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Phenotyping women with detrusor underactivity by presumed etiology: is it plausible?

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Abstract

Aims—Underactive bladder (UAB) is a symptom complex with poorly characterized causation. The aim of this study was to determine if clinical and UDS parameters differed between categories of presumed detrusor underactivity (DU) etiologies.

Methods—A retrospective review was performed at a single institution from 2011-2015 to identify patients with symptoms of UAB. Patients were excluded if they were male, had anti-incontinence or pelvic organ prolapse (POP) surgery within 1 year, or the UDS did not demonstrate DU as defined within. Subjects were stratified by etiology into 4 cohorts: cardiovascular disease manifestations (CV), cardiac risk factors (CVR), neurologic (N), or idiopathic (I). Patient demographics, comorbidities, symptomatology, physical exam, and UDS parameters were compared.

Results—200 patients met inclusion criteria [CV: n=53 (26.5%), CVR: n=44 (22%) N: n=81 (40.5%), I: n=22 (11%)]. Women in the CV cohort were significantly older and more likely to be post-menopausal ($p<0.001$). There were no differences between cohorts for BMI ($p=0.48$), recurrent UTI ($p=0.63$), history of urinary retention (AUR) ($p=0.65$), POP (0.49), American Urological Association Symptom Score ($p=0.06$), presenting symptomatology [urgency, frequency, urgency urinary incontinence, AUR, incomplete emptying, hesitancy, UTI ($p=0.97$)], or UDS parameters [first sensation ($p=0.25$), normal desire ($p=0.80$), strong desire ($p=0.58$), capacity ($p=0.11$), Q_{max} ($p=0.50$), P_{det} at Q_{max} ($p=0.22$), post-void residual ($p=0.82$)].

Conclusions—Though differences were observed between cohorts for age and menopausal status, clinical or urodynamic parameters did not demonstrate distinct differences across presumed categories of etiology, suggesting that the etiology of DU may be multifactorial.

Introduction

Underactive bladder (UAB) is a poorly understood clinical symptom complex lacking a definition consensus, but is known to involve incomplete or inefficient bladder emptying in the absence of significant bladder outlet obstruction (BOO). Frequently associated symptoms include hesitancy, straining to void, incomplete emptying, urgency, frequency,

nocturia, urinary incontinence (UI), and recurrent urinary tract infections (UTIs).¹ Chapple et al. proposed a working definition for UAB: “a symptom complex suggestive of detrusor underactivity (DU), usually characterized by prolonged urination time with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation on filling, and a slow stream.”² However, UAB symptomatology may be clinically indistinguishable from BOO.³ As such, UAB is currently indexed by identifying DU on urodynamics (UDS). The International Continence Society (ICS) defines DU as, “a detrusor contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span.”⁴

The etiology of DU, and thus the development of UAB symptoms remain unclear. DU has been associated with neurologic, idiopathic, iatrogenic, and myogenic factors, which can result from common comorbid conditions.³ It has been identified in 12-45% of older women undergoing UDS for lower urinary tract symptoms.^{3,5} DU is also independently associated with increased age and is often cited as an indication for bladder catheterization in elderly, institutionalized patients.⁶

The aim of this study was to determine if clinical and urodynamic parameters differed between categories of presumed DU etiologies. The rationale is that if clinical phenotypes can be identified for patients who present with symptoms of UAB, it may improve our understanding of this complicated disease process as well as guide future management and treatment options.

Materials and Methods

After Institutional Review Board approval, a retrospective chart review was performed to identify all patients with UAB at our institution from 2011-2015 using the International Classification of Diseases, version 9 diagnosis codes representative of UAB symptomatology (ICD-9): urinary retention (788.2x, 788.20, 788.29), incomplete emptying (788.21), slowing of urine stream (788.62), hesitancy (788.64), straining (788.65), atony of bladder (596.4), paralysis of bladder (596.53), and neurogenic bladder (596.54). Each UDS was reviewed to identify patients with DU using the current ICS definition.⁴ Patients were excluded from the study if they were male, if there was a history of anti-incontinence or pelvic organ prolapse (POP) surgery within 1 year, or if the UDS showed BOO or did not demonstrate DU. Patients without a UDS available for independent review were also excluded.

