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Original article

Neurourological assessment in people with multiple sclerosis (MS): a new evaluated algorithm

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ABSTRACT

Background: Neurogenic lower urinary tract dysfunction (NULTD) is common in patients with multiple sclerosis (MS); nevertheless, it is often underestimated, underdiagnosed, and undertreated due to patients' sense of shame, variability of symptoms, as well as lack of communication between neurologists and urologists, despite the availability of several guidelines based on scientific evidence and expert opinion.

Objective: This study was conducted to develop an easy-to-perform algorithm for diagnosing neurogenic lower urinary tract disease in patients with MS for daily neurological and urological routine, including the identification of red flags.

Methods: In consensus group meetings, interprofessional experts (neurologists, urologists, neurourologists, nurses, nurse practitioners, occupational therapists, physical therapists as well as representatives of national MS centers, self-care groups, social care, residential care, and health-aid-providers) developed a diagnostic algorithm to detect NULTD in patients with MS. Subsequently, the group evaluated the algorithm in 121 patients with MS using micturition diary, post-void residual volume, uroflowmetry, and urodynamic studies. Statistical analysis was conducted on the basis of logistic regression models to compare patients with normal and abnormal urodynamic examinations. Differentiation was performed using selected diagnostic parameters as well as standard performance measures for binary classifiers to assess prognostic quality.

Results: The following four parameters allowed to diagnose NLUTD in patients with MS: post-void residual urine volume, rate of urinary tract infections during the past 6 months, micturition frequency, and incontinence. According to statistical analysis, the following thresholds could be defined: post-void residual volume (PVR) ≥70 mL (Odds Ratio (OR) = 1.24; 95% CI:[1.07,1.62]), urinary tract infection (UTI) rate - none in 6 months (OR = 2.03; 95% CI:[1.04,6.68]), and micturition frequency >13/day, standardized on 2000 mL urine

Abbreviations: AIC, Akaike information criteria; CI, Confidence interval; DO, detrusor overactivity; DU, detrusor underactivity; EDSS, Expanded Disability Status Scale; NLUTD, Neurogenic lower urinary tract dysfunction; MS, Multiple sclerosis; NPV, Negative Prediction Value; OR, Odds Ratio; PPV, Positive Prediction Value; PVR, post void residual volume; RRMS, Relapsing-Remitting MS; SPMS, Secondary Progressive MS; PPMS, Primary Progressive MS; SD, standard deviation; UTI, Urinary Tract Infection

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complaints of NLUTD had an abn
a sensitivity of 95%.
Conclusions: All patients with MS
developed in this study, four eas

1. Introduction

The prevalence of NLUTD in patients with MS varies from 65% to 92% (Marrie et al., 2007; Khalaf et al., 2015). NLUTDs can progress measurably within 1 year, cause complications such as UTIs and hydronephrosis, and affect the quality of life of patients with MS (de Sèze M et al., 2007; Litwiller et al., 1999, Musco et al., 2018). A timely treatment of NLUTDs and a careful consideration of bladder management require a timely identification of NLUTD (Ulivelli et al., 2019; Seland et al., 1999; Sakakibara, 2019; Phé et al., 2016). Various special national guidelines have been developed to identify NLUTD in patients with MS. The guidelines differ in considering the necessity for screening asymptomatic patients, the clinical assessments, parameters, and cutoff points used for screening. Some guidelines applied Expanded Disability Status Scale (EDSS) with and without thresholds (Amarenco et al., 2014; Ghezzi et al., 2011; Barbalias et al. 2001; De Ridder et al., 2013; Averbeck et al., 2020). Some other guidelines recommended uroflowmetry (Krupin and Belova, 2011; Ghezzi et al., 2011; Çetinel et al., 2013). In the US, UK, and Greece guidelines, the bladder diary was not included (Fowler et al., 2009; Seland et al., 1999; Barbalias et al., 2001). Other expert groups and national guidelines recommended its use (Del Popolo et al., 2008; Krupin and Belova, 2011; Ghezzi et al., 2011; De Ridder et al., 2013; Amarenco et al., 2013; Tornic and Panicker, 2018; Averbeck et al., 2020).

In the French guidelines, the urinary bothersome questionnaire was validated for comprehensiveness and acceptance (Amarenco et al., 2013). The Italian guidelines evaluated the PVR, International Prostate Symptom Score (IPSS), and bladder diary to EDSS, to duration of MS, and to pyramidal involvement in patients without any urinary complaints (Ghezzi et al., 2016). Most of the national guidelines have an evidence category of III–IV (Holland and Reitman, 2012a; Aharony et al., 2017).

The role of urodynamic examination in the diagnosis of NLUTD has been in an intense debate (Fowler et al., 2009; Stoffel, 2017; Dillon and Lemack, 2014; Hernandez and Khavari, 2020). The popular British guidelines state that urodynamics are considered unnecessary (Fowler et al., 2009). The French guidelines assume that every patient should have access to an urodynamic examination (Amarenco et al., 2014).

The enumerated differences reflect the existing discussions. To find a satisfactory way of dealing with the points at issue, it is reasonable to standardize the assessments that are recommended in the guidelines and combine them with the necessity to conduct a complete urodynamic study of all symptomatic and asymptomatic patients with MS (Bemelsmans et al., 1993, de Sèze et al., 2007, Musco et al., 2018). A possible method to meet these requirements is to bring together the important parameters and examine them one by one from the point of view of their value to serve as a predictor of NLUTD in a new study using urodynamics as the target variable. This is exactly what the present study is aimed at.

2. Patients and methods

2.1. Development of the new algorithm

Four consensus meetings were organized to prepare the evaluation study and to specify the algorithm with participation of neurologists, urologists, neurourologists, nurses, nurse practitioners, occupational therapists, physical therapists as well as representatives of national MS centers, self-care groups, social care, residential care, and health-aid-providers in the MS Consensus Group (Figure 1).

