Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

# Urodynamic Evaluation in Multiple System Atrophy: A Retrospective Cohort Study

Sabine Eschlböck, MD,[1] Gustav Kiss, MD,[2] Florian Krismer, MD, PhD,[1] Alessandra Fanciulli, MD, PhD,[1] Christine Kaindlstorfer, MD, PhD,[1] Cecilia Raccagni, MD, PhD,[1,3] Klaus Seppi, MD,[1] Stefan Kiechl, MD,[1] Jalesh N. Panicker, MD, DM, FRCP,[4] and Gregor K. Wenning, MD, PhD, MSC[1,*]

**ABSTRACT:** Background: Urological dysfunction in patients with multiple system atrophy (MSA) is one of the main manifestations of autonomic failure. Urodynamic examination is clinically relevant since underlying pathophysiology of lower urinary tract (LUT) dysfunction can be variable.

Objective: Evaluation of the pathophysiology of urological symptoms and exploration of differences in urodynamic patterns of LUT dysfunction between MSA-P and MSA-C.

Methods: Retrospective study of patients with possible and probable MSA who were referred for urodynamic studies between 2004 and 2019. Demographic data, medical history, physical examination and urodynamic studies assessing storage and voiding dysfunction were obtained.

Results: Seventy-four patients were included in this study (MSA-P 64.9% n = 48; median age 62.5 (IQR 56.8–70) years). Detrusor overactivity during filling phase was noted in 58.1% (n = 43) of the patients. In the voiding phase, detrusor sphincter dyssynergia and detrusor underactivity were observed in 24.6% (n = 17) and in 62.1% (n = 41) of the patients, respectively. A postmicturition residual volume of over 100 ml was present in 71.4% (n = 50) of the patients. Comparison of MSA subtypes showed weaker detrusor contractility in MSA-P compared to MSA-C [pdetQmax 26.2 vs. 34.4 cmH20, $P = 0.04$]. In 56.2% (n = 41) of patients pathophysiology of LUT dysfunction was deemed to be neurogenic and consistent with the diagnosis of MSA. In 35.6% (n = 26) urodynamic pattern suggested other urological co-morbidities.

Conclusion: Urodynamic evaluation is an important tool to analyze the pattern of LUT dysfunction in MSA. Impaired detrusor contractility was seen more in MSA-P which needs to be investigated in further studies.

Multiple system atrophy is a rare neurological disorder, which is characterized by cerebellar, extrapyramidal and autonomic features in any combination.[1] Besides motor and cardiovascular autonomic symptoms, lower urinary tract (LUT) dysfunction is a cardinal feature. It often arises early in the course of the disease and is a predictor of reduced survival in MSA.[2–4] Although the presence of either cardiovascular or urogenital dysfunction is a diagnostic prerequisite for MSA,[5] LUT dysfunction is not pathognomonic to MSA and can occur due to a number of conditions, which is reflected by its greater prevalence with age and neurologic co-morbidities.[6,7] In MSA, natural history studies reported a prevalence of LUT symptoms in up to 87%.[2,3] Nonetheless, little is known regarding differences in LUT dysfunction between MSA subtypes and previous studies have reported different results.[8–12] In the last decade increasing attention has been paid to urodynamic examination as troublesome urinary symptoms emerge early in disease[3,13–16] prevailing patients to seek urological advice even before emergence of motor symptoms.[17,18]

In MSA, neuropathological correlates of LUT dysfunction exceeds degeneration of nigral dopaminergic pathways. Besides perturbed neuronal circuits involving the prefrontal/mediofrontal area and basal ganglia,[19] neurodegeneration in nondopaminergic

[1]Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria; [2]Division of Neurourology, Department of Urology, Medical University of Innsbruck, Innsbruck, Austria; [3]Department of Neurology, Regional General Hospital, Bolzano, Italy; [4]Department of Uro-Neurology, The National Hospital for Neurology and Neurosurgery, and UCL Queen Square Institute of Neurology, London, United Kingdom

***Correspondence to:** Prof. Gregor K. Wenning, Division of Clinical Neurobiology, Department of Neurology – Innsbruck Medical University, Anichstrasse 35, 6020 Innsbruck, Austria; E-mail: gregor.wenning@i-med.ac.at

**Keywords:** multiple system atrophy, urodynamic evaluation, urologic features, autonomic failure.



Received 3 June 2021; revised 13 June 2021; accepted 27 June 2021.
Published online 21 July 2021 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.13307

areas (pontine micturition center, periaqueductal gray, locus coeruleus, dorsal motor nucleus of the vagal nerve, intermediolateral columns of the spinal cord, Onuf's nucleus) may contribute to urogenital dysfunction.[18,20–23] Urodynamic examination yields important knowledge of underlying causes of LUT symptoms and might reveal other comorbidities such as bladder outlet obstruction or preceding surgeries (eg, transurethral resection of the prostate, prostatectomy, hysterectomy, lumbar discectomy) that contribute to the pathogenesis of LUT dysfunction.[19] As urological dysfunction is a major cause for morbidity and poor quality of life,[24,25] urodynamic assessment to characterize the underlying pathophysiology responsible for LUT symptoms is of paramount importance optimizing treatment and evaluating risk for developing upper urinary tract complications.

This retrospective study aims to evaluate the pathophysiology of urological symptoms in MSA and to explore differences in urodynamic patterns of LUT dysfunction between MSA-P and MSA-C.