Patient demographics, comorbidities, symptomatology, physical exam findings, American Urological Association Symptom Score (AUA-SS) questionnaire results, and UDS parameters were assimilated. Patients were stratified into 4 cohorts based on the potential underlying etiology, determined by the medical history. Inclusion criteria for the neurologic (N) cohort comprised diagnoses of: spinal cord injury, Parkinson's disease, multiple sclerosis, cerebrovascular accident (CVA) with neurologic sequelae, spinal surgery, peripheral neuropathy of any etiology including diabetes mellitus (DM), and other neurologic conditions. Inclusion criteria for the cardiovascular disease manifestations (CV) cohort required that the disease was severe enough to necessitate surgical or endoscopic

intervention for: severe coronary artery disease (CAD), severe peripheral vascular disease (PVD) or myocardial infarction (MI), cardiac arrhythmia, CVA, and structural/valve disease. Patients with a diagnosis of CAD or PVD managed with medical therapy alone were considered to be at risk for severe cardiac disease and included into a cardiac risk factor cohort (CVR). This cohort also included patients with hypertension, hyperlipidemia, DM without peripheral neuropathy, and tobacco use. All other patients were assigned to the idiopathic (I) cohort. The investigators assigned patients with multiple etiologies to the cohort for which the patient exhibited the most severe disease manifestations.

Patient variables were then compared between cohorts using t-test or Fisher exact test statistics. Statistical analyses were performed to identify individual predictors associated with DU. The criterion for statistical significance was set at $p < 0.05$. The statistical software program STATA version 13 (College Station, TX) was employed for all statistical analysis.

Results

Of the 200 women included in the study, 53 (26.5%) were categorized as CV; 44 (22%) as CVR; 81 (40.5%) as N; and 22 (11%) as I. Patient demographics, comorbidities, physical exam findings, and UDS are shown in Table I. Mean age was 61.9 ± 15.8 years (range 23 to 91).

There were no differences between cohorts for BMI ($p=0.48$), recurrent UTI ($p=0.63$), history of urinary retention (AUR) ($p=0.65$), or POP (0.49). AUA-SS was available for 98 of 200 patients, and also did not differ across categories ($p=0.06$) (Table II). There was no difference between groups in presenting symptomatology: urgency, frequency, urgency urinary incontinence (UUI), AUR, incomplete emptying, hesitancy, or UTI, ($p=0.97$). Women in the CV cohort were significantly older ($p<0.001$) and more likely to be post-menopausal ($p<0.001$).

Urodynamic parameters [first sensation ($p=0.25$), normal desire ($p=0.80$), strong desire ($p=0.58$), capacity ($p=0.11$), $Q_{\max}$ ($p=0.50$), $P_{\det}$ at $Q_{\max}$ ($p=0.22$), and post-void residual (PVR), ($p=0.82$)] did not significantly differ between cohorts (Table III). Detrusor overactivity (DO) was observed in 28 patients (14%) and compliance abnormalities were present in 15 patients (7.5%) and did not differ between groups ($p=1.00$, $p=0.67$, respectively).

Treatments for UAB symptomatology included self-intermittent catheterization (SIC) in 160 patients (80%), sacral neuromodulation and SIC in 17 patients (8.5%), sacral neuromodulation alone in 9 patients (4.5%), indwelling Foley catheter in 2 patients (1%), and other treatment in 12 patients (6%). Of the 26 patients treated with sacral neuromodulation: 6 (23%) were included in CVR; 6 (23%) in N; 4 (15%) in CV; and, 10 (39%) in I. Of these 10 patients without a neurologic or cardiac etiology, 6 presented with complex voiding dysfunction with incomplete emptying on UDS. Overall, 65% (17/26) of the patients treated with sacral neuromodulation had at least one episode of AUR in the clinical history, with 42% (11/26) having AUR as the initial presenting symptom.

Discussion

Our study identified differences in age and menopausal status between cohorts; patients with DU and extensive cardiovascular disease appear to be older. Age has been found to be independently associated with DU in prior studies.⁶ However, we were unable to identify any other clinical or urodynamic associations between groups. This inability to identify clinical phenotypes in women with DU is also consistent with the existing literature, suggesting that the underlying etiology for DU may be multifactorial.

It has been proposed that DU can result from neurologic, myogenic, iatrogenic, or idiopathic causes.³ The myogenic hypothesis suggests that smooth muscle changes within the bladder leading to reduced excitability and loss of intrinsic muscle contractility, which drives spontaneous detrusor contractions.⁷ Osman et al. include BOO and DM as myogenic causes for DU.³ The neurogenic hypothesis suggests defects in afferent innervation or the integrative control at spinal and supraspinal centers lead to poor efferent outflow.⁸ Iatrogenic causes may be related to denervation from pelvic surgery, radical hysterectomy, or anterior/abdominoperineal resection, and thus may be considered neurogenic as well.