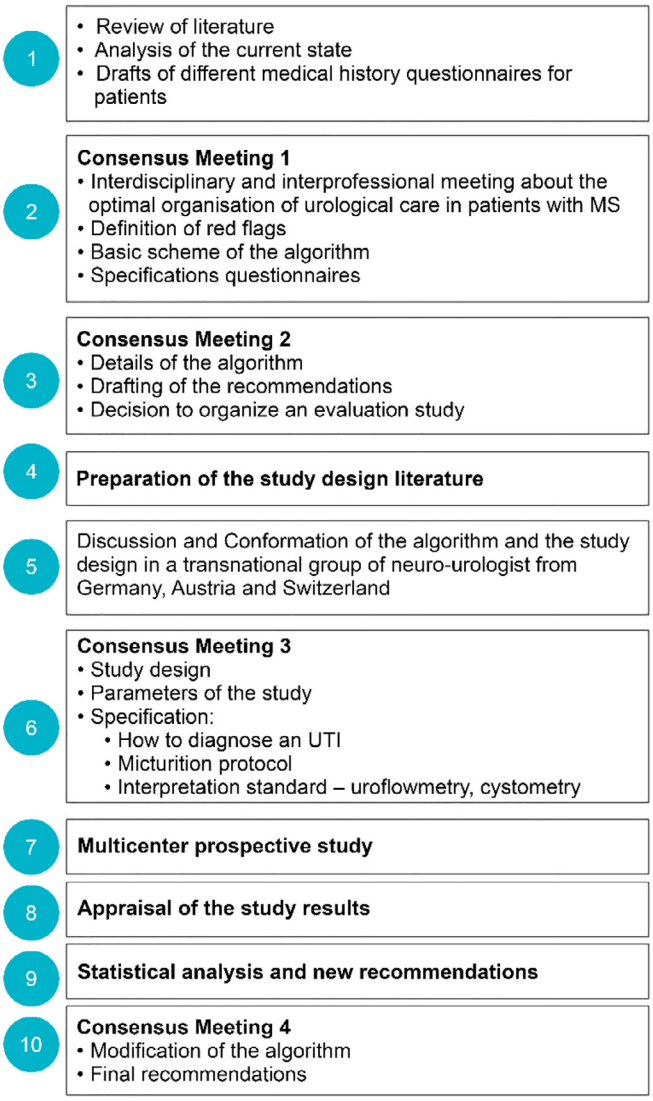

Figure 1. The consensus process steps.

2.2. Study design

We performed a prospective, noninterventional, multicenter study with the following inclusion criteria: patients with a diagnosis of MS (Relapsing-Remitting MS (RRMS), Secondary Progressive MS (SPMS), Primary Progressive MS (PPMS)) according to the McDonald criteria aged 18–80 years, irrespective of whether they reported voiding difficulties (McDonald et al., 2001; Polman et al., 2011).

The exclusion criteria were patients with indwelling catheters, patients who underwent a urodynamic examination in the past, and patients with an acute relapse of MS or acute UTI. Nevertheless, patients with an acute UTI or acute relapse of MS could be included in the study after adequate therapy (antibiotics or steroid pulse, respectively).

2.3. Micturition diary

To standardize the anamnesis and to objectify micturition habits, a patient questionnaire (including such aspects as age, gender, questions characterising the MS, questions about the urological situation) and a

micturition diary were used. To calculate the mean values of micturition frequency, micturition volume, and urine output, the data of two days within the bladder diary were considered. To compare micturition frequencies among patients, the mean micturition frequency was standardized to 2000 mL urine per day in accordance with the studies on a normal daily urine volume (Schoen et al., 2013; Lermen et al., 2019).

2.4. Urodynamic examination

Urodynamic studies, uroflowmetry, and PVR examination were performed according to the Good Urodynamic Practice (Schäfer et al., 2002). The terminology used in this study follows the last standardization reports published by the International Continence Society (D'Ancona et al., 2019). The patients underwent free uroflowmetry with different devices (Medical Measurement, Enshede, Netherlands (now Laborie, USA); Ceres Lite, Wiest Uropower, World of Medicine (W.O.M.), Ludwigshafen, Germany; Ellipse, Andromeda Medizinische Systeme, Taufkirchen, Germany; SEDIA NTV3, SEDIA Medizintechnik; Givisiez, Switzerland).

2.5. Data collection and dataset

On March 22, 2017, the vote of the ethics committee was positive (Medical Council of the State of Brandenburg, N° 4525). The patients signed an informed consent for data collection and were included in the study of the period between April 2017 and May 2018.

The participating neurological and neurourological hospitals are listed at the end of the manuscript.

The data collection included seven domains and 43 items (1. institutional – 2 items, 2. social – 2 items, 3. medical history – 7 items, 4. bladder diary – 7 items, 5. uroflowmetry – 4 items, 6. PVR – 1 item, 7. (video)-urodynamic – 20 items).

2.6. Statistical analysis

Logistic regression models were used to estimate the effect of selected parameters on the binary response variable – abnormal urodynamic examination. First, single regression models (including sex and age as additional covariates) were fitted to reveal independent effects on the outcome. Subsequently, a joint analysis using a logistic regression model for all parameters of interest was performed. To identify the most relevant parameters in a completely data-driven manner, a stepwise variable selection approach based on the Akaike information criteria (AIC) with a combination of forward and backward direction was applied on this model (Akaike, 1973).

To assess the prognostic quality of selected classifiers for the prediction of abnormal urodynamic examination, standard performance measures for binary classifiers were used, namely sensitivity (i.e., the proportion of correctly identified abnormal urodynamic examinations) and the positive predictive value (PPV, i.e., the proportion of cases that are correctly classified as abnormal urodynamic examinations to all classified abnormal urodynamics). The thresholds for the definition of red-flag predictors were identified using recursive partitioning (Breiman et al., 2017), i.e. a classification tree was constructed for the task of classifying abnormal urodynamic examinations by a selected set of predictors.

For all analyses, the R language for statistical computing (Version 3.44) was used (R Core Team, 2018).

3. Results

3.1. Patients' characteristics

We included 145 patients during the period of 13 months. A total of 24 datasets were unusable because of an incorrect bladder diary (N = 15), patients' refusal to undergo a urodynamic examination (N = 6), or an incomplete dataset (N = 3). Thus, data from 121 patients were available for evaluation.

Table 1
Patients' characteristics of the study population.

Parameter	Mean ± SD	Range
Age (years)	49.3 ± 11.3	19 -75
Gender	Male: 33 Female: 88	
EDSS	3.8 ± 2.1	0.5 – 8.0
MS-Course	RRMS – 56.8% SPMS – 31.3% PPMS – 11.9%	
Duration MS (years)	12.2 ± 9.6	0 – 42
Duration urological symptoms (years)	10.1 ± 5.7	0 – 37
UTI-rate (number of UTIs/6 months)	0.8 ± 2.1	0 – 10

Table 1 shows the patients' characteristics. There were more women than men (2.7:1).