# Methods

## Subjects

In this retrospective study urodynamic examination from patients that fulfilled the clinical criteria of possible or probable MSA,[5] and that were referred to the Neuro-urological department of the Medical University of Innsbruck between 2004 and 2019 were analyzed. The following data were obtained from medical records: disease onset (age at symptom onset and first reported motor or autonomic symptoms), age at examination, disease duration at examination, duration of urological dysfunction, urological symptoms at time of examination (urinary urgency, daytime frequency [defined as ≥8 micturition episodes per day], nocturia [≥ 2 micturition episodes per night], incontinence, sensation of incomplete bladder emptying). Global neurological disability was assessed using the Unified Multiple System Atrophy Rating Scale UMSARS part IV[26] and Hoehn and Yahr (H&Y) stage.[27] Medications and medical co-morbidities were also noted. Patients with incomplete medical records were excluded from this study.

This study was approved by the Institutional Review Board of Medical University of Innsbruck (AN2015-0224 353/4.15400/5.3 (4449a)) and conducted in accordance with the Declaration of Helsinki. Due to the retrospective study design no informed consent was obtained. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

## Urodynamic Examination

The urodynamic study was performed according to standardized protocol of the International Continence Society.[28] As a routine, medications prescribed for the treatment of LUT symptoms were ordinarily withheld 1 week prior to urodynamics assessment. Anti-parkinsonian medications were, however, continued to avoid motor deterioration.[29] Urinalysis was performed on the day of examination and the test was deferred in case there were signs of a urinary tract infection. A pelvic neurological examination (assessing anal sphincter tone, anal and bulbocavernosus reflex, voluntary command of anal sphincter, sensations in the sacral dermatomes) was performed, and thereafter urethral and rectal catheters were inserted to measure intravesical and intra-abdominal pressures. Concurrent with cystometric evaluation, EMG activity of the perineal region was recorded continually using surface electrodes. The bladder was filled with physiological saline and a filling rate of 50 ml/min. In the filling phase, the following parameters were assessed: bladder sensations (volume of first desire to void [bladder hypersensitivity <100 ml; normal bladder sensitivity at a volume of 100–300 ml; bladder hyposensitivity >300 ml]), cystometric bladder capacity (small capacity <200 ml; normal bladder capacity 200–550 ml, large capacity >550 ml), leakage volume and the presence of detrusor overactivity, characterized by involuntary detrusor contractions classified as phasic or terminal.[20,30] During the voiding phase, the maximum detrusor pressure generated (Pdetmax), maximum urinary flow rate (Qmax), the detrusor pressure generated at the maximum urinary flow rate (PdetQmax), time and volume of micturition, and residual volume (cut off >100 ml) were assessed. The presence of detrusor sphincter dyssynergia (detrusor contraction concurrent with involuntary urethral contraction) was assessed using perineal surface electrodes. Detrusor underactivity was defined as a bladder contractility index (BCI) of <100 (calculated as PdetQmax $+5 \times$ Qmax).[30,31] Bladder outlet obstruction in men was defined by Schäfer's nomogram (no obstruction 0–1; equivocal 2; > 3 obstruction).[32] Only the first urodynamic examination was analyzed if patients had undergone repeated urodynamic evaluation. An example for normal and pathological urodynamic pattern is illustrated in Fig. S1.

## Statistics

Statistical analyses were performed using SPSS (IBM SPSS Statistics, Chicago, IL, USA, Version 24). Chi-square or Fisher's exact test were used to calculate differences of categorical data as appropriate. For analysis of quantitative variables, Mann–Whitney U test or t-test was conducted according to the distribution of data. P values less than 0.05 were considered as statistically significant. Due to the explorative nature of the study no correction for multiple testing was performed.

# Results

## Demographic Data

Seventy-four patients (see study flow-chart Fig. 1) with a diagnosis of possible 10 (13.5%) or probable 64 (86.5%) MSA (35 (47.3%) men; median age at examination 62.5 (IQR 56.8–70.0) years) were included in the study. Forty-eight patients (64.9%) were diagnosed with Parkinson-predominant MSA. Median disease duration at examination was 36 months (IQR 24–48) with a median H&Y and UMSARS IV of three (IQR 3–4). 80% of the patients were treated with levodopa and reported a subjective benefit lasting only for a short period of

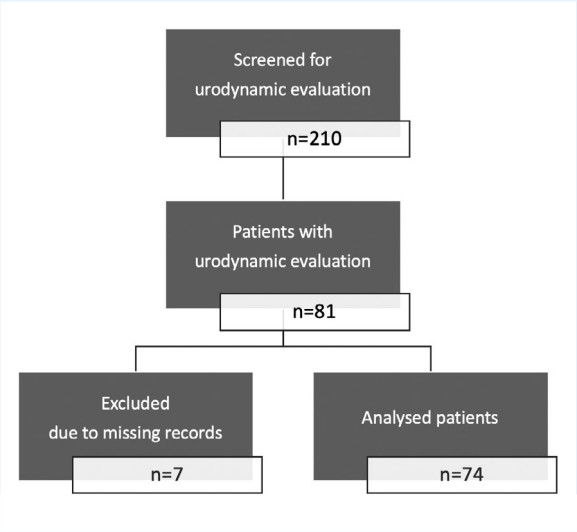


FIG. 1. Flow-chart of patients screened for urodynamic evaluation. Flow-chart.

