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Assessment of renal deterioration and associated risk factors in patients with multiple sclerosis

Nabeel A. Shakir[1], Arthi Satyanarayan[1], Jessica Eastman[1], Benjamin M. Greenberg[2], Gary E. Lemack[1,2]

1. Department of Urology, University of Texas Southwestern Medical Center
2. Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center

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Corresponding author: Gary E. Lemack, MD
Professor of Urology and Neurology
Rose Mary Haggar Professor
Residency Program Director in Urology
Department of Urology
University of Texas Southwestern Medical Center
Room JA5.130D
5323 Harry Hines Blvd.
Dallas, TX 75390-9110
Telephone: 214-648-7190
Gary.Lemack@UTSouthwestern.edu

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Abstract

Objective
To evaluate predictors of renal deterioration (RD) in patients with multiple sclerosis (MS) at a tertiary referral center.

Methods
We reviewed adult patients with MS presenting for evaluation of lower urinary tract symptoms, with baseline UDS and either serum creatinine (SCr) or renal ultrasound (RUS), from a prospectively maintained database, and excluded patients with abnormal renal function. RD was defined as doubled SCr, new hydronephrosis, or renal atrophy on follow-up US. Demographic and UDS parameters were evaluated in multivariable models of RD.

Results
From 1999-2016, 660 patients were evaluated, and 355 met criteria with median followup of 79 months. SCr doubled in 8 patients, 4 had decline by RUS, and 1 by both (3%). Overall, 46 patients met less strict criteria of decrease in estimated glomerular filtration rate (eGFR) by ≥30%. Using the less rigid criterion, detrusor overactivity (DO) remained associated with RD on multivariable analysis. 11/355 patients had RD by either imaging or doubled Cr, with which only history of diabetes mellitus and nephrolithiasis were associated.

Conclusions
By strict criteria, the rate of RD in patients with NGB due to MS was low (3%) at intermediate-term followup and was not associated with UDS parameters. Using more liberal criteria, DO was associated with deterioration, suggesting that study of the impact of more aggressive control of DO in this population may be warranted.

Introduction

Patients suffering from neurogenic bladder (NGB) related to Multiple Sclerosis (MS) often report lower urinary tract symptoms (LUTS), have urodynamic (UD) abnormalities on functional testing, and may develop renal deterioration (RD).[1] Of all patients with MS, 65-75% report moderate to severe LUTS, and symptom prevalence increases progressively with disease duration.[2] Concomitantly, UD findings in symptomatic patients include detrusor overactivity (DO) most commonly (mean 70%), followed by detrusor-external sphincter dyssnergia (DESD, 28%) and detrusor underactivity (15%).[3] Despite the high proportion of LUTS and UD abnormalities, the incidence of RD secondary to NGB in patients with MS appears to be low overall.[4]

Although studies to date have identified duration of disease and Expanded Disability Status Scale score (EDSS) as potential predictors of RD[5], and EDSS in particular as a predictor of UD abnormalities[6], whether the association established in other populations (ie. abnormal compliance in patients with myelomeningocele) also holds true for those with MS is uncertain.[7,8]. In this study, we evaluated the risk and potential predictors of RD, assessed clinically and radiographically, in a population of patients with NGB secondary to MS followed over time at a tertiary referral center.

Materials and methods

Patient selection

Following Institutional Review Board approval, we reviewed a prospectively maintained database of consecutive adult patients with MS referred for evaluation of LUTS to our center from December 1999 to September 2016. Patients underwent detailed history and physical examination, baseline measurement of serum creatinine (SCr), and most underwent a recommended baseline, urodynamics, renal ultrasound (RUS), as well as repeat studies as clinically appropriate. We included subjects who had at least two office visits and serial determination of SCr, RUS or both with follow-up ≥6 months. Patients with elevated SCr at the initial visit, prior nephrectomy, or other neurologic diagnosis were excluded. Demographic and clinical data including type of MS (primary progressive, relapsing-remitting, secondary progressive), time since diagnosis, and bladder management at presentation (voiding spontaneously, clean intermittent catheterization, or indwelling catheter) were recorded. As EDSS was unavailable for a majority of patients, we determined physical mobility status in terms of wheelchair use, as patients with lower extremity motor loss are more likely to have lower urinary tract dysfunction.[9]