3.2. Methods of bladder emptying

Patients used very different methods of bladder emptying. In total, 84 patients could empty the bladder voluntarily, 11 patients performed bladder emptying via straining, 6 patients preferred reflex voiding (with a half of them using an additional intermittent catheterization), 4 patients exclusively used intermittent catheterization, and 3 patients suffered from total incontinence. The remaining 13 patients used various combinations of voluntary emptying, straining, and reflex voiding.

3.3. Identification of red-flags predictors

To identify red flags, we applied an AIC-based stepwise variable selection approach.

Table 2 depicts the marginal effects of 9 parameters of interest on the independent variable "abnormal urodynamic examination". After the variable selection processes, the remaining parameters were micturition frequency, incontinence, UTI rate, and PVR. According to this analysis, a 1-unit increase in the frequency of micturition increased the risk of an abnormal urodynamic examination by approximately 21% (OR = 1.21, 95% CI: [0.99–1.47]). Furthermore, a 10-mL increase in PVR increased the risk for an abnormal urodynamic examination by approximately 26% (OR = 1.26, 95% CI: [1.01–1.57]). Finally, patients with a UTI in the past 6 months had a 2.0 fold, incontinent patients had a 3.9 fold increased risk of an abnormal urodynamic examination.

EDSS did not correlate with an abnormal urodynamic examination (OR = 0.91; 95% CI: [0.69–1.2]). There were no significant correlations between sex, age, and an abnormal urodynamic examination (Table 2). The disease course (RRMS, SPMS, and RRMS) did not

Table 2
Results of the logistic regression analyses.

Parameter	Independent analysis Odds Ratio and 95% CI	Joint analysis, stepwise variable selection, AIC Odds Ratio and 95% CI
Sex: female vs. male	0.84 [0.22; 2.65]	
Age (years)	1.05 [1.00; 1.11]	
UTI rate (6 months)	2.03 [1.04; 6.68]	
Frequency (24 h)	1.24 [1.07; 1.49]	1.21 [0.99; 1.47]
Incontinence: yes vs. no	3.93 [1.17; 15.7]	4.78 [1.06; 21.41]
Disease duration (years)	1.07 [0.99; 1.18]	
Expanded Disability Status Scale (EDSS)	0.91 [0.69; 1.2]	
PVR: 10 mL scale	1.25 [1.07; 1.62]	1.26 [1.01; 1.57]
Uroflowmetry: normal vs. abnormal	4.80 [1.41; 19.21]	

influence either the probability of an NLUTD or the type of urinary bladder dysfunction.

To assess the prognostic quality of the selected parameters with respect to the prediction of an abnormal urodynamic examination, standard performance measures for binary classifiers were used such as sensitivity (i.e., the proportion of correctly identified abnormal urodynamic examinations) and the positive predictive value (PPV).

Uroflowmetry identified patients with a detectable urinary bladder dysfunction with a sensitivity of 69%, a specificity of 71%, and a high PPV of 93.5%.

3.4. Cutoff values of predictors of abnormal urodynamic findings

The mean standardized micturition frequency from the bladder diary was 13.2 ± 5.9 in 24 h. Most of the patients (64.4%) had a micturition frequency of ≤13 times daily.

All patients with a normal urodynamic examination had a PVR value of <67 mL. For practical reasons, we chose 70 mL as the cutoff (Figure 2). In this study, 30.1% of the patients had no PVR and 67.3% had a PVR of <70 mL.

In the present study, the identified red flags predicted a NLUTD in patients with MS as well. Urodynamic abnormalities were observed in all patients with a PVR of >70 mL, in 95.5% of patients with a standardized micturition frequency >13 times/day, and in 84.8% of patients with UTIs and/or incontinence but without elevated PVR (>70 mL) and without a higher micturition frequency.

3.5. NLUTD in the study population

No significant correlation was found between incontinence and detrusor overactivity (DO) (OR = 1.82; 95% CI: 0.83; 4.07) nor between detrusor underactivity (DU) and incontinence (OR = 0.95; 95% CI: 0.36–2.54). The absence of incontinence did not correlate with DU, neither did DU correlate with higher PVR (OR = 1.04; 95% CI: 0.64–1.57). A significant correlation was found between standardized frequency of micturition and DO (Table 3). Detrusor sphincter dyssynergia (DSD), a simultaneous contraction of the detrusor and the rhabdosphincter, was observed in 36 patients, with 13 of them having a PVR >70 mL.

3.6. Definition of diagnostic groups

The goal of consensus conferences was to define groups (clusters) from which the required diagnostics may be derived. The new algorithm comprises four groups according to the predictors and thresholds identified by recursive partitioning (Table 4).

Table 3
Correlation between certain symptoms and type of NLUTD

Symptom	Type of NLUTD	OR	Confidence-Interval (CI)
Incontinence	**DU**	0.95; 95%	0.36; 2.54
Incontinence	**DO**	1.82; 95%	0.83; 4.07
PVR	**DU**	1.04; 95%	0.64; 1.57
PVR	**DO**	1.20; 95%	0.84; 1.73
Frequency of micturition	**DU**	0,91; 95%	0,81; 1.01
Frequency of micturition	**DO**	1.16; 95%	1.07; 1.26

Group 1 (N = 23, 19.7%) included patients without any complaints of NLUTD, without pathologic PVR (<70 mL), and with a normal standardized frequency of micturition (≤13 times daily). All patients in this group were continent and did not report a UTI within the past 6 months. Nevertheless, 12 patients in this group (52.2%) had an NULTD according to the urodynamic examination.

Group 2 (N = 23, 19.7%) comprised patients with a normal PVR (<70 mL) but with a higher micturition frequency (>13 times daily, normalized to 2000 mL). An increased micturition frequency positively correlated with DO in the logistic regression analysis (Table 3, OR = 1.16 (95% CI: [1.07; 1.26])).

Group 3 was the largest, with all the patients in this group (N = 38, 32.5%) having a PVR of ≥70 mL (Figure 3).

Group 4 (N = 33, 28.2%) included patients with normal PVR (<70 mL) and a normal frequency of micturition (≤13/24 h), but with other red flags, such as UTIs in the past 6 months and/or incontinence.

Figure 3 demonstrates the distribution of the predictors included in the four groups of the new algorithm.

Using the proposed four red-flags predictors and the corresponding threshold values from Table 4, the odds ratio for an abnormal urodynamics was 17.4 with a 95% CI of 4.7–75.1.

Comparing these data with the observed outcome of the urodynamic examination, we obtained the given performance values of the proposed new algorithm: the sensitivity was 95%, the PPV – 91%, the specificity - 44% and the Negative Prediction Value (NPV) – 54%.