12 months. Forty patients (54%) experienced early autonomic involvement as characterized by LUT dysfunction (n = 28), cardiovascular dysfunction (n = 5) or both, LUT and cardiovascular dysfunction (n = 7). Overall, with progression of disease and regardless of motor signs, LUT dysfunction manifested prior to cardiovascular failure in 56.8% (n = 42) or occurred concurrently with cardiovascular failure in 32.4% of patients (n = 24). Twenty patients (27.0%) were on oral agents for LUT symptoms and 12 patients were using catheters (intermittent catheter n = 7, transurethral indwelling catheter n = 4, suprapubic indwelling catheter n = 1). 29.7% of the patients (n = 22) had a history of pelvic organ surgery (men: prostate surgery n = 10, women: hysterectomy n = 10, cystoplasty n = 1, suburethral sling operation n = 1) and in 54.3% of the men benign prostate enlargement was listed as comorbidity in the medical history. Ten men underwent prostate surgery (n = 9 transurethral resection, n = 1 prostatectomy), of which 70% reported worsening of urological symptoms after surgery. Demographic data is summarized in Table 1.

## Urodynamic Examination

The frequency of urinary symptoms at time of examination are listed in descending order: urinary urgency (81.4%), urinary incontinence (73%), nocturia (65.1%), urinary frequency (43.1%) and sensation of incomplete bladder emptying (39.2%). Physical examination revealed loss of voluntary contractions of the anal sphincter in 49.1%, reduced anal sphincter tone in 34% and impaired sacral reflexes (anal reflex, bulbocavernosus reflex) in 26.4%.

In the filling phase, patients reported the first desire to void at a median volume of 240 ml (IQR 153–350). A pathological pattern of bladder hypersensitivity or hyposensitivity was noted in 11.3% and in 33.8% of the patients, respectively. The median cystometric bladder capacity was 316.5 ml (IQR 200.5–413.8) and in 23.6% bladder capacity was classified as small and in 12.5% as large. In 43 patients (58.1%) involuntary detrusor contractions was noted, of which 31.3% (n = 15) were classified as phasic, 52.1% (n = 25) as terminal and 6.3% (n = 3) as phasic and terminal detrusor overactivity. Involuntary detrusor contraction was accompanied with leakage of varying degrees in 42.6% (n = 29).

The voiding phase was characterized by detrusor underactivity in 62.1% (n = 41) with a median BCI of 68.0 (IQR 48.7–108.6). The median postvoid residual urine volume was 183 ml (IQR 87.8–319.3), and incomplete bladder emptying with a postvoid residual volume of >100 ml was present in 71.4% (n = 50) of the patients. Urethral contraction concurrent with detrusor contraction showing detrusor sphincter dyssynergia was noted in 24.6%. According to Schaefer's nomogram in men, 6.5% had bladder outlet obstruction.

Overall, in consideration of neuro-urological examination and urodynamic pattern, in 41 patients (56.2%) pathophysiology was presumed basically as neurogenic and supported the diagnosis of MSA. In 26 (35.6%) patients urodynamic pattern did not support MSA diagnosis suggesting other comorbidities as predominating cause for LUT symptoms. In 6 patients (8.2%) urodynamic examination was normal. All results are summarized in Table 2.

## MSA Subtypes and Gender

The comparison of MSA subtypes has shown, that median detrusor pressure at maximum urinary flow rate (MSA-P vs. MSA-C; 26.2 vs. 34.4 cmH20, $\boldsymbol{P} = 0.04$), the frequency of detrusor underactivity (MSA-P vs. MSA-C 72.5% (n = 29) vs. 46.2% (n = 12) $\boldsymbol{P} = 0.03$) and median score on Schaefer's nomogram in men ($\boldsymbol{P} = 0.03$) was significantly different between MSA-P and MSA-C. No further differences of urodynamic examination were found.

In consideration of gender differences, at the time of examination 84.6% of the women and 60% of the men reported urinary incontinence ($P = 0.02$). The volume of the first desire to void was significantly lower in women than in men (221.5 ml vs. 250 ml, $P = 0.03$). Moreover, median maximum detrusor pressure during micturition (men vs. women; pdetmax 46.1 vs. 29.4 cmH20, $P = 0.01$; pdetQmax 39.3 vs. 21.5 cmH20) $P = 0.02$) and the postvoid residual urine volume (232 ml vs. 148 ml, $P = 0.02$) were significantly higher in men compared to women. Data are summarized as supplement in Tables S1 and S2.

## Time Dependent Change of LUTS

Median disease duration (36 months) at time of examination was selected to define a cut-off value for comparison of the LUT symptoms and urodynamic profile of early versus late disease course. Bladder sensitivity significantly changed over time. Whereas 34.1% of the patients showed a pathological bladder sensitivity during the filling phase within the first 3 years of disease duration, after 3 years the frequency

