





Urodynamic Evaluation in Multiple System Atrophy: A Retrospective Cohort Study

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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 cmH₂O, 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/medial frontal area and basal ganglia,¹⁹ neurodegeneration in nondopaminergic

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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 IV²⁶ 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.

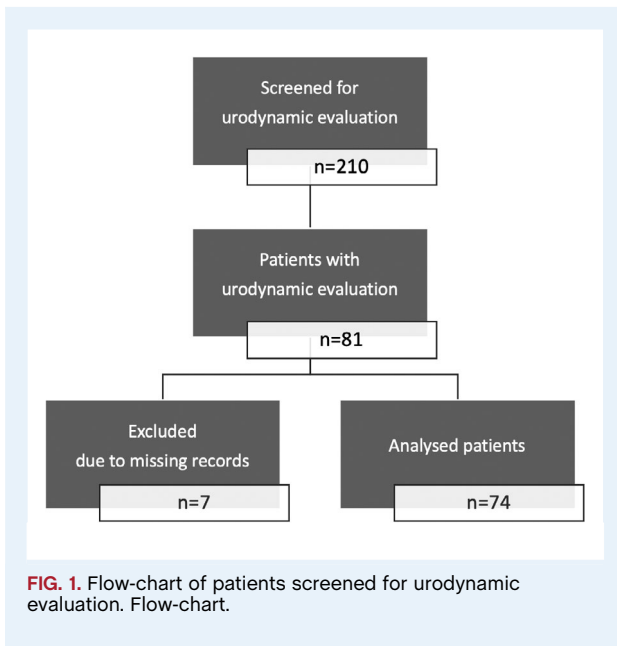
Statistics

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



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 cmH₂O, $P = 0.04$), the frequency of detrusor underactivity (MSA-P vs. MSA-C 72.5% ($n = 29$) vs. 46.2% ($n = 12$) $P = 0.03$) and median score on Schaefer's nomogram in men ($P = 0.03$) 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 cmH₂O, $P = 0.01$; pdetQmax 39.3 vs. 21.5 cmH₂O) $P = 0.02$ 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
5 α -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 features⁵ 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,⁴⁶ 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 standards²⁸ 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.

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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.

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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.