4. Discussion

There is insufficient progress in the diagnosis and therapy of NLUTD in patients with MS (Fowler et al., 1992; Mahajan et al., 2013; Stahmann et al., 2017; Rommer et al., 2019). The aim of the present

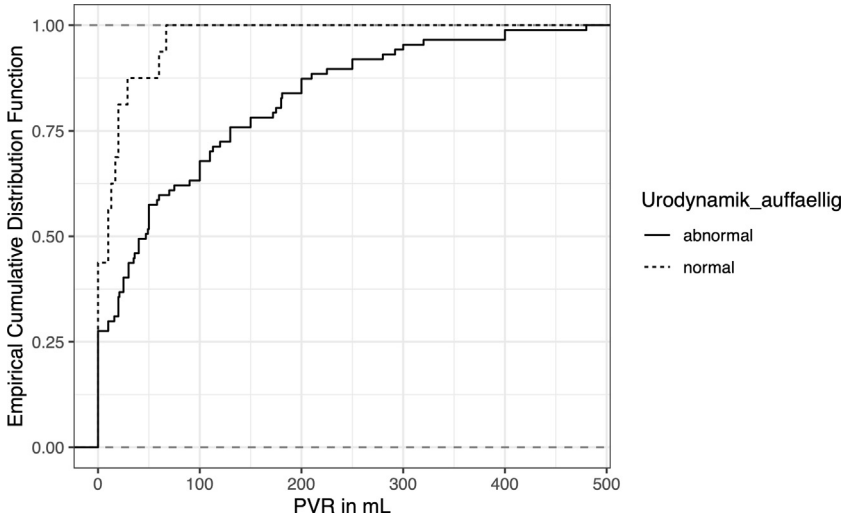

Figure 2. Cumulative distribution function of PVR vs. results of urodynamic examinations.

Table 4
Characteristics of the patient groups (N = 117). In 4 patients, PVR data were missing outside of cystomanometry. For the sake of inner logic, a grouping in the algorithm was not performed for these 4 patients and the classification process was continued with 117 patients.

Diagnostic Method	Parameter	Definition of the diagnostic groups			
		Group 1 (n = 23)	Group 2 (n = 23)	Group 3 (n = 38)	Group 4 (n = 33)
Micturition diary (at least 3 days)	Micturition Frequency (number /24h, standardized on 2.000mL)	≤13	>13	variable	≤13
Sonography	PVR (mL)	<70	<70	≥70	<70
Medical history	>0 UTI last 6 Months and/ or Incontinence	no	no or yes	no or yes	yes

study is to develop an algorithm that in a routine medical practice will allow to identify NLUTD in patients with MS early, easily, and in a precise manner. To our knowledge, this is the first completely evaluated neurourological algorithm for patients with MS.

There was no statistically significant correlation between the complaints of NLUTD reported by patients with MS and the results of urodynamic examinations. This conclusion is confirmed by some other authors (Amundsen et al., 1999; Wiedemann et al., 2013; Haggiag et al., 2017; Fragalà et al., 2015). Blaivas found that a treatment based exclusively on reported symptoms was ineffective for at least 50% of patients with MS (Blaivas, 1980). In our study, we examined those parameters that made it possible to objectify the subjective view of patients on urological complaints. It was found out that four such predictors taken together could provide the diagnosis of NLUTD with a sufficient reliable certainty. These parameters have been already used in a qualitative manner in other national guidelines in different combinations and with different significances.

Our research confirmed the assumption that all patients with MS, even those who are asymptomatic (1st group, 20.6% of patients), should be examined for NLUTD. Some other national guidelines have considered these patients as well (De Ridder et al., 2013; Amarenco et al., 2014; Ghezzi et al., 2016). In the present study, 23 patients did not declare urological complaints. However, twelve of them had abnormal urodynamic findings. To identify these patients at risk of neurogenic bladder dysfunction, uroflowmetry can be used owing to its good sensitivity (69%), specificity (71%), and high PPV (94%). Some other