**TABLE 1** *Demographic data*

| | Overall | MSA-P | MSA-C | *P* |
|---|---|---|---|---|
| n (%) | 74 (100) | 48 (64.9) | 26 (35.1) | |
| Gender | | | | |
| Male, n (%) | 35 (47.3) | 23 (47.9) | 12 (46.2) | NS |
| Diagnostic certainty | | | | |
| Probable MSA, n (%) | 64 (86.5) | 42 (87.5) | 22 (84.6) | NS |
| Clinical features | | | | |
| Age symptom onset, median (25;75) | 58.5 (53–66) | 59.5 (51.5–65.5) | 58.0 (54–66.8) | NS |
| Type of symptom onset | | | | NS |
| Autonomic onset, n (%) | 12 (16.2) | 8 (16.7) | 4 (15.4) | |
| Motor onset, n (%) | 34 (45.9) | 20 (41.7) | 14 (53.8) | |
| Autonomic and motor onset, n (%) | 28 (37.8) | 20 (41.7) | 8 (30.8) | |
| Type of autonomic dysfunction onset | | | | NS |
| OH, n (%) | 8 (10.8) | 5 (10.4) | 3 (11.5) | |
| LUT symptoms, n (%) | 42 (56.8) | 27 (56.3) | 15 (57.7) | |
| OH and LUT symptoms, n (%) | 24 (32.4) | 16 (33.3) | 8 (30.8) | |
| Age at examination, median (25;75) | 62.5 (56.8–70) | 62.5 (55–70) | 62.5 (57–70.3) | NS |
| Disease duration (months), median (25;75) | 36 (24–48) | 32 (24–48) | 36 (29–49) | NS |
| Duration of urinary symptoms (months), median (25;75) | 22.5 (12–36) | 24 (12–33) | 21 (7–36) | NS |
| UMSAR IV, median (25;75) | 3 (3–4) | 3 (2–4) | 3 (3–4) | NS |
| H&Y median (25;75) | 3 (3–4) | 3 (2–4) | 3 (3–4) | NS |
| Medical history | | | | |
| Pelvic organ surgery, n (%) | 22.0 (29.7) | 17 (35.4) | 5 (19.2) | NS |
| Spinal surgery, n (%) | 8 (10.8) | 7 (14.6) | 1 (3.8) | NS |
| Diabetes mellitus, n (%) | 6 (8.1) | 5 (10.4) | 1 (3.8) | NS |
| Benign prostate enlargement, n (%) | 19 (54.3) | 11 (47.8) | 8 (66.7) | NS |
| Medication | | | | |
| Levodopa | 59 (79.7) | 47 (97.9) | 12 (46.2) | 0.001 |
| Duration of L-Dopa benefit (months), median (25;75) | 12 (0–36) | 12 (6–36) | 0 | 0.001 |
| Parasympathomimetic agent | 1 (1.4) | 1 (2.1) | 0 | NS |
| Anticholinergic agent | 12 (16.2) | 7 (14.6) | 5 (19.2) | NS |
| Catheterization | 12 (16.2) | 7 (14.6) | 5 (19.2) | NS |
| Alpha-blockers | 7 (9.5) | 5 (10.4) | 2 (7.7) | NS |
| 5α-*Reductase inhibitors* | 3 (8.6) | 1 (4.3) | 2 (16.7) | NS |

increased to 63% (p 0.02). In addition, the frequency of pelvic organ surgeries (18.2% vs. 46.7%, $P = 0.01$) and sensation of incomplete bladder emptying (29.5% vs. 53.3%, $P = 0.04$) increased, whereas nocturia (75.6% vs. 45.5%, $P = 0.03$) reduced over time.

# Discussion

Multiple system atrophy is a rare, devastating neurodegenerative disorder. Due to its underlying neuropathology, disturbances in bladder function are one of the hallmarks of MSA, which are a

**TABLE 2** *Neuro-urological and urodynamic examination*

| | Overall | MSA-P | MSA-C | P |
|---|---|---|---|---|
| Urological symptoms—at time of examination | | | | |
| Urinary frequency, n (%) | 28 (43.1) | 20 (46.5) | 8 (36.4) | NS |
| Frequency of micturition (day), median (25;75) | 7 (5–9) | 7 (5–9) | 7 (5–9) | NS |
| Nocturia, n (%) | 41 (65.1) | 26 (61.9) | 15 (71.4) | NS |
| Frequency of micturition (night), median (25;75) | 2 (1–3) | 2 (1–4) | 2 (1–3) | NS |
| Urinary urgency, n (%) | 57 (81.4) | 39 (86.7) | 18 (72) | NS |
| Urinary incontinence, n (%) | 54 (73) | 35 (72.9) | 19 (73.1) | NS |
| Sensation of incomplete bladder emptying, n (%) | 29 (39.2) | 18 (37.5) | 11 (42.3) | NS |
| Abnormal neuro-urological examination findings | | | | |
| Voluntary contraction of anal sphincter, n (%) | 26 (49.1) | 15 (48.4) | 11 (50.0) | NS |
| Anal sphincter tone, n (%) | 18 (34) | 13 (41.9) | 5 (22.7) | NS |
| Sacral reflexes, n (%) | 14 (26.4) | 9 (29) | 5 (22.7) | NS |
| Urodynamic parameters | | | | |
| Maximum cystometric bladder capacity (ml), median (25;75) | 316.5 (200.5–414) | 325 (201.5–457.8) | 307 (183.5–365.8) | NS |
| Cystometric bladder capacity: | | | | NS |
| *Normal, n (%)* | 46 (63.9) | 29 (63) | 17 (65.4) | |
| *Small capacity, n (%)* | 17 (23.6) | 10 (21.7) | 7 (26.9) | |
| *Large capacity, n (%)* | 9 (12.5) | 7 (15.2) | 2 (7.7) | |
| First desire to void (ml), median (25;75) | 240 (153–350) | 256 (153.5–354) | 231 (150–303.5) | NS |
| Bladder sensitivity | | | | NS |
| *Normal, n (%)* | 39 (54.9) | 24 (53.3) | 15 (57.7) | |
| *Bladder hypersensitivity; n (%)* | 8 (11.3) | 4 (8.9) | 4 (15.4) | |
| *Bladder hyposensitivity, n (%)* | 24 (33.8) | 17 (37.8) | 7 (26.9) | |
| Maximum detrusor pressure (Pdetmax), (cmH20), median (25;75) | 37.3 (24.9–56.2) | 33.1 (21.9–51.6) | 37.8 (27.5–59.1) | NS |
| Detrusor pressure at maximum urinary flow rate (PdetQmax) (cmH20), median (25;75) | 29.6 (18.2–45.3) | 26.2 (14.9–40.5) | 34.4 (23.7–51.4) | 0.04 |
| Maximum urinary flow rate (Qmax), (ml/s), median (25;75) | 7.7 (4.4–11.5) | 7.7 (3.9–11.8) | 8.1 (5.4–11.0) | NS |
| Duration of void (sec), median (25;75) | 32 (18.5–46.8) | 34 (18–60) | 31 (18–44) | NS |
| Voided Volume (ml), median (25;75) | 94.5 (51.5–174.3) | 111 (40.3–180.3) | 84.5 (57.3–169.3) | NS |
| Postvoid residual urine volume (ml), median (25;75) | 183 (87.8–319.3) | 198 (76.3–339.5) | 164 (108.3–274.5) | NS |
| Bladder outlet obstruction in men, n(%) | 2 (6.5) | 1 (5.3) | 1 (8.3) | NS |
| Score on Schaefer's nomogram, median (25;75) | 1 (0–2) | 1 (0–2) | 2 (1–2.8) | 0.03 |
| Leakage volume | | | | NS |
| *Leakage > 15 ml, n(%)* | 12 (17.6) | 7 (16.3) | 5 (20) | |
| *Leakage < 15 ml, n(%)* | 17 (25) | 7 (16.3) | 10 (40) | |
| *No Leakage, n(%)* | 39 (57.4) | 29 (67.4) | 10 (40) | |