Urodynamic assessment

For patients who underwent UD testing, the study was performed and interpreted by one investigator (G.E.L.) under guidelines established by the International Continence Society.[10] All patients who had UDS were without urinary tract infection at the time of

the procedure. Our multichannel videourodynamics protocol utilized a dual lumen 6 French vesical and 10 French rectal catheter with fill rates of 25-50 mL/min and external urethral sphincter activity measured with surface electromyographic (EMG) electrodes (Laborie Medical Technologies Inc., Toronto, Canada). Maximum cystometric capacity (MCC), DESD by surface EMG and fluoroscopic evidence during voiding, maximum flow rate (Q_{max}) and detrusor pressure at Q_{max}, and post-void residual (PVR) were recorded. DO was defined as involuntary rise in detrusor pressure of ≥5 cm H_2O during filling, and decreased compliance was defined as vesical pressure ≤10 mL/cm H_2O from initial measurement to MCC.

Outcomes

RUS abnormalities were defined as new onset hydronephrosis or cortical atrophy on repeat RUS if a baseline study was performed. All ultrasound studies were performed as part of clinical care and interpreted at our institution by radiologists uninvolved in the study protocol. Estimated glomerular filtration rate (eGFR) was calculated for all patients with measured SCr using the Cockcroft-Gault formula and the body weight corresponding to the date of SCr. RD was defined as either doubling of SCr, or development of new abnormalities on most recent RUS. A more liberal criterion of ≥30% decline in eGFR was also used based on its potential prognostic significance for the development of end-stage renal disease (ESRD), relative to the traditional cutoff of doubled SCr.[11] Interventions during the study period, including starting anticholinergics or alpha-blockers de novo, change in bladder management, or undergoing intravesical

botulinum toxin injection, were recorded for each patient. For patients who underwent urinary diversion, the SCr and RUS just prior to surgery was utilized.

Statistical analysis

The R software package was used for all analyses. Continuous variables were compared with the Mann-Whitney U test and categorical variables with Fisher's exact test. To determine whether UD parameters were associated with the development of RD, they were evaluated via univariate and multivariable logistic regression together with potential demographic and clinical covariates among patients with initial UDS. Parameters meeting a threshold $p<0.15$ were included in a final multivariable model where significance was defined as $p<0.05$.

Results

Demographics

Of 660 patients who were evaluated during the study period, 355 met criteria with median overall follow-up of 79 months (interquartile range: 49-122). One patient who had previous nephrectomy, two whose neurologic diagnosis was reclassified as acute demyelinating encephalomyelitis, 120 who did not undergo baseline UDS, and 183 who did not have follow-up imaging or SCr were excluded. Demographic and clinical data is summarized in Table 1. History of nephrolithiasis was noted in 10% of patients. Of 223/355 patients who had baseline RUS, abnormalities were present in 14/223 (6%) and were principally unilateral hydronephrosis.

Rate of renal deterioration

Serial SCr measurements were available for 340/355 patients and follow-up RUS for 146/355. For the 146 patients with serial imaging, the median interval follow-up between the initial and most recent imaging study was 94 months (interquartile range: 54-140). The overall rate of RD by strict criteria (doubled SCr or new RUS abnormality) was 11/355 (3%), and by liberal criteria 46/355 (13%, Table 1). RD was driven primarily by decline in eGFR; only 5 patients had new RUS abnormalities. There was no association between change in imaging findings and decline in eGFR (p=0.5). Most patients (235/355) had follow-up >60 months and the majority of RD occurred at or beyond this time point (Figure 1). Supplementary Figure 1 summarizes follow-up and outcomes for the study population.

Urodynamic assessment and bladder management

DO was noted on UDS in 153/355 patients, DESD in 107/355, and decreased compliance in 25/355 (Table 2). The only UD parameter associated with development of RD by liberal criteria was DO (p=0.01). Patients with both DO and DESD (62/355) were not more likely to have RD (12/62 vs 34/293, p=0.1). Patients with RD had similar MCC, Q_{max}, and PVR as those without RD. Most patients (293/355) were voiding at initial visit, and of these 293, 233 were voiding at most recent follow-up. Clean intermittent catheterization (CIC) was ultimately employed by 72/355, indwelling catheter by 45/355, and 5/355 underwent urinary diversion during the study period (two for bladder cancer). There was no association between change in bladder management and development of RD (p=0.7).