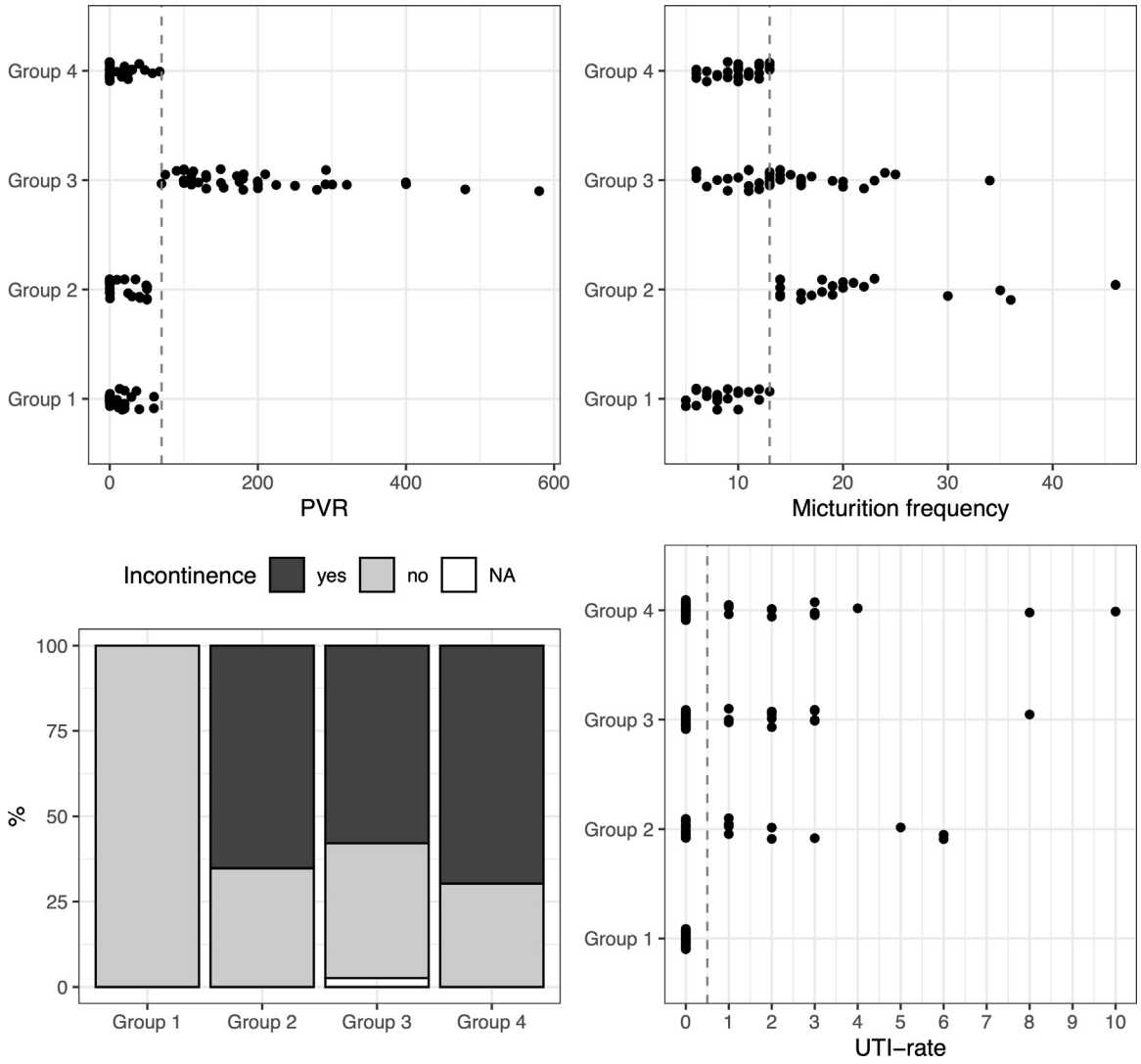

Figure 3. Attributes used to classify the groups (PVR, incontinence, micturition frequency and UTI rate). The dashed lines indicate the cutoff values.

authors using urodynamic examination detected NULTDs in 10%–81% of patients without NLUTD symptoms (Cofield et al., 2014; Wiedemann et al., 2013: Bemelsmans et al., 1993). Tayyaddon et al. emphasized that 94% of patients without urological symptoms underwent symptomatic NLUTD within one year of follow-up (Tadayyon et al., 2012).

The 2nd group in this evaluation corresponded to the patient group with urgency and frequency as reported in other guidelines (Fowler et al., 2009). In general, in different studies (Betts et al., 1993) this group of patients is the largest (from 33% to 82%), but in our study, the group with frequency was considerably smaller (19.7%). This can be accounted for by the fact that the term “frequency” is not clearly defined by the International Continence Society (Abrams et al., 1988). In the present study, we apply the term frequency to indicate precise statistics (more than 13 micturitions /24 h). This approach makes the group under discussion more homogeneous. An increased micturition frequency positively correlated with DO in the logistic regression analysis (Table 3, OR = 1.16 (95% CI: [1.07; 1.26]). Drug therapy to suppress DO is recommended.

In all guidelines, the intermittent catheterization is favored for patients with pathological PVR (3rd group in this study). Nevertheless, there is no widely accepted threshold for an abnormal PVR in different patient populations, and the cutoff points used in practice vary arbitrarily (Abrams et al., 2001). The UK guidelines determined a threshold for an abnormal PVR of 100 mL (Fowler, 1996). In 2005, Wu and Baguley found that a PVR of >150 mL correlates with a higher UTI rate (Wu and Baguley, 2005). PVR >150 mL was defined as pathological by the Belgium guidelines (De Ridder et al., 2013). The American Multiple Sclerosis Society considered a PVR of >200 mL as an indication of urine retention (Holland and Reitman, 2012b). In 2017, Stoffel recommended a threshold value of 300 mL for PVR in patients with MS. Our PVR cutoff of >70 mL was the first statistically confirmed PVR in patients with MS. Furthermore, a PVR of ≥70 mL correlated well with an abnormal urodynamic examination (Figure 2). Patients with a higher PVR should learn intermittent self-catheterization. The beginning and the frequency of catheterization depend on the severity of PVR and the corresponding symptoms.

In this study, 28.2% of patients (4th group) had a normal frequency of micturition and a PVR of <70 mL but suffered from incontinence and/or UTIs. A calculated first-line therapy was impossible due to the heterogeneity of NLUTD (27% - DU, 37.5% - DO, 40% - DSD, 20% - incontinence of different types). Moreover, 15.2% of patients in this group had a normal urodynamic examination. The UTIs in these patients were caused by reasons other than neurogenic bladder dysfunction. Patients from group 4 should undergo cystometry as the second diagnostic step before an adequate therapeutic decision is possible.

Our algorithm revealed a high sensitivity of 95%. Because of the PPV of 91%, the algorithm is likely to be appropriate as the first step of a noninvasive screening for NLUTD in patients with MS (Spix and Blettner, 2012; Rothschild and Xu, 2019).

5. Limitations

The proportion of patients with abnormal urodynamics was relatively high in the present study, despite the consideration of asymptomatic patients. To further improve the negative predictive value, a greater number of patients with normal urodynamic are to be examined.

Another limitation was the low proportion of patients with detrusor underactivity. There-fore, a possible subgrouping looks doubtful.

Our strict thresholds are due to the limited number of the patients included in the study. With a larger number of patients, the so-called gray zone thresholds would be more practical in daily routine. Further investigations with more participants are to be conducted.

6. Conclusions

We developed and evaluated a consensus algorithm for a simplified diagnosis of NLUTD in patients with MS and validated its sensitivity and predictive value through analysis of a large cohort of patients.

All patients with MS should be examined for NLUTD irrepective of their urological complaints. The proposed algorithm with four easy to collect parameters - PVR, micturition frequency, UTI-rate, incontinence, and additionally uroflowmetry can complete the neurological assessment standards to ameliorate diagnosis and management of NLUTD in patients with MS. Algorithm points out that further diagnostics is required to provide the patient with a specific therapy based on the results.

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CRediT authorship contribution statement

Burkhard Domurath: Conceptualization, Methodology, Funding acquisition, Data curation, Investigation, Writing - original draft, Writing - review & editing, Formal analysis. **Ines Kurze:** Funding acquisition, Data curation, Investigation. **Ruth Kirschner-Hermanns:** Funding acquisition, Data curation, Investigation, Writing - review & editing. **Albert Kaufmann:** Funding acquisition, Data curation, Investigation. **Wolfgang Feneberg:** Funding acquisition, Data curation, Investigation, Writing - review & editing. **Paul Schmidt:** Funding acquisition, Methodology, Writing - original draft, Writing - review & editing, Formal analysis, Validation. **Thomas Henze:** Funding acquisition, Writing - original draft, Writing - review & editing. **Peter Flachenecker:** Funding acquisition, Writing - original draft, Writing - review & editing. **Anna Brandt:** Data curation, Investigation. **Will Nelson Vance:** Investigation. **Janina Beck:** Investigation. **Manuela Vonthien:** Conceptualization, Writing - review & editing, Data curation. **Kerstin Ratering:** Conceptualization, Data curation, Writing - review & editing.