*(Continues)*

**TABLE 2** *Continued*

| | Overall | MSA-P | MSA-C | P |
|---|---|---|---|---|
| Detrusor activity | | | | |
| Detrusor overactivity, n (%) | 43 (58.1) | 27 (56.3) | 16 (61.5) | NS |
| *Phasic overactivity, n (%)* | 15 (31.3) | 11 (37.9) | 4 (21.1) | NS |
| *Terminal overactivity, n (%)* | 25 (52.1) | 15 (51.7) | 10 (52.6) | |
| *Phasic and terminal overactivity, n (%)* | 3 (6.3) | 1 (3.4) | 2 (10.5) | |
| Detrusor underactivity as per bladder contractility index, n (%) | 41 (62.1) | 29 (72.5) | 12 (46.2) | 0.03 |
| Bladder contractility index, median (25;75) | 68.0 (48.7–108.6) | 62.0 (45.6–98.8) | 95.9 (56.5–118.1) | NS |
| Detrusor sphincter dyssynergia, n (%) | 17 (24.6) | 13 (30.2) | 4 (15.4) | NS |

debilitating quality of life issue and a socially disabling aspect of this disease. In the following retrospective study, we assessed clinical features and urodynamic pattern in 74 MSA patients.

The presence of incomplete bladder emptying is an important clinical bedside marker, which can be measured without urodynamic examination and which in previous reports has been defined as a useful discriminator to distinguish MSA from PD.[8,9,20,33–38] In 71.4% of the patients in the present cohort, postvoid residual volume was over 100 ml. Nonetheless, urodynamic evaluation might allow further important insights, which are discussed in detail in the following. Detrusor overactivity was detected in 58.1%, detrusor underactivity in 62.1% and detrusor sphincter dyssynergia in 24.6% of the patients. Although all MSA patients reported urological symptoms, 8.2% had a normal urodynamic profile. Our data are comparable with those from other MSA studies, that reported percentages with a wide range of urodynamic pattern (detrusor overactivity 34–90%,[8–12,14,20,33,35,36,39–41] detrusor sphincter dyssynergia 16–56%,[8,10,14,20,35,36,41] detrusor underactivity 24–88%[8,10–12,20,34,36,40]) likely based on different methodical issues. The urodynamic profile between MSA subtypes was basically equivalent with exception of one interesting finding reported in the following. In this study median detrusor pressure at maximum urinary flow rate was significantly lower and the frequency of detrusor underactivity was significantly higher in MSA-P than MSA-C. These results are also confirmed by recent studies that have shown a more severely impaired bladder contraction in patients with MSA-P compared to MSA-C.[9,11,12] In neurological diseases, urodynamic detected detrusor underactivity reflects involvement of the brainstem, sacral and infrasacral areas.[42] Recently, in a subset of patients presenting initially with urinary retention and only subtle neurological symptoms, urodynamic examination showed detrusor underactivity and an abnormal anal sphincter EMG, suggesting possible onset of disease in the spinal cord.[16] It may therefore be hypothesized that in patients with MSA-P, the sacral spinal cord, specifically the detrusor motor neuron in the intermediolateral cell columns, may be more severely involved than in MSA-C and this requires further study.