Multivariable analysis

Demographic and clinical parameters meeting a threshold p<0.15 on univariate logistic regression models of RD by liberal criteria (Table 3) were body-mass index (p=0.04), history of nephrolithiasis (p=0.02), hypertension (p=0.1), type 2 diabetes mellitus (p=0.08), presence of DO (p=0.01), and detrusor pressure at Q_{max} (p=0.1). In the final multivariable model, presence of DO remained associated with development of RD (using liberal criteria) when controlling for potentially confounding parameters, with odds ratio (OR) 3.80 (95% confidence interval 1.34-10.8, p=0.006). Of note, change in bladder management, de novo use of anticholinergic or alpha blocker medication, or intravesical botulinum toxin injection following UDS were not associated with RD.

Due to the small number of patients with RD by strict criteria (11/355), multivariable analysis was not performed for this outcome to avoid possible overfitting. However, the only variables significantly associated with RD by strict criteria in patients who had initial UDS were history of diabetes (OR 7.69, 95% confidence interval 1.86-31.8, p=0.02) and history of nephrolithiasis (OR 8.72, 95% confidence interval 2.51-30.3, p=0.002).

Discussion

While early studies indicated rates of upper urinary tract dysfunction as high as 25% in patients with MS, more current epidemiologic data suggests that the risk for RD may have been significantly overestimated.[12, 13] Improved and earlier diagnosis of MS, availability of disease-modifying therapies, and advances in the identification and treatment of LUTS may have contributed to this decrease. Since urodynamics are commonly employed to assess LUTS in patients with MS, identification of UDS parameters associated with RD would be of significant value.[14] Our group and others previously estimated the rate of abnormalities on initial and short term follow-up RUS in patients with MS as 4-5%.[4, 15, 16] The present report builds on these data, incorporating imaging and renal functional outcomes and demonstrating that the overall development of RD at intermediate-term follow-up is low – 3% by strict criteria – regardless of UD or demographic predictors.

Since it is clear that RD can and does occur late (>60 months) in other neurogenic bladder conditions, continued surveillance in this population is appropriate. Although MS burden was not specifically quantified in this study, proxy variables such as the proportions of patients who were on anticholinergic therapy or wheelchair-bound at initial visit were instead evaluated. Furthermore, potentially confounding covariates, including interventions following UDS (starting anticholinergic or alpha blocker medications de novo, changing bladder management or undergoing intravesical botulinum toxin injection) were found not to be significantly associated with RD on univariate analysis or were controlled for in multivariable analysis. Nevertheless, other

parameters could have contributed to the outcome. For example, while not available for review in this population, EDSS scoring may be useful in renal risk stratification, and merits further study.[5]

For patients undergoing UDS, the only factor remaining significantly associated with RD by liberal criteria on multivariable regression was the presence of DO. Previous studies have yielded conflicting results regarding the possible prognostic value of decreased compliance, DESD, male gender or change in bladder management[15, 17, 18]; however, none of these parameters were predictive of RD in the current analysis. The relative infrequency of poor compliance, and the recognition that DESD does not result in greatly elevated intravesical pressures in MS patients may partially explain the failure to find an association with these urodynamic variables and RD.[8, 19] Further, DO due to MS has been associated with greater amplitude and increased threshold volume for detrusor contraction than idiopathic DO, again suggesting upper tracts may be at greater risk than most patients with OAB.[20] The impact of early treatment of DO and close monitoring of renal function for patients found to have DO on initial testing should be studied on the basis of our findings.

Despite the low risk of RD in the patient cohorts, the retrospective nature of this study limits direct comparison, in addition to resulting in incomplete data for follow-up imaging. We excluded patients with multiple neurologic diagnoses or prior nephrectomy, and additional scrutiny in such populations may be indicated. Patients with abnormal compliance or DESD, or male patients, may be considered for closer follow-up with

RUS and UDS due to conflicting literature regarding increased risk of RD, though the current study did not indicate an enhanced risk.[21] Lastly, data regarding other risk factors for RD, including recurrent urinary tract infections, was not available for review due to the referral nature of our patient population.

Conclusions

The rate of RD in patients referred with NGB due to MS was low (3%) at median follow-up of 79 months. Using more liberal criteria, DO was associated with renal deterioration, suggesting that study of the impact of more aggressive control of DO in this population may be warranted.