Declaration of Competing Interest

M. Vonthien and K. Ratering from Coloplast GmbH, Hamburg, Germany reviewed the literature, the analysis of the current state of urological diagnostics, and the therapy of patients with MS to prepare questionnaires and to design the algorithm. They did not influence the discussions, results, and recommendations.

Paul Schmidt was paid by Coloplast GmbH, Hamburg, Germany for performing the statistical evaluations.

The other authors declare no conflict of interests.

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References

Abrams, P., Blaivas, J.G., Stanton, S.L., Andersen, J.T., 1988. The standardisation of terminology of lower urinary tract function. The International Continence Society Committee on Standardisation of Terminology. Scand. J. Urol. Nephrol. Suppl. 114, 5–19.

Abrams, P., Griffiths, D., Hoefner, K., Liao, L., Schafer, W., Tubaro, A., Zimmern, P., 2001. In: Chatelain, C., Denis, L., Foo, K., Khoury, S., McConnell, J. (Eds.), Benign Prostatic Hy- perplasia, Health Publication Ltd., Plymouth, pp. 370.

Aharony, S.M., Lam, O., Corcos, J., 2017. Evaluation of lower urinary tract symptoms in multiple sclerosis patients: review of the literature and current guidelines. Can. Urol. Assoc. J 11 (1-2), 61–64. https://doi.org/10.5489/cuaj.4058.

Akaike, 1973. Information theory and an extension of the maximum likelihood principle. In: Petrov, B.N., Csáki, F. (Eds.), 2nd International Symposium on Information Theory, Tsahkadsor, Armenia, USSR, September 2–8, 1971. Akadémiai Kiadó, Budapest, pp. 267–281.

Amarenco, G., de Sèze, M., Ruffion, A., Sheikh Ismael, S.S., 2014. Clinical and urodynamic evaluations of urinary disorders in multiple sclerosis, Ann. Phys. Rehabil. Med 57 (5), 277–287. https://doi.org/10.1016/j.rehab.2014.05.006.

Amarenco, G., Chartier-Kastler, E., Denys, P., Jean, J.L., de Sèze, M., Lubetzski, C., 2013. First-line urological evaluation in multiple sclerosis: validation of a specific decision-making algorithm. Mult. Scler 19 (14), 1931–1937. https://doi.org/10.1177/1352458513489758 Pubmed:23698129.

Amundsen, C., Lau, M., English, S.F., McGuire, E.J., 1999. Do urinary symptoms correlate with urodynamic findings? J. Urol. 161 (6), 1871–1874.

Averbeck, M.A., Iacovelli, V., Panicker, J., Schurch, B., Finazzi Agrò, E., 2020. Urodynamics in patients with multiple sclerosis: A consensus statement from a urodynamic expert working group. Neurourol. Urodyn. 39 (1), 73–82. https://doi.org/10.1002/nau.24230.

Barbalias, G.A., Liatsikos, E.N., Passakos, C., Barbalias, D., Sakelaropoulos, G., 2001. Urologic manifestations of multiple sclerosis: proposed treatment algorithms. Int. Urol. Nephrol. 32 (3), 345–348. https://doi.org/10.1023/a:1017532631643 Pubmed:11583349.

Bemelsmans, B.L.H., Hommes, O.R., van Kerrebroek, P.E.V., Lemmens, W.A., Doeburg, W.H., Debruyne, F.M., 1993. Evidence for early lower urinary tract dysfunction in clinically silent multiple sclerosis. J. Urol 145 (6), 1219–1224.

Betts, C.D., D'Mellow, M.T., Fowler, C.J., 1993. Urinary symptoms and the neurological features of bladder dysfunction in multiple sclerosis. Neurol Neurosurg Psychiatry 56 (3), 245–250.

Blaivas, J.G., 1980. Management of bladder dysfunction in multiple sclerosis. Neurology 30 (7 Pt2), 12–18. https://doi.org/10.1212/wnl.30.7_part_2.12.

Breiman, L., Friedman, J.H., Olshen, R.A., Stone, C.J., 2017. Classification and Regression Trees. Chapman&Hall/CRC. https://doi.org/10.1201/9781315139478.

Çetinel, B., Tarcan, T., Demirkesen, O., Özyurt, C., Şen, İ, Erdoğan, S., Siva, A., 2013. Management of lower urinary tract dysfunction in multiple sclerosis: a systematic review and Turkish consensus report. Neurourol. Urodyn 32 (8), 1047–1057. https://doi.org/10.1002/nau.22374.

Cofield, S. S., Tang, Y., Salter, A., Tyry, T., Yang, H., Onyenwenyi, A., Marrie, R. A., 2014. Severity and characteristics of overactive bladder condition in MS: an ancillary analysis of the NARCOMS Registry Data, Poster SX08. CMSC ACTRIMS Cooperative, Dallas.

D'Ancona, C., Haylen, B., Oelke, M., Abranches-Monteiro, L., Arnold, E., Goldman, H., Hamid, R., Homma, Y., Marcelissen, T., Rademakers, K., Schizas, A., Singla, A., Soto, I., Tse, V., de Wachter, S., Herschorn, S., Standardisation Steering Committee ICS and the ICS Working Group on Terminology for Male Lower Urinary Tract & Pelvic Floor Symptoms and Dysfunction, 2019. The International Continence Society (ICS) report on the terminology for adult male lower urinary tract and pelvic floor symptoms and dysfunction. Neurourol. Urodyn. 38 (2), 433–477. https://doi.org/10.1002/nau.23897 Epub January 25 2019. Pubmed:30681183.

Del Popolo, G., Panariello, G., Del Corso, F., De Sciscilo, G., Lombardi, G., 2008. Diagnosis and therapy for neurogenic bladder dysfunctions in multiple sclerosis patients. Neurol. Sci 29 (Suppl. 4), S352–S355. https://doi.org/10.1007/s10072-008-1042-y.

