Overactive bladder phenotypes: development and preliminary data

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Introduction: *The purpose of this study is to develop overactive bladder (OAB) phenotypes that can be used to develop diagnostic and treatment pathways and offer clues to the underlying etiologies of patients with OAB.*

Materials and methods: *This is a retrospective, multicenter study of patients with lower urinary tract symptoms (LUTS). Evaluation included a 24-hour bladder diary (24HBD), the lower urinary tract symptoms score (LUTSS) questionnaire, uroflowmetry (Q), and post-void residual urine (PVR) measurement. Patients completed the 24HBD and LUTSS on a smartphone application or paper. Those with an OAB symptom sub-score (OABSS) ≥ 8 were included. An expert panel developed a phenotype classification system based on variables considered to be important for treatment.*

Results: *The following variables were selected for inclusion in the phenotype modeling: 24-hour voided volume (24HV), maximum voided volume (MVV), Qmax and PVR. Subjects were divided into three phenotypes based on the 24HV: polyuria (24HV > 2.5 L), normal (24 HV 1-2.5 L), and oliguria (24HV < 1 L). Each phenotype was subdivided based on MVV, Qmax & PVR, resulting in 18 sub-types. Five hundred thirty-three patients, 348 men and 185 women, completed the LUTSS and 24HBD. OAB was present in 399 (75%) - 261 men and 138 women. The prevalence of the primary phenotypes was polyuria (25%), normal (63%), and oliguria (11%).*

Conclusions: *Classification of OAB variants into phenotypes based on 24HV, MVV, Qmax, and PVR provides the substrate for further research into the diagnosis, etiology, treatment outcomes and development of granular diagnostic and treatment algorithms.*

Key Words: overactive bladder, phenotypes, treatment algorithms

Introduction

Overactive bladder (OAB) was originally defined as a syndrome,[1] but is now recognized as a symptom complex characterized by four intimately linked symptoms: urinary frequency, urgency, urge incontinence, and nocturia.[2,3] The definition of OAB is not mere semantics. If one considers OAB to be a syndrome, patients typically undergo a rudimentary evaluation, and treatment is largely empiric—all patients are treated similarly and go on to more definitive diagnostic testing only when treatment fails. All OAB guideline algorithms recommend this.[4,5]

A symptom complex, in contradistinction, assumes that OAB has a differential diagnosis and requires a more thorough diagnostic approach before treatment to optimize therapeutic outcomes.[6-8] The purpose of a thorough diagnostic evaluation is twofold—firstly, to identify remediable conditions like benign prostatic obstruction (BPO) or pelvic organ prolapse (POP) whose treatment usually alleviates the overactive bladder symptoms[6,9] and, secondly, to categorize patients according to pathophysiologic subgroups

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that require a different approach to diagnosis and treatment.

Herein, we propose a phenotypic classification of OAB and apply it in a multicenter study to determine the prevalence of each of the phenotypes.

Materials and methods

This is a retrospective, IRB approved, multicenter study of men and women referred for the evaluation of lower urinary tract symptoms (LUTS). The patient population was derived from six sites—a veterans' administration hospital, a military practice, two academic practices, a large urology group private practice, and a large managed care consortium. A database was searched for patients who completed a 24-hour bladder diary (24HBD) and the Lower Urinary Tract Symptoms Score on a mobile application (WeShare URO, Symptelligence Medical Informatics, LLC, Franklin, MA, USA).

The 24HBD recorded the time and amount of each micturition, incontinence episodes (stress, urge, or unaware incontinence), and answers to a series of questions about each of these events. Incomplete diaries, and diaries with a total 24-hour voided volume less than 500 mL and/or less than 3 voids per day were excluded from analysis. Incomplete diaries were defined as those that were of less than 24 hours, did not measure each voided volume, or failed to answer the associated questions.

The following data was recorded from the 24HBD for each patient: 24-hour voided volume (24HV), total voids, night-time voids, maximum voided volume (MVV), urgency voids (urge perception score = 3 or 4),[10] incontinence episodes, difficulty voiding episodes, nocturnal polyuria index (NPi), nocturia index, daytime volume, and nighttime volume. Primary nocturia voids and insomnia voids were recorded for bladder diaries completed on the mobile app.