Epidemiological studies have suggested bladder ischemia, hypoxia, and metabolic syndrome are likely etiological factors of DU, though the pathological mechanisms have not been clearly defined.⁷ In animal models, cystometry of MI-prone Watanabe heritable hyperlipidemic (WHHLMI) rabbits showed significantly shorter micturition intervals, smaller voided volume with non-voiding contractions, and lower micturition pressure compared to controls.⁷ Vascular compromise can be represented by CV risk factors: tobacco use, hyperlipidemia, hypertension, and DM. As such, it appears that DU in women may primarily be due to neurologic, early or late CV disease, or may be idiopathic in nature. As such, we elected to evaluate patients using these 4 cohorts.

While there are several review articles discussing the inherent difficulties in defining and treating symptoms of UAB, there is a paucity of literature evaluating patients with DU using actual clinical data. Gammie et al. evaluated a large UDS database of 1,788 patients to identify clinical features associated with DU. The study identified interrupted urinary stream, absent and/or decreased sensation, incomplete bladder emptying, and hesitancy for women with DU (n=308).⁹ While this symptomatology supports the proposed definition by Chapple et al.², the study does not identify any differences in etiology or clinical history among patients with DU. Several small series have attempted to identify predictive factors for impaired detrusor contractility in men, but similar to our study in women, failed to identify any significant differences.^{10,11} Hoag et al. evaluated 79 patients with DU, 68.4% of which were female. The most common symptoms were: urgency (63.3%), weak stream (61.0%), straining (57.0%), nocturia (48.1%), and frequency (46.8%). Among patients who were able to void, mean P_{det} @ Q_{max} was 22.3 (5-37) and mean Q_{max} was 9.3 (1-22), which is similar to the value in our study. Surgical history (pelvic 40.5%, back 19.0%), DM (11.4%), and medications promoting AUR (32.9%) were cited as the most prevalent risk factors, but the study did not address any other patient characteristics.¹² To our knowledge, our study is the largest series to date to evaluate potential underlying etiologies of female

patients with DU and assess urodynamic parameters and clinical factors contributing to their UAB symptomatology.

Several study limitations are noteworthy. As a retrospective review, ICD-9 diagnosis codes were used to identify patients with symptoms of UAB. Unfortunately, there is not an ICD-9 code for UAB specifically, which may have prevented the electronic search from including all potential patients. As a result, codes were used which represent established symptoms of UAB, and then UDS were independently reviewed to identify patients with DU. Since there is not currently a universal measurement to define DU, our use of $P_{det} @ Q_{max}$ as an index of bladder contractility may have also limited our findings. Men were excluded from the study due to the potentially different pathophysiologies in men and women, as in the case of BOO secondary to benign prostatic enlargement in men.^{13,14}

DO was present in 14% of the patients. The presence of both DO and DU may have confounded the UDS analysis, limiting our ability to identify associations between groups. Chancellor recently hypothesized that chronic untreated or treatment-refractory overactive bladder (OAB) may progress to detrusor hyperreflexia/impaired contractility (DHIC) and ultimately UAB.¹⁵ As such, these 14% may represent patients with DHIC on this continuum rather than a unique disease state. However, further study is needed to substantiate this hypothesis.

Patients were stratified into cohorts using predefined criteria; yet, many patients had comorbidities across all 4 cohorts, and stratifying them by the most significant manifestations may have introduced bias. Previous studies have categorized DM as either a neurogenic¹⁶ or myogenic etiology.¹ We were unable to accurately measure the severity of the disease or the clinical time course for all patients; thus, we assigned patients with DM without peripheral neuropathy to the CVR cohort, and those with peripheral neuropathy to the N cohort. Diabetic cystopathy, which can include symptoms of sensory-urgency, impaired bladder emptying, and DU, can occur in up to 50% of patients with DM and may be due to peripheral neuronal dysfunction and/or microvascular disease.⁷ As such, certain comorbidities could not be compartmentalized due to the presence of neurologic and cardiovascular compromise, suggesting that the etiology of DU may truly be multifactorial.

Conclusions

Though differences were observed between cohorts for age and menopausal status, categorizing patients by clinical or urodynamic parameters did not demonstrate distinct differences, suggesting that the etiology of DU may be multifactorial. As in the existing literature, we were unable to identify common characteristics, which also suggests that the pathophysiology of DU still remains unclear. As a result, future opportunities exist to identify clinical phenotypes for patients presenting with UAB symptomatology.

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Table I

Patient Demographics.