De Ridder, D., Van Der Aa, F., Debruyne, J., D'hooghe, M.B., Dubois, B., Guillaume, D., Heerings, M., Ilsbroukx, S., Medaer, R., Nagels, G., Seeldrayers, P., Van Landegem, W., Willekens, B., Zicot, A.F., 2013. Consensus on the neurologist's role in the management of neurogenic lower urinary tract dysfunction in multiple sclerosis. Clin. Neurol. Neurosurg 115 (10), 2033–2040. https://doi.org/10.1016/j.clineuro.2013.06.018.

de Sèze, M., Ruffion, A., Denys, P., Joseph, P.A., Perrouin-Verbe, B., GENULF, 2007. The neurogenic bladder in multiple sclerosis: review of the literature and proposal of management guidelines. Mult. Scler 13 (7), 915–928. https://doi.org/10.1177/1352458506075651.

Dillon, B.E., Lemack, G.E., 2014. Urodynamics in the evalua- tion of the patient with multiple sclerosis: when are they helpful and how do we use them? Urol. Clin. North Am 41 (3), 439–444. ix. https://doi.org/10.1016/j.ucl.2014.04.004.

Fowler, C.J., 1996. Investigation of the neurogenic bladder, J. Neurol. Neurosurg. Psychiatry. 60 (1), 6–13. https://doi.org/10.1136/jnnp.60.1.6.

Fowler, C.J., Panicker, J.N., Drake, M., Harris, C., Harrison, S.C.W., Kirby, M., Lucas, M., Macleod, N., Mangnall, J., North, A., Porter, B., Reid, S., Russell, N., Watkiss, K., Wells, M., 2009. A UK consensus of the management of the bladder in multiple sclerosis, J. Neurol. Neurosurg. Psychiatry. 80 (5), 470–477. https://doi.org/10.1136/jnnp.2008.159178.

Fowler, C.J., van Kerrebroeck, P.E., Nordenbo, A., van Poppel, H., 1992. Treatment of lower urinary tract dysfunction in patients with multiple sclerosis. Committee of the European Study Group of SUDIMS (Sexual and Urological Disorders in Multiple Sclerosis). J. Neurol. Neurosurg. Psychiatry. 55 (11), 986–989. https://doi.org/10.1136/jnnp.55.11.986.

Fragalà, E., Russo, G.I., Di Rosa, A., Giardina, R., Privitera, S., Favilla, V., Patti, F., Welk, B., Cimino, S., Castelli, T., Morgia, G., 2015. Association between the neurogenic bladder symptom score and urodynamic examination in multiple sclerosis patients with lower urinary tract dysfunction. Int Neurourol J 19 (4), 272–277. https://doi.org/10.5213/inj.2015.19.4.272.

Ghezzi, A., Carone, R., Del Popolo, G., Amato, M.P., Bertolotto, A., Comola, M., Del Carro, U., Di Benedetto, P., Giannantoni, A., Lopes de Carvalho, M.L., Montanari, E., Patti, F., Protti, A., Rasia, S., Salonia, A., Scandellari, C., Sperli, F., Spinelli, M., Solaro, C., Uccelli, A., Zaffaroni, M., Zipoli, V., Multiple Sclerosis Study Group, 2011. Recommendations for the management of urinary disorders in multiple sclerosis: a consensus of the Italian multiple sclerosis Study Group. Neurol. Sci 32 (6), 1223–1231. https://doi.org/10.1007/s10072-011-0794-y.

Ghezzi, A., Mutta, E., Bianchi, F., Bonavita, S., Buttari, F., Caramma, A., Cavarretta, R., Centonze, D., Coghe, G.C., Coniglio, G., Del Carro, U., Ferrò, M.T., Marrosu, M.G., Patti, F., Rovaris, M., Sparaco, M., Simone, I., Tortorella, C., Bergamaschi, R., 2016. Diagnostic tools for assessment of urinary dysfunction in MS patients without urinary disturbances. Neurol. Sci 37 (3), 437–442. https://doi.org/10.1007/s10072-015-2415-7.

Haggiag, S., Bolla, G., Picconi, O., Galgani, S., Gasperini, C., 2017. Discrepancies between urinary symptoms assessment and objective bladder dysfunctions in multiple sclerosis. Mult. Scler. Demyelinating Disord 2, 11. https://doi.org/10.1186/s40893-017-0029-z.

Hernandez, N., Khavari, R, 2020. Neurourology in multiple sclerosis and other demyelinating disorders. In: Stoffel, J., Dray, E. (Eds.), Urological Care for Patients with Progressive Neurological Conditions. Springer, Cham, Switzerland, pp. 117–126.

Holland, N.J., Reitman, N.C., 2012a. Bladder Dysfunction in Multiple Sclerosis Vol. 7p.

Holland, N.J., Reitman, N.C., 2012b. In: Bladder Dysfunction in Multiple Sclerosis, . https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Clinical-Bulletin-Bladder-Dys.pdf Accessed May 15 2019, Vol. 7p, National Multiple Sclerosis Society.

Khalaf, K.M., Coyne, K.S., Globe, D.R., Armstrong, E.P., Malone, D.C., Burks, J., 2015. Lower Urinary tract symptom prevalence and management Among patients with multiple sclerosis. Int. J. MS Care 17 (1), 14–25. https://doi.org/10.7224/1537-2073.2013-040.

Krupin, V.N., Belova, A.N., 2011. Neurogenic bladder and multiple sclerosis. Sovrem. Tehnol. Med 4, 126–135.

Lermen, D., Bartel-Steinbach, M., Gwinner, F., Conrad, A., Weber, T., von Briesen, H., Kolossa-Gehring, M., 2019. Trends in characteristics of 24-h urine samples and their relevance for human biomonitoring studies − 20 years of experience in the German Environmental Specimen Bank. Int. J. Hyg. Environ. Health 222 (5), 831–839. https://doi.org/10.1016/j.ijheh.2019.04.009 Epub April 26 2019.

Litwiller, S.E., Frohman, E.M., Zimmern, P.E., 1999. Multiple sclerosis and the urologist. J. Urol. 161 (3), 743–757. https://doi.org/10.1016/S0022-5347(01)61760-9.

Mahajan, S.T., Frasure, H.E., Marrie, R.A., 2013. The prevalence of urinary catheterization in women and men with multiple sclerosis. J Spinal Cord Med 36 (6), 632–637. https://doi.org/10.1179/2045772312Y.0000000084.

Marrie, R.A., Cutter, G., Tyry, T., Vollmer, T., Campagnolo, D., 2007. Disparities in the management of multiple sclerosis-related bladder symptoms. Neurology 68 (23), 1971–1978. https://doi.org/10.1212/01.wnl.0000264416.53077.8b Pubmed:17548546.