The LUTSS is a 14-item questionnaire comprised of a total score and five subscores.[11] The LUTSS, completed on the app or on paper, was included when completed within 2 weeks of the diary date, provided that there was no change in symptoms nor any new treatment initiated during that time period. Contemporaneous maximum uroflow (Q_{max}) and post-void residual (PVR) urine (within 2 weeks of the diary date) were also included.

Inclusion criteria were men and women with OAB symptom sub-score (OABSS)[12] ≥ 8, as determined by the LUTSS questionnaire, who completed the 24HBD. For patients who completed more than one bladder diary, the first diary was analyzed. Q_{max} and PVR (estimated by ultrasound) were obtained and utilized when contemporaneous (within 2 weeks) of the diary date, provided that there was no intervening treatment or change in symptoms. Q_{max} and PVR completed greater than 2 weeks from the diary date were included if the patient's clinical diagnosis remained the same. Exclusion criteria were incomplete 24HBD data, diaries reporting 24HV < 500 mL and diaries reporting < 3 voids per one 24-hour period. Incomplete LUTSS, uroflow and PVR data were also excluded from analysis.

Development of the overactive bladder phenotypes

A panel of experts, comprised of four urologists and a urogynecologist expert in OAB diagnosis and treatment, designed the conceptual framework around which OAB phenotypes would be constructed. The panel considered two approaches—classifying patients according to age, sex, disease states such as BPO and POP, diabetes, neurogenic bladder, etc, or according to symptoms and physiologic variables such as bladder capacity, Q, and PVR. The panel chose the latter approach because they believe the underlying pathophysiology dictates the rationale for treatment and that there is a commonality of therapeutic choices that transcends disease states.

To that end, the panel considered using the following variables in constructing the phenotypes: age, sex, 24-hour voided volume, number of voids per 24 hours, daytime voids, nighttime voids, number of urgency episodes, number of urge incontinence episodes, number of voiding difficulty episodes, dysuria, maximum voided volume, duration of OAB symptoms, prior lower urinary tract surgeries, prior prolapse surgery, uroflow, and PVR urine. After debate and revisions, the panel agreed on the 24-hour voided volume, maximum voided volume, Q, and PVR as the variables to be used for the development of OAB phenotypes.

For each variable we decided to use empiric (rather than normative) cut off values because we believed that these would more accurately impact the development of treatment pathways. For example, there are two extremes based on 24HV, MVV, Q and PVR—1) polyuria, large bladder capacity, normal Q and PVR, 2) oliguria, small capacity bladder and abnormal Q and PVR. A rudimentary, empiric treatment algorithm can be devised from these two examples. In the former instance, the patient has sufficient reserve so that a behavior modification program comprised of restricting fluid intake and voiding before the bladder becomes too full is likely to be successful. The latter patient, who restricts his or her fluid intake and has a small bladder capacity, with abnormal uroflow and/or residual urine, would be suspected of having urethral obstruction or detrusor underactivity and evaluated accordingly.

Subjects were first categorized into three major phenotypes according to the 24HV as follows: Phenotype 1 = polyuria [24HV > 2.5 L]; Phenotype 2 = normal [24HV 1 L-2.5 L]; Phenotype 3 = oliguria [24HV < 1 L]. These cut off values for the OAB phenotypes are based on published data modified by panel consensus.[13-18]

Each major phenotype was then divided according to the MVV, resulting in 9 intermediate phenotypes: large MVV [> 350 mL]; normal MVV [150 mL-350 mL]; small MVV [< 150 mL]. Finally, each of the 9 intermediate phenotypes was subdivided according to the Q_{max} and PVR data as follows: normal [Q_{max} > 12 mL/s and/or PVR ≤ 100 mL] or abnormal [Q_{max} ≤ 12 mL/s and/or PVR > 100 mL], resulting in a total of 18 final phenotypes.

Results

A total of 618 patients completed 1411 bladder diaries between August 2007 and April 2018 at six sites (average = 2.3 diaries/patient). Multiple diaries by a single patient and diaries with incomplete and/or erred data were excluded from analysis, see Figure 1.

A total of 604 patients (1 diary/patient) were identified; of those, 533 (88%) completed a contemporaneous LUTSS questionnaire and 399/533 (75%) were OAB patients, with OABSS ≥ 8 (261 men, 138 women). The mean age, Q_{max}, voided volume, PVR, total number of voids per day, daytime voids, nighttime voids, and incontinence episodes are displayed in Table 1. Figure 2 depicts the distribution of the 3 overarching major phenotypes, 9 intermediate phenotypes, and the further refined 18 final phenotypes. Two of the phenotypes did not have any conforming patients.