Patient Demographics	
Patient Variable	Mean (SD)
Age	61.9 (15.8)
BMI	28.2 (6.6)
AUA-SS	21.4 (7.4)
	n (%)
Diabetes mellitus	49 (24.5)
Bowel dysfunction:	86 (43.0)
Constipation	37 (43.0)
IBS	35 (40.7)
Other	14 (16.3)
Cardiovascular disease:	53 (26.5)
CAD/PVD/MI	32 (60.4)
Arrhythmias	6 (11.3)
Structural/valve disease	7 (13.2)
CVA	8 (15.1)
Tobacco use	35 (17.5)
Hyperlipidemia	91 (45.5)
Hypertension	110 (55.0)
Peripheral vascular disease	21 (10.5)
Post-menopausal	141 (70.5)
Neurologic disease:	105 (52.6)
Multiple sclerosis	23 (21.9)
Spinal cord injury	11 (10.5)
Parkinson's disease	2 (1.9)
CVA with neurologic sequelae	17 (16.2)
Spinal surgery	32 (30.5)
Other	20 (19.0)
Peripheral neuropathy	45 (22.5)
Pelvic radiation	6 (3.0)
Recurrent UTI	94 (47.0)
History of AUR	83 (41.5)

Patient Demographics	
Patient Variable	Mean (SD)
Presenting Symptomatology *	
OAB (urgency, frequency, UUI)	– (29.0)
AUR	– (32.5)
Recurrent UTI	– (31.5)
Incomplete emptying, hesitancy	– (7.0)
POP	
Grade:	8 (25.0)
1	11 (34.4)
2	12 (37.5)
3	12 (37.5)
4	1 (3.1)
Compartment:	
Anterior/Anterior +Apical	26 (81.3)
Isolated Apical	3 (9.4)
Isolated Posterior	3 (9.4)
UDS DO	28 (14.0)
UDS compliance abnormality	15 (7.5)

* Only % shown as patients may have initially presented with more than 1 symptom

Table II

Statistical analysis of patient variables by cohort.

Patient Variables by Cohort					
Patient Variable	Cardiovascular Manifestations (CV) n=53 (26.5%)	Cardiac Risk Factors (CVR) n=44 (22%)	Neurologic Etiology (N) n=81 (40.5%)	Idiopathic Etiology (I) n=22 (11%)	p value
	Mean (SD)				
Age	66.9 (12.3)	60.5 (15.3)	57.0 (14.4)	46.1 (16.4)	<0.001
BMI	27.8 (5.4)	29.0 (7.5)	28.4 (7.1)	26.3 (5.5)	0.48
AUA-SS	22.0 (7.0)	17.7 (6.7)	22.9 (7.1)	21.7 (8.8)	0.06
	n (%)				
Compliance abnormality	3 (5.7)	5 (11.4)	5 (6.2)	2 (9.1)	0.67
Detrusor overactivity	8 (15.1)	6 (13.6)	11 (13.6)	3 (13.6)	1.00
Post-menopausal	48 (90.6)	35 (79.6)	50 (61.7)	8 (36.4)	<0.001
Recurrent UTI	25 (47.2)	17 (38.7)	41 (50.6)	11 (50.0)	0.63
History of AUR	25 (47.2)	15 (34.1)	34 (41.9)	9 (40.9)	0.65
Presenting Symptomatology [*] :					
OAB (urgency, frequency, UUI)	– (37.7)	– (40.9)	– (34.6)	– (31.8)	0.97
AUR	– (28.3)	– (27.3)	– (25.9)	– (27.3)	
Recurrent UTI	– (30.2)	– (22.7)	– (32.1)	– (31.8)	
Incomplete emptying, hesitancy	– (3.8)	– (9.1)	– (7.4)	– (9.1)	
POP	12	6	12	2	0.49

* Only % shown as patients may have initially presented with more than 1 symptom

Table III

Urodynamic parameters by cohort.

Urodynamic Parameters Mean (Standard Deviation)					
UDS	Cardiovascular Manifestations CV	Cardiac Risk Factors CVR	Neurologic Etiology N	Idiopathic Etiology I	p value
First sensation	169 (187)	191 (198)	162 (187)	160 (174)	0.25
Normal desire	251 (153)	292 (181)	286 (195)	284 (220)	0.80
Strong desire	366 (22)	418 (230)	418 (211)	392 (235))	0.58
Capacity	471 (260)	579 (225)	545 (209)	552 (225)	0.11
P _{det} @ Q _{max}	11.3 (15.2)	9.8 (13.2)	12.0 (17.3)	18.5 (19)	0.22
Q _{max}	7.6 (6.2)	9.7 (8.5)	9.7 (8.4)	7.4 (6.6)	0.50
PVR	332 (232)	378 (248)	366 (241)	362 (286)	0.82