Evaluation of lower urinary tract symptoms in multiple sclerosis patients: Review of the literature and current guidelines

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Read a followup of this article, "Treatment of lower urinary tract symptoms in multiple sclerosis patients," in next month's online issue of *CUAJ* (*www.cuaj.ca*).

Abstract

Multiple sclerosis (MS) is a unique neurological disease with a broad spectrum of clinical presentations that are time- and disease course-related. MS plaque location (intracranial and/or spinal) is a key feature in the pathophysiology of disease-related lower urinary tract symptoms (LUTS). The prevalence of these symptoms in MS patients is very high, with nearly 90% of them experiencing some degree of voiding dysfunction and/or incontinence. LUTS rarely present as primary MS manifestations and usually appear 6–8 years after the initial diagnosis. Symptom severity usually correlates with the disability status of patients.

Patient assessment comprises clinical and advanced investigations. Each patient should be evaluated uniquely, after taking into account his/her symptoms, disease course and length, comorbidities, physical status, and medications. Basic investigation includes detailed history-taking, physical examination, and post-void residual volume measurement. Advanced evaluation consists of imaging and specific testing, with pivotal importance on urodynamic study.

Introduction

Multiple sclerosis (MS) is a unique, inflammatory central nervous system (CNS) disease with a broad spectrum of clinical presentations that are time- and disease progression-related. It usually affects young adults, with a female predominance of 3:1. Men are more likely to develop symptoms at a slightly older age, with a more rapidly progressing disease course.

Although urological symptoms as first presentation of MS are rare (3–10%), almost two-thirds of MS patients will suffer from moderate to severe urinary disturbances related to their disease. These can result in significant morbidity and impairment of their quality of life (QOL).[1] Urologists must have a thorough knowledge of the disease process, as we have discussed in a prior article,[2] to tailor the right evaluation tools to each specific case.

Pathophysiology of lower urinary tract symptoms (LUTS) in MS

MS plaques can be found anywhere in the CNS, including the spinal cord. Their exact location will profile unique features of lower urinary tract dysfunction (LUTD). Intracranial lesions occur in up to 90% of MS patients nearly everywhere along the white matter. Lesions in cortical regions related to urinary tract regulation (medial prefrontal cortex, insula, and pons) are thought to be the cause of detrusor overactivity (DO). Spinal cord, and particularly suprasacral lesions, are common in MS patients, as described by Oppenheimer.[3] The prevalence of cervical cord plaques is almost 80% in these cases, predominantly in the lateral corticospinal (pyramidal) and reticulospinal tracts. Lumbar and dorsal cord involvement is less frequent (40% and 18%, respectively). Suprasacral spinal lesions may cause DO by impacting the descending inhibition of bladder contraction. On the other hand, damage to the reticulospinal tracts may lead to detrusor-sphincter-dyssynergia (DSD).[4] Sacral cord lesions are less common (18–60%) and their role in LUTD is still questionable. Plaques in efferent or afferent pathways may impair emptying and urinary retention.[5] Although 63% of patients with sacral lesions show detrusor hypocontractility, only 5% present bladder areflexia.[6]

Prevalence of LUTS in MS

LUTS are common in MS patients. Based on the North American Research Committee on Multiple Sclerosis Registry , a large survey of more than 9700 MS patients,[7] 65% reported moderate to severe urinary complaints. Nocturia, followed by urinary urgency and frequency were the most prevalent signs. Urinary incontinence and poor bladder emptying were noted less frequently. Table 1 summarizes the data on and prevalence of LUTS in these patients.

Table 1. Percentage of MS patients experiencing LUTS

Study	No. of patients	Urgency	Frequency	Incontinence	Hesitancy	Retention
Miller et al[36]	321	60	50	36	33	2
Bradley et al[37]	90	86	60		28	20
Hennessey et al[38]	191	71	76	19	48	
Borello-France et al[39]	133	61	71	83		
Ukkonen et al[40]	24	83	54	75	58	
Quarto et al[31]	107	61	83	32		

Modified from Fernández[28] and Quarto et al.[31] LUTS: lower urinary tract symptoms; MS: multiple sclerosis.