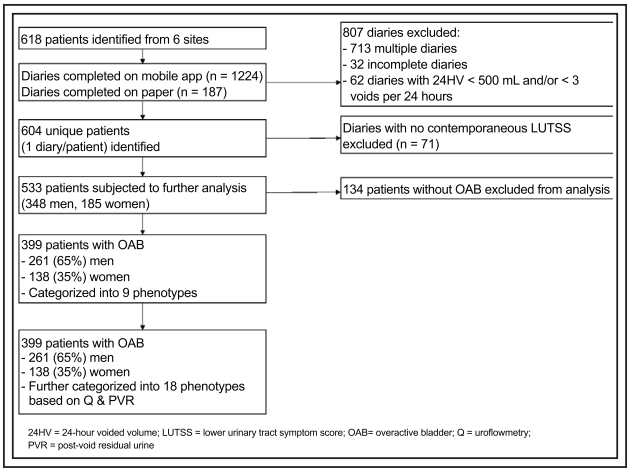

Figure 1. Flowchart detailing inclusion and exclusion criteria.

Discussion

Phenotype refers to the physical appearance or characteristics of a person that results from the interaction of his or her genotype and the environment.[19] For our purposes, phenotype refers to a set of mutually exclusive characteristics that distinguish one group from another and has both diagnostic and therapeutic implications. In this context, establishing phenotypes for OAB has relevance only if one considers OAB to be a symptom complex with a differential diagnosis that requires different approaches to diagnosis and treatment.[6,7]

In 2011, the Canadian Urology Forum conducted a workshop to answer just this question—whether OAB is a symptom complex caused by, or associated with,

TABLE 1. **Mean uroflow and bladder diary measures**

	OAB patients	**Men**	**Women**
n	399	261	138
Age (yrs.)	61	63	58
Qmax (mL/s)	14.2	11.7	19.6
Voided volume (mL)	211	192	253
PVR (mL)	68	78	47
# voids/24 hours	11.3	11.4	11.2
# daytime voids	9.2	9.2	9.2
# nighttime voids	2.1	2.2	2.0
# incontinence episodes	0.3	0.4	0.2