The diagnosis of MSA is based on the occurrence of either parkinsonian and/or cerebellar symptoms as well as on unexplained orthostatic hypotension and/or genitourinary dysfunction.[5] Urological symptoms frequently manifest earlier in the course of disease than symptoms of cardiovascular failure.[11,13,14] In this study we confirmed this observation by demonstrating that more than half of the patients reported urological disturbances before symptoms of blood pressure dysregulation were present. The diagnosis of MSA, remains challenging, especially if motor symptoms are mildly pronounced or supporting features[5] are not yet present. The evaluation of bladder symptoms might be important in directing diagnosis and therapy. Although several urodynamic studies have been performed in MSA,[8–12,33,35,36,39–41,43] these studies did not analyze the pathophysiology of LUT symptoms. In the interpretation of urodynamic studies it has to be taken into consideration that urodynamic pattern of neurogenic and non-neurogenic causes might be similar.[44] Therefore, detailed consideration of medical history, neuro-urological examination and urodynamic assessment is essential. In the following study we have demonstrated a high frequency of patients, whose underlying pathophysiology possibly might result from other causes than MSA (eg, preceded surgeries, diabetes mellitus, benign prostate hyperplasia in 35.6%; normal urinary examination in 8.2%). The combination of clinical (weakness of anal sphincter and absence of sacral reflexes) and urodynamic features (detrusor overactivity, detrusor sphincter dyssynergia, leakage during filling phase, a postvoid residual volume of over 100 ml, bladder hypersensitivity) counting five or more or the presence of detrusor sphincter dyssynergia alone or in combination with detrusor overactivity is highly suggestive for neurogenic pathophysiology in this patient cohort. This characteristic pattern was present in 56.2% of patients and supported the diagnosis of MSA. Thus, these results emphasize that besides the application of clinical criteria, neuro-urological and urodynamic examination may be indispensable in a subset of patients. A detailed assessment of LUT dysfunction is important to underpin diagnosis of MSA as well as to anticipate potential coexisting conditions and thus, to avoid unnecessary surgeries.[45] It is important to note, that in contrast to Parkinson's disease, benign prostatic hypertrophy (BPH) surgery worsens bladder function and is contraindicated in MSA patients.[19] In the following study we have demonstrated that surgery due to prostate hypertrophy worsened bladder function in

MSA in 7 of 10 patients and did not improve bladder function considerably in the remaining. Therefore, the knowledge of underlying pathophysiology, clarified by using urodynamic assessment, is not only important for diagnosis. It enables the optimization of clinical management and possibly improves the quality of life.

Since this study is of retrospective study design, it is necessary to report possible bias and limitations. In daily routine, MSA patients are not examined with urodynamic assessment. The following study may be biased as MSA patients were referred to urodynamic examination if they experienced bothersome symptoms. Therefore, urodynamic features in urologically silent MSA patients may not be detected. Secondly, although patients were encouraged not to take anticholinergics before urodynamics, premedication with levodopa was not stopped possibly interfering with bladder function.[19,29,46] Thirdly, patients were diagnosed on the basis of clinical criteria and neuropathological confirmation is not available for this patient cohort. Furthermore, due to the explorative nature of the study, no correction for multiple testing was performed. Thus, it has to be noted that some observed differences may not survive after correction.

However, it has to be emphasized that the study contains a respectable patient cohort and aims to classify the pathophysiology of LUT dysfunction in MSA, which to our knowledge has not been evaluated before. Urodynamic has been performed according to international standards[28] by urologists of a specialized center with experience in diagnosis and treatment of patients with neurological diseases.

In conclusion, this study emphasizes the importance of detailed medical history, physical examination and where applicable urodynamic examination to detect neurogenic features of urological failure in MSA. Detrusor contractility was more impaired in MSA-P compared to MSA-C which needs to be investigated in further studies.

# Acknowledgments

We want to thank our patients and their families for the support of this research. Jalesh N. Panicker is supported in part by funding from the United Kingdom's Department of Health NIHR Biomedical Research Centres.

# Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

SE: 1A, 1C, 2A, 2B, 3A
GK: 1B, 1C, 2C, 3B
FK: 1A, 2C, 3B
AF: 1A, 2C, 3B
CK: 1A, 2C, 3B
CR: 1A, 2C, 3B
KS: 2C, 3B
SK: 2C, 3B
JNP: 2C, 3B
GKW: 1A, 1B, 2A, 2C, 3B

# Disclosures

**Ethical Compliance Statement:** This study was approved by the Institutional Review Board of Medical University of Innsbruck (AN2015-0224 353/4.15400/5.3 (4449a)) and conducted in accordance with the Declaration of Helsinki. Informed patient consent was not necessary for this retrospective work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

**Funding Sources and Conflicts of Interest:** The authors report no conflict of interest related to this work. There was no specific funding for this study.

**Financial Disclosures for the Previous 12 months:** *Sabine Eschlböck*: Employment: Medical University Innsbruck.

*Gustav Kiss*: Nothing to disclose.

*Florian Krismer*: Consultancies: Institut de Recherches Internationales Servier, Clarion Healthcare, LLC, Employment: Medical University Innsbruck, Grants: MSA Coalition.

*Alessandra Fanciulli*: Employment: Medical University of Innsbruck, Honoraria: Theravance Biopharma, Abbvie, IOS Press, Impact Medicom, Royalties: Springer Nature Publishing Group, Thieme, Grants: MSA Coalition, Stichting Parkinson Fond, Österreichischer Austausch Dienst, Johannes Tuba Stiftung.

*Christine Kaindlstorfer*: Employment: Medical University Innsbruck.

*Cecilia Raccagni*: Employment: Regional General Hospital of Bolzano.

*Klaus Seppi*: Employment: Medical University Innsbruck, Honoraria from the International Parkinson and Movement Disorders Society, Grants: the FWF Austrian Science Fund, Michael J. Fox Foundation, and International Parkinson and Movement Disorder Society, Other: Personal fees from Teva, UCB, Lundbeck, AOP Orphan Pharmaceuticals AG, Roche, Grünenthal, and Abbvie.

*Stefan Kiechl*: Employment: Medical University Innsbruck.

