 ± 2.13 points. Mean LUTS progression time was 10 ± 5.9 months. LUTS comprised filling symptoms in 65 patients (57%), voiding symptoms in 29 (25%), and mixed symptoms in 17 (15%). LUTS type could not be determined in 3 patients. Five patients (4%) were on clean intermittent catheterisation; one patient (1%) used a permanent catheter. The remaining patients did not use any type of urinary catheter. The free uroflowmetry study revealed a voided volume of 179 ± 185.3 mL, a maximum flow rate (Qmax) of 14 ± 8.7 mL/s, a post-void residual volume of 78 ± 124.8 mL, and a bladder voiding efficiency (BVE) of 25% ± 30.0%. In filling cystometry, the cystometric capacity was 227 ± 125.5 mL and bladder compliance were 60 ± 56.3 mL/cm H_2O. Detrusor overactivity was observed in 46 patients (40%). The maximum detrusor pressure during involuntary contractions was 39 ± 27.4 cm H_2O; the cystometric capacity at first involuntary contraction was 126 ± 89.6 mL Stress Urinary Incontinence (SUI) was diagnosed in 23 patients (20%). In pressure-flow study, the mean maximum detrusor pressure (PdetMax) was 41 ± 29.8 cm H_2O, the mean detrusor pressure at maximum flow (PdetQmax): 27 ± 20.38 cm H_2O, the BCI: 83 ± 45.3 cm H_2O, and the BOOI: 5 ± 24.7 cm H_2O. DEED was diagnosed in 37 patients (32%).

Inferential statistics

The relationship between clinical factors and rUTIs was shown in Table 1. We observed significant differences between patients with of rUTIs and: longer symptom progression time, longer MS duration, higher EDSS score and greater frequency of PPMS and SPMS MS types.

Table 1. Relationship between clinical data and occurrence of recurrent lower urinary tract infections

Variable	Patients with rUTIs	Patients without rUTIs	Significance level
Women*	31 (84%)	47 (6159	0.068
Age (years)†	51 ± 10.8	49 ± 9.5	0.091
Storage LUTS*	23 (62%)	43 (56%)	0.339
Voiding LUTS*	10 (27 %)	19 (25%)	0.494
Mixed LUTS*	5 (15%)	12 (16%)	0.483
Symptom progression	9 ± 6.5	6 ± 5.4	0.016‡
time (months)†			

Performing CIC*	3 (8%)	2 (3%)	0.197
MS duration	20 ± 9.2	16 ± 7.6	0.010‡
(months)†			
EDSS score†	5.3 ± 2.11	4.4 ± 2.08	0.015‡
PPMS or SPMS MS	19 (51%)	25 (32%)	0.042‡
type*			
MS treatment*	None: 12 (32%)	None: 21 (27%)	0.819
	First line: 13 (36%)	First line: 31 (41%)	
	Second line 12 (32%)	Second line: 25 (32%)	

Note: *Absolute frequency (percentage); †Mean ± SD; ‡Statistically significant.

Abbreviation: CIC: Clean Intermittent Catheterisation; LUTS: Lower Urinary Tract Infection; MS: Multiple Sclerosis; PPMS: Primary Progressive MS; rUTI: recurrent Urinary Tract Infection; SPMS: Secondary Progressive MS.

The relationship urodynamic factors and rUTIs were shown in Table 2. We observed significant differences between patients with rUTIs and: lower voided volume, lower Qmax, greater BE, greater frequency of SUI, lower PdetQmax and lower BCI.

Table 2. Relationship between urodynamic study findings and occurrence of recurrent lower urinary tract infections.

Variable	Patients with rUTIs	Patients without rUTIs	Significance level
Voided volume (mL)†	10 ± 135.3	216 ± 195.5	0.000‡
Maximum flow rate (mL/s)†	9 ± 7.8	15 ± 8.6	0.002‡
Post-void residual volume (mL)†	73 ± 84.7	80 ± 137.5	0.416
Bladder voiding efficiency (%)†	35 ± 37.0	21 ± 26.2	0.026‡
Cystometric capacity (mL)†	208 ± 124.8	235 ± 125.8	0.145
Bladder compliance (mL/cm H_2O)†	62 ± 64.9	58 ± 51.8	0.362
Detrusor overactivity*	12 (26%)	25 (38%)	0.135
Maximum detrusor pressure during involuntary contraction (cm H_2O)†	44 ± 22.9	36 ± 29.2	0.339
Stress urinary incontinence	12 (52%)	25 (28%)	0.030‡
Maximum detrusor voiding pressure (cm H_2O)†	36 ± 27.1	44 ± 30.9	0.093
Detrusor pressure at maximum flow (cm H_2O)†	22 ± 19.8	29 ± 20.3	0.046‡
BCI†	72 ± 45.3	88 ± 44.6	0.045‡
BOOI†	3 ± 27.1	6 ± 23.5	0.278
Detrusor-sphincter dyssynergia*	14 (32%)	20 (29%)	0.222

Note: *Absolute frequency (percentage); †Mean ± SD; ‡Statistically significant.

Abbreviation: BCI: Bladder Contractility Index; BOOI: Bladder Outlet Obstruction Index; rUTI: recurrent Urinary Tract Infection.

In order to perform a logistic regression analysis, clinical and urodynamic variables with a signification level below 10% in univariate analysis were included in the model (Table 3).

Table 3. Initial logistic regression model.

Variables	ß	p	R2
MS type	0.595	0.430	0.357
Maximum Flow rate	-0.110	0.081	
Sex	-1.224	0.267	
MS duration	0.053	0.427	
Symptoms progression time	0.041	0.631	
EDSS score	-0.139	0.405	
Bladder voiding efficiency	0.003	0.405	
Stress urinary incontinence	1.495	0.037	

Maximum detrusor voiding pressure	0.016	0.454
Detrusor pressure at máximum flow		
BCI	-0.003	0.785
Constant	-0.849	0.564

Note: ß: Multivariate logistic regression coefficient; p: Significance level (Wald); R2: Determination coefficient; BCI: Bladder Contractility Index.