OAB = overactive bladder; Qmax = peak uroflow; PVR = post-void residual urine

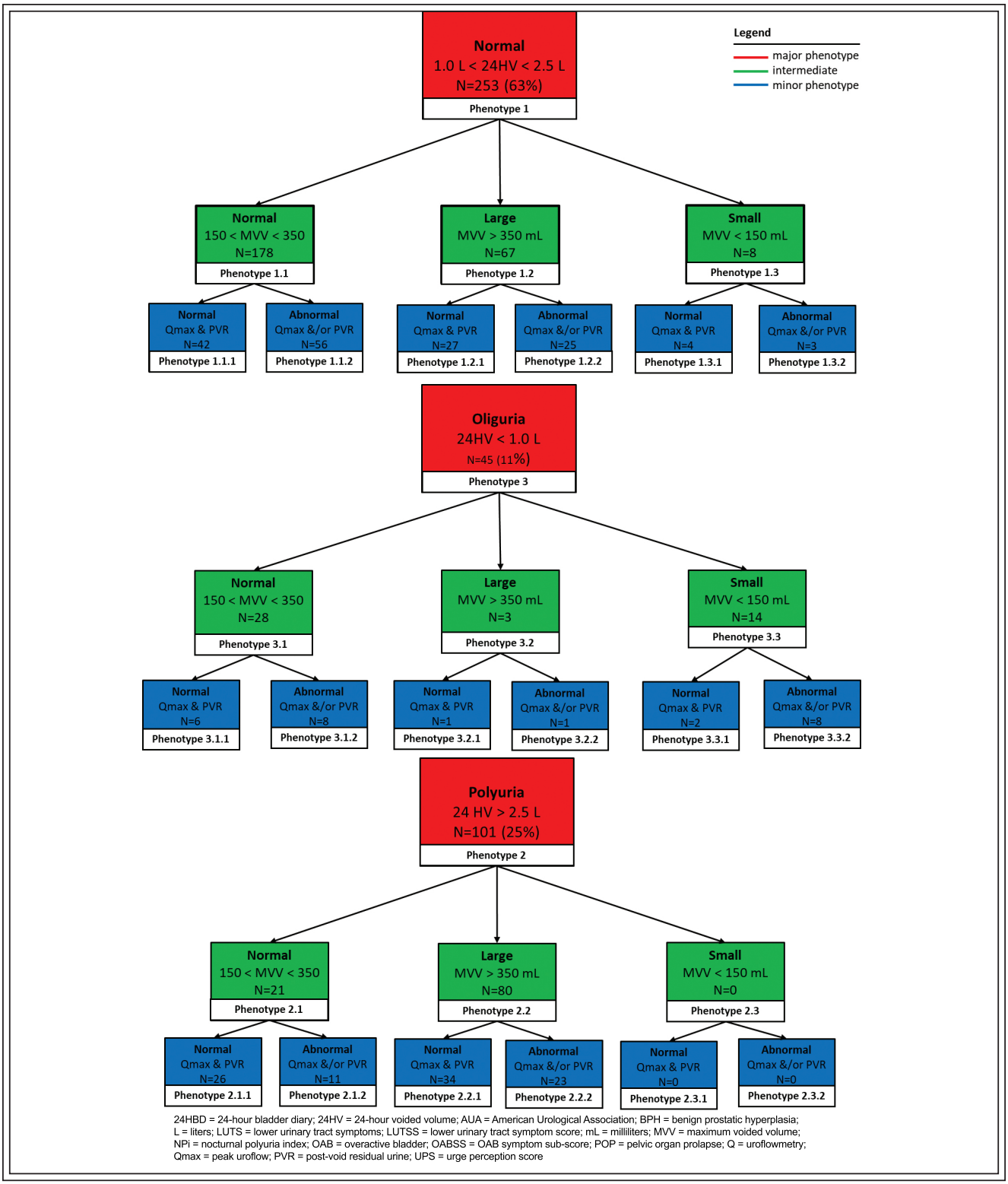

Figure 2. OAB phenotypes. All patients with OAB are first classified into three major phenotypes (n = 399). They are then classified into nine intermediate phenotypes. OAB patients with contemporaneous Q and PVR testing are further classified into 18 minor phenotypes (n = 277). Normal Qmax > 12 mL/s and PVR ≤ 100 mL; abnormal Qmax ≤ 12 mL/s and/or PVR > 100 mL.

other conditions or a unique entity akin to the syndrome described by the International Continence Society. In so doing, they identified four rudimentary, but distinct clinical phenotypes: men, women, neurogenic bladder and elderly patients linked to underlying physiology. For example, specific clinical phenotypes identified in men with obstruction and benign prostatic hyperplasia (BPH), "tight bladder neck," strictures, and acquired voiding dysfunction. Reported phenotypes for neurogenic OAB included Parkinson's Disease, spinal cord injury, and suprapontine neurologic lesions. At the conclusion of the sessions, the vote was 21 to 5 in favor of defining OAB as a symptom complex rather than as a unique entity akin to the syndrome described by the International Continence Society.[8]

A PubMed search failed to come up with other articles describing OAB phenotypes, but there were several studies utilizing clustering and statistical methodology to classify LUTS patients based on patient-reported symptoms. For example, Andreev et al[20] described four distinct clusters in women with LUTS based on the LUTS Tool and the American Urological Association (AUA) Symptom Index. The data was analyzed using a probability-based consensus clustering algorithm. Their premise was that the paradigm of grouping patients into clinical groups like OAB, nocturia and incontinence is flawed because of its limitations—"as often patients present with multiple urinary symptoms that do not perfectly fit the pre-established diagnoses." Examples of other clusters are seen in the work by Coyne et al[21] and Hall et al.[22] All of these authors discussed the potential impact of associated symptoms which they believe may be clinically important for both diagnosis and treatment.

We applaud their effort to categorize symptoms in such a granular way, but knowing that the "bladder is an unreliable witness,"[23] we believe that symptom analysis alone is not a reliable means of diagnosing underlying etiologies. Instead, symptoms and bother alert the clinician to the patient's perspective and what s/he wants treated. Accurate phenotyping requires a better understanding of the underlying causes, and that understanding itself requires further (physiologic) testing such as bladder capacity, Q, PVR, physical exam to test for stress incontinence and urodynamic testing.