McDonald, W.I., Compston, A., Edan, G., Goodkin, D., Hartung, H.P., Lublin, F.D., McFarland, H.F., Paty, D.W., Polman, C.H., Reingold, S.C., Sandberg-Wollheim, M., Sibley, W., Thompson, A., van den Noort, S., Weinshenker, B.Y., Wolinsky, J.S., 2001. Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. Ann. Neurol 50 (1), 121–127. https://doi.org/10.1002/ana.1032.

Musco, S., Padilla-Fernández, B., Del Popolo, G., Bonifazi, M., Blok, B.F.M., Groen, J., 't Hoen, L., Pannek, J., Bonzon, J., Kessler, T.M., Schneider, M.P., Gross, T., Karsenty, G., Phé, V., Hamid, R., Ecclestone, H., Castro-Diaz, D., 2018. Value of urodynamic findings in predicting upper urinary tract damage in neuro-urological patients: A systematic review. Neurourol. Urodyn 37 (5), 1522–1540. https://doi.org/10.1002/nau.23501.

Phé, V., Chartier-Kastler, E., Panicker, J.N., 2016. Management of neurogenic bladder in patients with multiple sclerosis. Nat. Rev. Urol 13 (5), 275–288. https://doi.org/10.1038/nrurol.2016.53 Pubmed:27030526.

Polman, C.H., Reingold, S.C., Banwell, B., Clanet, M., Cohen, J.A., Filippi, M., Fujihara, K., Havrdova, E., Hutchinson, M., Kappos, L., Lublin, F.D., Montalban, X., O'Connor, P., Sandberg-Wollheim, M., Thompson, A.J., Waubant, E., Weinshenker, B., Wolinsky, J.S., 2011. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. Ann. Neurol. 69 (2), 292–302. https://doi.org/10.1002/ana.22366 Pubmed:21387374.

R Core Team, 2018. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.

Rommer, P.S., Eichstädt, K., Ellenberger, D., Flachenecker, P., Friede, T., Haas, J., Kleinschnitz, C., Pöhlau, D., Rienhoff, O., Stahmann, A., Zettl, U.K., 2019. Symptomatology and symptomatic treatment in multiple sclerosis: results from a nationwide MS registry. Mult. Scler 25 (12), 1641–1652. https://doi.org/10.1177/1352458518799580 Epub September 19 2018.

Rothschild, J., Xu, C.W., 2019. Historical and current concepts Regarding urodynamics in multiple sclerosis patients. Curr. Bladder Dysfunct. Rep 14, 168–173. https://doi.org/10.1007/s11884-019-00525-8.

Sakakibara, R., 2019. Neurogenic lower urinary tract dysfunction in multiple sclerosis, neuromyelitis optica, and related disorders. Clin. Auton. Res 29, 313–320. https://doi.org/10.1007/s10286-018-0551-x.

Schäfer, W., Abrams, Liao, P., Mattiasson, L., Pesce, A., Spangberg, F., Sterling, A., Zinner, A.M., van Kerrebroeck, N.R., International Continence Society, P., 2002. Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. Neurourol. Urodyn 21 (3), 261–274. https://doi.org/10.1002/nau.10066.

Schoen, T., Blum, J., Paccaud, F., Burnier, M., Bochud, M., Conen, D., 2013. Factors associated with 24-hour urinary volume: the Swiss salt survey. BMC Nephrology 14, 246. http://www.biomedcentral.com/1471-2369/14/246 (accessed 14 June 2019).

Seland, T.P., Brunette, J., Clesson, I.M., Halper, J., Haselkorn, J., Holland, N., La Rocca, N., Namey, M., Nanninga, J., Rosenberg, J., Soderberg, J., Wilder, S., 1999. Urinary Dysfunction in Multiple Sclerosis. Multiple Sclerosis Council for Clinical Practice Guidelines Multiple Sclerosis Council for Clinical Practice Guidelines Paralyzed Veterans of America. www.pva.org/media/pdf/urinary_ms79c8.pdf (accessed 05 May 2019).

Spix, C., Blettner, M., 2012. Screening—Part 19. Dtsch. Arztebl. Int. 109, 385–390. https://doi.org/10.3238/arztebl.2012.0385 Pubmed:22690254.

Stahmann, A., Eichstädt, K., Ellenberger, D., Meißner, T., Meyer, C., Zettl, U.K., Rommer, P.S., et al., 2017. In: MS in Deutschland: Symptome und Behandlungsdefizite Aktuelle Daten aus dem MS-Register der DMSG für die MS-Forschung, Poster P013, Jahrestagung DGN.

Stoffel, J.T., 2017. Chronic urinary retention in multiple sclerosis patients. Urol. Clin. N. Am 44 (3), 429–439. https://doi.org/10.1016/j.uci.2017.04.009.

Tadayyon, F., Etemadifar, M., Bzeih, H., Zargham, M., Nouri-Mahdavi, K., Akbari, M., Tadayyon, B., 2012. Association of urodynamic findings in new onset multiple sclerosis with subsequent occurrence of urinary symptoms and acute episode of disease in females, J. Res. Med. Sci. 17 (4), 382–385.

Tornic, J.N., Panicker, J.N., 2018. The management of lower urinary tract dysfunction in multiple sclerosis. Curr. Neurol. Neurosci. Rep 18 (8), 54. https://doi.org/10.1007/s11910-018-0857-z.

Ulivelli, M., Monti, L., Ballerini, M., Bartalini, S., Cerase, A., Cecconi, F., Pizzirusso, G., Bezzini, D., Rossi, A., Rossi, S., 2019. Prospective study of clinical, neurophysiological and urodynamic findings in multiple sclerosis patients undergoing percutaneous transluminal venous angioplasty. Clin. Neurophysiol 130 (1), 138–144. https://doi.org/10.1016/j.clinph.2018.10.015.

Wiedemann, A., Kaeder, M., Greulich, W., Lax, H., Priebel, J., Kirschner-Hermanns, R., Füsgen, I., 2013. Which clinical risk factors determine a pathological urodynamic evaluation in patients with multiple sclerosis? An analysis of 100 prospective cases. World J. Urol. 31 (1), 229–233. https://doi.org/10.1007/s00345-011-0820-y.

Wu, J., Baguley, I.J., 2005. Urinary retention in a general Rehabilitation Unit: prevalence, clinical outcome, and the role of screening. Arch. Phys. Med. Rehabil 86 (9), 1772–1777. https://doi.org/10.1016/j.apmr.2005.01.012.