*Jalesh N. Panicker*: Advisory Boards: Allergan, Employment: UCL Queen Square Institute of Neurology, Honoraria: Wellspect, Coloplast, Royalties: Cambridge University Press.

*Gregor K. Wenning*: Consultancies: consultancy and lecture fees from AbbVie, Affiris, AstraZeneca, Biogen, Lundbeck, Merz, Novartis, Ono, Teva, and Theravance, Employment: Medical University Innsbruck. ■

# References

1. Fanciulli A, Wenning GK. *Multiple System Atrophy*. Vienna: Springer Vienna; 2014.
2. Low P, Reich S, Jankovic J, et al. Natural history of multiple system atrophy in the USA: A prospective cohort study. *Lancet Neurol* 2015;14 (7):710–719.

3. Wenning G, Geser F, Krismer F, et al. The natural history of multiple system atrophy: A prospective European cohort study. *Lancet Neurol* 2013;12(3):264–274.

4. Coon EA, Sletten DM, Suarez MD, et al. Clinical features and autonomic testing predict survival in multiple system atrophy. *Brain* 2015;138 (12):3623–3631.

5. Gilman S, Wenning G, Low P, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology* 2008;71(9): 670–676.

6. Sakakibara R, Kishi M, Ogawa E, et al. Bladder, bowel, and sexual dysfunction in Parkinson's disease. *Parkinsons Dis* 2011;2011:924605.

7. Yamamoto T, Sakakibara R, Uchiyama T, et al. Neurological diseases that cause detrusor hyperactivity with impaired contractile function. *NeurourolUrodyn* 2006;25(4):356–360.

8. Kim M, Jung JH, Park J, et al. Impaired detrusor contractility is the pathognomonic urodynamic finding of multiple system atrophy compared to idiopathic Parkinson's disease. *Parkinsons Relat Disord* 2015;21 (3):205–210.

9. Shin JH, Park KW, Heo KO, Chung SJ, Choo MS. Urodynamic study for distinguishing multiple system atrophy from Parkinson disease. *Neurology* 2019;93(10):E946–E953.

10. Tsuchiya A, Terayama K, Sakakibara R, et al. Urodynamic and gait analyses in multiple system atrophy. *J Neurol Sci* 2020;411: 116676.

11. Yamamoto T, Asahina M, Yamanaka Y, et al. Urinary dysfunctions are more severe in the Parkinsonian phenotype of multiple system atrophy. *Mov Disord Clin Pract* 2016;3(3):275–281.

12. Xing T, Ma J, Jia C, Ou T. Neurogenic lower urinary tract dysfunction predicts prognosis in patients with multiple system atrophy. *Clin Auton Res* 2020;30(3):247–254.

13. Kirchhof K, Apostolidis AN, Mathias CJ, Fowler CJ. Erectile and urinary dysfunction may be the presenting features in patients with multiple system atrophy: A retrospective study. *Int J Impot Res* 2003;15(4): 293–298.

14. Sakakibara R, Hattori T, Uchiyama T, et al. Urinary dysfunction and orthostatic hypotension in multiple system atrophy: Which is the more common and earlier manifestation? *J Neurol Neurosurg Psychiatry* 2000;68 (1):65–69.

15. Wenning GK, Scherfler C, Granata R, et al. Time course of symptomatic orthostatic hypotension and urinary incontinence in patients with postmortem confirmed parkinsonian syndromes: A clinicopathological study. *J Neurol Neurosurg Psychiatry* 1999;67(5):620–623.

16. Panicker JN, Simeoni S, Miki Y, et al. Early presentation of urinary retention in multiple system atrophy: Can the disease begin in the sacral spinal cord? *J Neurol* 2020;267(3):659–664.

17. Jecmenica-Lukic M, Poewe W, Tolosa E, Wenning GK. Premotor signs and symptoms of multiple system atrophy. *Lancet Neurol* 2012;11(4): 361–368.

18. Sakakibara R, Panicker J, Simeoni S, et al. Bladder dysfunction as the initial presentation of multiple system atrophy: A prospective cohort study. *Clin Auton Res* 2019;29(6):627–631.

19. Sakakibara R, Panicker J, Finazzi-Agro E, Iacovelli V, Bruschini H. Parkinson's disease Subcomittee TNPC in TICS. A guideline for the management of bladder dysfunction in Parkinson's disease and other gait disorders. *NeurourolUrodyn* 2016;35(5):551–563.

20. Sakakibara R, Hattori T, Uchiyama T, Yamanishi T. Videourodynamic and sphincter motor unit potential analyses in Parkinson's disease and multiple system atrophy. *J Neurol Neurosurg Psychiatry* 2001;71(5):600–606.

21. McKay JH, Cheshire WP. First symptoms in multiple system atrophy. *Clin Auton Res* 2018;28(2):215–221.

22. Winge K, Fowler CJ Bladder dysfunction in parkinsonism: Mechanisms, prevalence, symptoms, and management. *Mov Disord* 2006;21(6): 737–745.

23. Benarroch EE. Neural control of the bladder: Recent advances and neurologic implications. *Neurology* 2010;75(20):1839–1846.

24. McGrother CW, Jagger C, Clarke M, Castleden CM. Handicaps associated with incontinence: Implications for management. *J Epidemiol Community Health* 1990;44(3):246–248.

25. Sakakibara R, Shinotoh H, Uchiyama T, et al. Questionnaire-based assessment of pelvic organ dysfunction in Parkinson's disease. *Auton Neurosci Basic Clin* 2001;92(1–2):76–85.