The phenotypic description we described herein is based on the observation that OAB is a symptom complex with a differential diagnosis that requires different approaches to diagnosis and treatment. The differential diagnosis of OAB symptoms has received scant attention in the peer review literature, yet the underlying mechanisms that cause those symptoms (e.g. detrusor overactivity, sensory urgency, urethral obstruction, impaired sphincter function, and low bladder compliance) are, or at least should be, an integral part of the fund of knowledge of urologists and urogynecologists.[2,6-8,24,25]

Our goal is to utilize our collective, existing knowledge base regarding the causes and treatment paradigms for OAB symptoms to create unique diagnostic and treatment pathways. Our expert panel decided on a physiologic approach based on symptoms, bladder diaries, uroflow, and PVR urine. Regardless of the underlying disease entity, we believe that the principles of diagnosis and treatment remain the same. A disease-driven categorization[8] approach relying on mathematical modeling, cluster analyses, and/or machine learning techniques[26] was not utilized. The panel believed they understood the physiologic principles underlying diagnosis and treatment and could, a priori, stratify the patient's into mutually exclusive phenotypic groups that provided a rational substrate for developing diagnostic and treatment algorithms. They further believed that the heterogeneity based on disease states (e.g. diabetes, neurogenic bladder) and other clinical variables, without considering pathophysiology, would not impact treatment algorithms in a meaningful enough way.

The panel decided on a three-tier phenotype system. The first tier divides all OAB patients into three groups based on 24-hour voided volume as extracted from the bladder diary, categorizing patients as polyuric, [2.5 L or above], normal [1 L-2.5 L] or oliguric [less than 1 L]. Each major phenotype group is further divided into the second tier consisting of three mutually exclusive sub-groups, resulting in a total of 9 intermediate sub-groups based on maximum voided volume (a proxy for bladder capacity), with MVV either large [350 mL or above], normal [150 mL-350 mL], or small [less than 150 mL]. The third tier divides the 9 intermediate sub-groups into 18 minor phenotype groups based on normal or abnormal Q_{max} and post-void residual urine.

To illustrate the potential diagnostic and therapeutic implications that can be derived from this approach, consider the patient with polyuria, large bladder capacity, normal Q and PVR. After ruling out serious or remedial conditions, such as poorly controlled diabetes mellitus, s/he would be advised to undergo behavior modification. Only when that failed would a bladder diary, uroflow, and residual urine be assessed.

On the other hand, if the patient fits into the phenotype of oliguria, small capacity bladder, low flow and large PVR, if treated according to the current guidelines,[4] s/he would endure at least a month, and possibly many months, of ineffective (behavior modification) and possibly harmful (anticholinergic) treatments until the proper diagnosis was made (e.g. prostatic obstruction, pelvic organ prolapse,

urethral stricture) and effective treatment instituted.

It could be argued that existing OAB guidelines already suggest an approach like we described herein. This contention operates under the assumption that the majority of health care providers are familiar with a myriad of potential phenotypes, which, we believe, is not the case. A codified phenotype classification would explicitly provide practitioners with a frame of reference to enable them to more effectively diagnose and treat patients suffering from OAB symptoms. To our knowledge, nothing like this exists in the literature, and that is why we emphasize the importance of such a classification.

There are a number of weaknesses to this study. Firstly, it is retrospective, and it does not account for clinical variables that can be gleaned from an electronic medical record. Secondly, it includes data from a tertiary care practice that may affect the prevalence of different phenotypes compared to the general OAB population. Finally, the utility of the proposed phenotypes was based on panel consensus and not on actual treatment data, but it is our hope that future research will refine and consolidate the cut off values and, perhaps, add new variables for inclusion.

Conclusions

A panel of experts considered many empiric variables for inclusion in a phenotype classification system and narrowed their search to include 24-hour and maximum voided volume, uroflow, and residual urine. Utilizing these variables, 18 theoretic phenotypes emerged and could provide the substrate for further research into the etiology of OAB, new treatments, and more precise treatment algorithms.

Disclosure

This research was funded by the Institute for Bladder and Prostate Research, New York, NY. Dr. Blaivas is Co-Founder and Chief-Scientific Officer of Symptelligence Medical Informatics, LLC. Dr. Chaikin is a consultant/advisor for Avadel Pharmaceuticals. Dr. Weiss is a consultant/advisor for Ferring Pharmaceuticals. □

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