The final model identified only two variables that were independently associated with occurrence of rUTIs. These were the urodynamic variables Qmax (Odds Ratio (OR)=0.90) and SUI (OR=2.95) (Table 4).

Table 4. Final logistic regression model.

Variables	ß	p	R2
Maximum Flow rate	-0.11	0.081	0.407
Stress urinary incontinence	1.495	0.037	

Note: ß: Multivariate logistic regression coefficient; p: Significance level (Wald); R2: Determination coefficient; BCI: Bladder Contractility Index.

DISCUSSION

We found several urodynamic risk factors associated to rUTIs, in both filling and voiding phase. The only filling phase factors was the presence of SUI (more frequent in patients with rUTIs). The voiding phase factors were a lower voided volume, Qmax, BE, pdetQmax and BCI in MS patients with rUTIs. There are scarce studies which analyse the urodynamic risk factors associated to rUTIs in MS patiens. Most of them have not found any urodynamic risk factors such as Castel-Lacanal et al [15]. Who did not find any relationship between urodynamic findings and urinary complications (including pyelonephritis and urosepsis). However, as not all patients in this study underwent urodynamic testing, its results are not reliable. Nakipoglu et al [16], neither identifies association between urodynamic data and UTIs in patients with MS. However, these researchers provide very few data; their urodynamic diagnoses include "detrusor hyporeflexia" (which is not defined in the ICS terminology) and do not describe how this diagnosis was made. Only Gallien et al. found that post-void residual volume was a risk factor for pyelonephritis but not for lower urinary tract infection. In patients with NLUD residual urine favours rUTIs, because the rapid grow of bacteria in such residual urine [17]. Although we found no association between rUTIs and post-void residual volume in absolute terms, post-void residual volume as a percentage of total bladder capacity (BVE) was significantly greater in patients with rUTIs. Detrusor underactivity results in a low PdetQmax and post void residual urine. In our study patients with rUTIs had lower BCI and PdetQmax compared with patients without infections. Van Batavia et al [18], also concluded that children with detrusor underactivity were more likely to have a history of infection. This relationship was attributed to urinary stasis which predispose to rUTIs. Other urodynamic risk factor associated to rUTIS in our study was lower voided volume. This factor was also found by Arya et al [19]. In women with rUTIs who attributed this finding to a lower bladder capacity due to increased bladder sensitivity trigged by rUTIs. In our study, patients with rUTIs also had lower cystometric capacity, although this reduction was not statistically significant. These differences may be less pronounced in our series because it included both men and women. However, the main finding of our study was that multivariate analysis showed that clinical risk factors and other urodynamic factors depend on two independent urodynamic risk factors. The presence of SUI in the filling phase and a lower Qmax in the voiding phase. Furthermore, we can state that the clinical risk factors showed in the univariate analysis are expression of those two urodynamic dysfunctions. Other authors like Athanasiou et al [20], also observed a lower maximum flow rate in women with rUTIs. A low Qmax may result from dysfunctional voiding. Dysfunctional voiding disrupts the laminar urinary flow through the urethra causing UTIs as bacteria are transferred back from the meatus to the bladder as a result of the milk back phenomenon [21]. Our study did not find any relationship between detrusor-sphincter dyssynergia and rUTIs. Nevertheless, perineal EMG is not accurate enough to measure external sphincter activity during voiding [22]. Studies have revealed that MS patients have poor control on their pelvic floor, which can lead to a dysfunctional voiding and that pelvic floor physiotherapy. Improves Qmax in MS patients [23], the second urodynamic independent factor found in our study: The presence of SUI is also related to pelvic floor injuries Ahmed, et al. [24], found in women of childbearing age that low urinary flow and genital prolapse are independent risk factors for rUTs. In this study urinary incontinence and genital prolapse were observed more frequently in patients with rUTIs. Altered anatomy may predispose to rUTIs in women due to a shorter distance between anus, vagina and urethra. The power of pelvic floor is reduced in patients with MS. Pelvic floor muscle training improves SUI in these patients with a significant reduction of 24 hr pad testing [25]. Therefore, there is a possible common point in both urodynamic dysfunctio an alteration of pelvic floor. Should other studies confirm? If these relationships between pelvic floor dysfunction and rUTIs in MS patients were confirmed, pelvic floor rehabilitation may prevent rUTIs in those patients. The main limitation of this study is its external validity, because we performed urodynamic study only in patients with LUTS, consequently we cannot extrapolate those funding to other MS patients without these symptoms. However, since there are a sizable percentage of patients with MS with lower urinary tract symptoms, the external validity of our study is preserved. Conversely, the main strength of the study is its prospective characteristic, the fact that all patients underwent a comprehensive urodynamic study and the multivariate analysis, enabling us to establish for the first time that the independent risk factors for rUTIs in patients with MS are urodynamic and probably related to pelvic floor dysfunction.

CONCLUSION

Urodynamic dysfunctions are risk factors for rUTIs. Clinical risk factors and other urodynamic factors are dependent on two independent urodynamic risk factors a diminished urinary flow and the existence of SUI. These findings suggest that pelvic floor dysfunction might play a role in MS patients with rUTIs. Because we only conducted the urodynamic research in patients with LUTS, we are unable to extend the results to other MS patients without similar symptoms. This is the fundamental drawback of the study. The external validity of our study is nonetheless maintained because a large proportion of MS patients also experience symptoms of the lower urinary tract.

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