26. Wenning GK, Tison F, Seppi K, et al. Development and validation of the unified multiple system atrophy rating scale (UMSARS). *Mov Disord* 2004;19(12):1391–1402.

27. Hoehn M, Yahr M. Parkinsonism: Onset, progression and mortality. *Neurology* 1967;17(5):427–442.

28. Abrams P, Blaivas J, Stanton S, Andersen J. Standardisation of terminology of lower urinary tract function. *Neurourol Urodynam* 1988;7:403–407.

29. Fanciulli A, Wenning GK. Multiple-system atrophy. *N Engl J Med* 2015; 372(3):249–263.

30. Gajewski JB, Schurch B, Hamid R, et al. An international continence society (ICS) report on the terminology for adult neurogenic lower urinary tract dysfunction (ANLUTD). *NeurourolUrodyn* 2018;37(3):1152–1161.

31. Abrams P. Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: Three simple indices to define bladder voiding function. *BJU Int* 1999;84(1):14–15.

32. Schäfer W. Analysis of bladder-outlet function with the linearized passive urethral resistance relation, linPURR, and a disease-specific approach for grading obstruction: From complex to simple. *World J Urol* 1995;13(1):47–58.

33. Yamamoto T, Asahina M, Yamanaka Y, et al. Postvoid residual predicts the diagnosis of multiple system atrophy in Parkinsonian syndrome. *J Neurol Sci* 2017;381:230–234.

34. Yamamoto T, Asahina M, Yamanaka Y, et al. The utility of post-void residual volume versus sphincter electromyography to distinguish between multiple system atrophy and Parkinson's disease. *PLoS One* 2017;12(1):1–12.

35. Yamamoto T, Tateno F, Sakakibara R, et al. Urinary dysfunction in progressive supranuclear palsy compared with other parkinsonian disorders. *PLoS One* 2016;11(2):1–12.

36. Kim KJ, Jeong SJ, Kim JM. Neurogenic bladder in progressive supranuclear palsy: A comparison with Parkinson's disease and multiple system atrophy. *NeurourolUrodyn* 2018;37(5):1724–1730.

37. Fanciulli A, Goebel G, Lazzeri G, et al. Early distinction of Parkinson-variant multiple system atrophy from Parkinson's disease. *Mov Disord* 2019;34(3):440–441.

38. Fanciulli A, Goebel G, Lazzeri G, et al. Urinary retention discriminates multiple system atrophy from Parkinson's disease. *Mov Disord* 2019;34 (12):1926–1928.

39. Stocchi F, Carbone A, Inghilleri M, et al. Urodynamic and neurophysiological evaluation in Parkinson's disease and multiple system atrophy. *J Neurol Neurosurg Psychiatry* 1997;62(5):507–511.

40. Bonnet AM, Pichon J, Vidailhet M, et al. Urinary disturbances in striatonigral degeneration and Parkinson's disease: Clinical and urodynamic aspects. *Mov Disord* 1997;12(4):509–513.

41. Yamamoto T, Yamanaka Y, Sugiyama A, et al. The severity of motor dysfunctions and urinary dysfunction is not correlated in multiple system atrophy. *J Neurol Sci* 2019;400:25–29.

42. Panicker J, Fowler C, Kessler T. Lower urinary tract dysfunction in the neurological patient: Clinical assessment and management. *Lancet Neurol* 2015;14:720–732.

43. Ito T, Sakakibara R, Yasuda K, et al. Incomplete emptying and urinary retention in multiple-system atrophy: When does it occur and how do we manage it? *Mov Disord* 2006;21(6):816–823.

44. Andersson KE. Storage and voiding symptoms: pathophysiologic aspects. *Urology* 2003;62:3–10.

45. Magari T, Fukabori Y, Ogura H, Suzuki K. Lower urinary tract symptoms of neurological origin in urological practice. *Clin Aut Res* 2013;23: 67–72.

46. Aranda B, Cramer P. Effects of apomorphine and L-dopa on the parkinsonian bladder. *NeurourolUrodyn* 1993;12(3):203–209.

# Supporting Information

Supporting information may be found in the online version of this article.

**Figure S1. Normal and pathological urodynamic pattern. 1.a.** Normal urodynamic trace demonstrating filling and voiding phase. **Pves (cmH2O):** intravesical pressure measured

by inserted transurethral catheter. **Pabd (cmH2O):** intra-abdominal pressure measured by inserted rectal catheter. **Pdet (cmH2O):** the detrusor pressure is calculated by subtraction of the intraabdominal pressure from intravesical pressure. **Pdet max (cmH2O):** maximum detrusor pressure. **EMG:** Surface electromyography measures activity of the perineal region. **Qura ml/s:** volume of micturition. **Vinf ml:** infused volume. **1.b.** Abnormalities in the filling phase. Black arrow indicates involuntary detrusor contractions (Pdet) during filling phase and is defined as phasic or terminal detrusor overactivity. **1.c**. Abnormalities in the voiding phase. Black arrow illustrates **detrusor underactivity** and concurrent sphincter activity during contraction of detrusor is defined as **detrusor sphincter dyssynergia.**

**Table S1.** Demographic data. Gender differences. Abbreviations: H&Y = Hoehn and Yahr, LUT = lower urinary tract, OH = orthostatic hypotension, UMSAR = Unified Multiple System Atrophy Rating Scale

**Table S2.** Neuro-urological and urodynamic examination. Gender differences. Abbreviations: BCI = Bladder contractility index.