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Figure legends

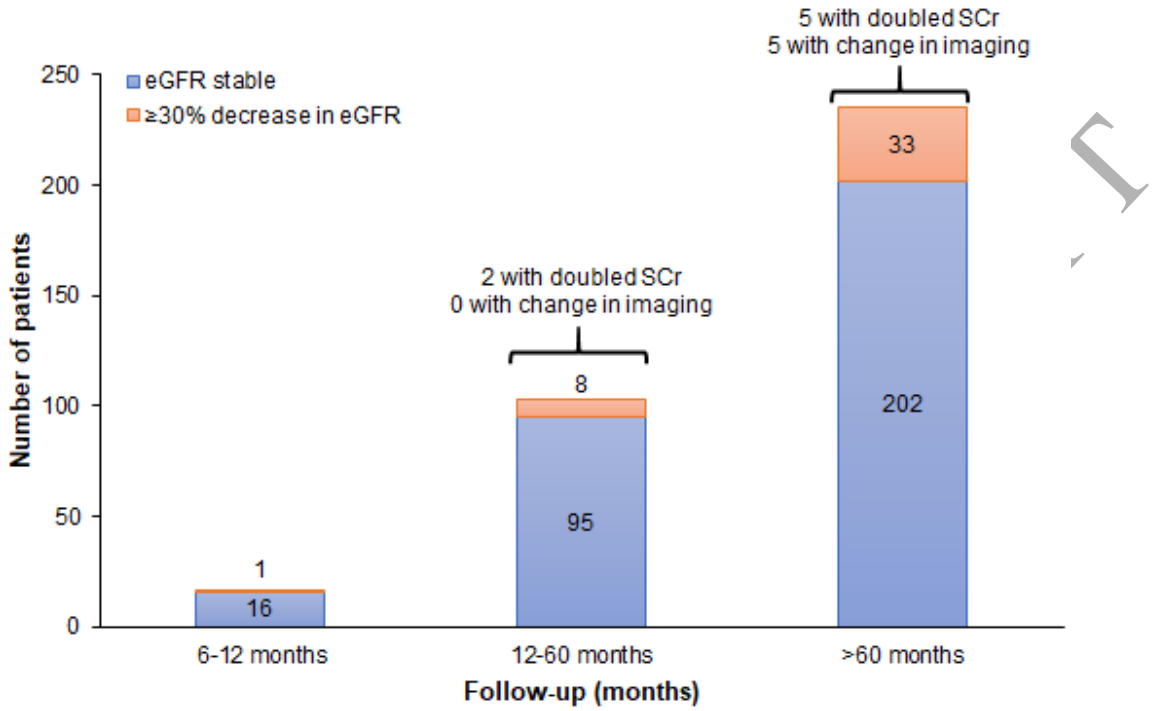

Figure 1 Renal deterioration by time of follow-up for all patients in the study. eGFR, estimated glomerular filtration rate. SCr, serum creatinine.

Supplementary Figure 1 Flowchart of patients in study. Cr, serum creatinine. eGFR, estimated glomerular filtration rate.

Table 1 Demographic data for the 355 patients in the study. Continuous variables are reported as medians with interquartile ranges (IQR) in parentheses. eGFR, estimated glomerular filtration rate. SCr, serum creatinine. UDS, urodynamic study.

Parameter	
Age at presentation	51 (43-58)
Body-mass index, kg/m^2	25 (22-30)
Gender, no. (%)	
Female	271 (76%)
Male	84 (24%)

Race, no. (%)	
Black	17 (5%)
Hispanic	10 (3%)
Other or unknown	48 (14%)
White	280 (79%)
Taking anticholinergics at baseline, no. (%)	148 (42%)
Wheelchair bound, no. (%)	42 (12%)
Time since diagnosis of multiple sclerosis, years	11 (5-18)
Type of multiple sclerosis, no. (%)	
Primary progressive	36 (10%)
Relapsing-remitting	191 (54%)
Secondary progressive	123 (35%)
Unknown	5 (1%)
History of nephrolithiasis, no. (%)	35 (10%)
Hypertension, no. (%)	102 (29%)
Type 2 diabetes, no. (%)	19 (5%)
SCr at baseline, mg/dL	0.8 (0.7-0.9)
eGFR at baseline, mL/min	102 (84-127)
Renal ultrasound at baseline, no. (%)	
Cortical atrophy, unilateral	4 (1%)
Hydronephrosis, unilateral	10 (3%)
Normal	209 (59%)
Unavailable	132 (37%)
Follow-up, months	79 (49-122)
Renal deterioration, no. (%)	
By change in imaging	5 (1%)
By decline in eGFR by ≥30%	42 (12%)
By doubled SCr	7 (2%)
By either imaging or doubled SCr	11 (3%)
By either imaging or eGFR	46 (13%)
Started following UDS, no. (%)	
Alpha blockers	9 (3%)
Anticholinergics	11 (3%)
Change in bladder management	90 (25%)
Intravesical Botox	34 (10%)

Table 2 Urodynamic parameters of patients in the study. Renal deterioration is defined here as either at least 30% decline in eGFR, or change in follow-up imaging.

Continuous variables are reported as medians with interquartile ranges (IQR) in parentheses. DESD, detrusor-external sphincter dyssynergia. DO, detrusor overactivity.

Parameter	Renal deterioration		p
	No (n=309)	Yes (n=46)	
Decreased bladder compliance	21 (7%)	4 (9%)	0.5
DESD, no. (%)	94 (30%)	13 (28%)	0.9
Detrusor overactivity, no. (%)	125 (40%)	28 (61%)	**0.01**
Amplitude of DO, cm H_2O	29 (10-50)	28 (20-51)	0.7
End-fill bladder pressure, cm H_2O	42 (31-57)	36 (28-43)	0.3
Maximum cystometric capacity, mL	331 (185-500)	265 (152-469)	0.2
Detrusor leak point pressure, cm H_2O*	36 (26-64)	43 (35-50)	0.9
Voiding spontaneously, no. (%)	84 (27%)	13 (28%)	0.9
Maximum flow, mL/sec	8 (4-14)	8 (5-11)	0.5
Detrusor pressure at maximal flow, cm H_2O	34 (20-48)	25 (18-37)	0.1
Post-void residual	95 (7-247)	32 (0-144)	0.2

*Measurable in 7 patients

Table 3 Univariate and multivariable analysis of predictors of renal deterioration by liberal criteria (≥30% decline in eGFR or change in imaging) in patients with UDS. DESD, detrusor-external sphincter dyssynergia. DO, detrusor overactivity. RRMS, relapsing-remitting multiple sclerosis.

Parameter	Univariate		Multivariable	
	OR	p	OR	p
Age, per year	0.99 (0.97-1.03)	0.9	-	-
Body-mass index, per kg/m^2	1.05 (1.00-1.09)	0.04	1.06 (1.00-1.13)	0.06
Gender, female vs male	1.32 (0.61-2.86)	0.5	-	-
Taking anticholinergics at baseline, yes/no	1.20 (0.65-2.24)	0.6	-	-
Time since diagnosis of MS, per year	0.99 (0.96-1.03)	0.7	-	-
Type of MS, RRMS vs others	1.26 (0.67-2.35)	0.5	-	-
Wheelchair bound, yes/no	1.14 (0.45-2.87)	0.8	-	-
History of nephrolithiasis, yes/no	2.65 (1.15-6.08)	0.02	1.86 (0.57-6.04)	0.3
Hypertension, yes/no	1.72 (0.91-3.28)	0.1	2.29 (0.94-5.62)	0.07
Type 2 diabetes, yes/no	2.57 (0.88-7.51)	0.08	1.43 (0.29-7.07)	0.7

Decreased bladder compliance, yes/no	1.31 (0.43-3.99)	0.6	-	-
DESD, no. (%)	0.89 (0.45-1.76)	0.7	-	-
DO, yes/no	2.29 (1.21-4.32)	0.01	3.80 (1.34-10.8)	**0.006**
Amplitude of DO, per cm H_2O	1.00 (0.99-1.02)	0.7	-	-
End-fill bladder pressure, per cm H_2O	0.96 (0.88-1.05)	0.3	-	-
Maximum cystometric capacity, per mL	0.99 (0.99-1.00)	0.2	-	-
Detrusor leak point pressure, per cm H_2O	0.99 (0.92-1.08)	0.9	-	-
Voiding spontaneously, yes/no	1.06 (0.53-2.10)	0.9	-	-
Maximum flow, per mL/sec	0.99 (0.94-1.03)	0.5	-	-
Detrusor pressure at maximum flow, per cm H_2O	0.98 (0.97-1.00)	0.1	0.98 (0.95-1.00)	0.06
Post-void residual, per mL	0.99 (0.99-1.00)	0.2	-	-
Change in bladder management after UDS, yes/no	0.86 (0.42-1.64)	0.8	-	-
Received intravesical Botox after UDS, yes/no	1.12 (0.43-3.21)	0.7	-	-
Started alpha blocker after UDS, yes/no	1.96 (0.39-9.74)	0.4	-	-
Started anticholinergics after UDS, yes/no	2.63 (0.67-10.3)	0.2	-	-