Urinary symptoms rarely represent the first manifestations of MS (up to 10%) and usually appear 6–8 years after the initial diagnosis.[8] The presence or absence of symptoms is an unreliable indicator of voiding dysfunction extent. Although most symptomatic patients will manifest some objective features on urodynamic study (UDS), lack of symptoms corresponds poorly with this test.[1] Storage symptoms correlate well with the Expanded Disability Status Scale (EDSS)[9] and pyramidal tract involvement; however, their association with voiding symptoms is much weaker.[10]

LUTS in MS may be influenced by gender and age. While their exact impact on patient symptoms has not been thoroughly investigated, cumulative action of other diseases is possible, eliciting bladder dysfunction — benign prostate obstruction, pelvic relaxation, or stress urinary incontinence (SUI). There appears to be no significant relationship between the overall incidence of symptoms and gender. However, men with MS have a higher prevalence of voiding symptoms and complications, especially after age 50.[11]

Evaluation of LUTS in MS

MS is characterized by heterogeneous clinical presentation and evolution. Patient profiles vary greatly. Although most patients urinate by themselves, they may suffer from overactive bladder (OAB) symptoms or recurrent urinary tract infections (UTIs). Other common complaints are voiding and emptying difficulties with a smaller group of patients who cannot void at all.

Evaluation has to be uniquely tailored for every patient after taking into account his/her symptoms, disease course and length, comorbidities, physical status, and medications. However, complete history, including QOL assessment, physical examination, and urine culture and analysis with post-void residual (PVR) measurements, should be obtained systematically for all patients. More advanced evaluation, including UDS, may be reserved for cases where the results may change the treatment regimen chosen.

At present, international management guidelines, developed by the International Consultation on Incontinence (ICI)[12] and the European Association of Urology (EAU),[13] exist for neurogenic LUTD (NLUTD) in general, but not specifically for MS patients. Unlike spinal cord injury (SCI), MS patients, even with detrusor external sphincter dyssynergia (DESD) and neurogenic detrusor overactivity (NDO), rarely suffer from upper urinary tract (UUT) deterioration.[1,11] Therefore, active and invasive evaluation of NLUTD patients, as proposed by these guidelines, does not seem fully applicable to the MS population.

Several expert European national panels published their own management consensus on MS.[14-20] Unfortunately, the scarcity of good-quality studies assessing the efficacy and safety of various treatments in MS lessens their levels of evidence. There are considerable differences between these guidelines, depending on the target population to whom they are addressed. They vary slightly if they have been laid down for general practitioners, rehabilitation specialists and neurologists,[15,17,19,20] urologists,[16] or neurourologists.[18]

Table 2. Which MS patients should be screened for LUTS?

	Italy[20]	France[15]	Belgium[17]
EDSS	≥3	≥6	Significant impact on QOL
MS duration	Long-term	N/A	≥15 years
Gender and age	Male ≥50 years	Male ≥55 years	Male ≥50 years
PVR	≥100 cc or 1/3 BC	≥100 cc	≥100–150 cc
Recurrent UTIs	Yes	Associated with fever or lumbar pain	Yes
Abnormal ultrasound findings*	Yes	Yes	Yes
Failure of conservative treatment	Medications and catheterizations	Medications	Medication and catheter bypass
Other	Impaired Cr blood levels	Immunosuppression	Incontinence More than 2 risk factors**

*Abnormal ultrasound findings: hydronephrosis, cystolithiasis, bladder diverticulum; **risk factors adapted from de Sèze et al.[18] BC: bladder capacity; Cr: creatinine; EDSS: Expanded Disability Status Scale; LUTS: lower urinary tract symptoms; MS: multiple sclerosis; N/A: not available; PVR: post-void residual; QOL: quality of life; UTI: urinary tract infection.

While all groups advocate urological evaluation of symptomatic patients, there is no consensus regarding the necessity of urinary tract evaluation in MS patients without LUTS. Litwiller et al[1] showed that even asymptomatic MS patients can suffer from LUTS. This has led a few groups to develop specific screening questionnaires,[15,21] while others based their profiling on combination of patients' properties with different test results.[18,20] Table 2 lists the recommendations made for different screening criteria.

Critical analysis of different guidelines[15-21] has resulted in dividing MS-related LUTS evaluation into basic and advanced testing.

Basic testing

History-taking should include detailed clinical background with emphasis on symptoms of urgency, frequency, incontinence (stress- and urgency-related), hesitancy, retention, and nocturia. LUTS may disturb QOL as much as motor disability does in MS patients.[22] Therefore, non-specific QOL instruments, such as King's Health Questionnaire,[23] OAB symptom scores,[24] and condition-specific Qualiveen,[25] are useful in evaluating daily impact and disease progression over time.

Physical examination should include appraisal of motor and sensory dysfunctions of the lower extremities, pelvic and sacral dermatomes. Neurologist review of physical examination may add important information. Pontine signs (dizziness, visual disturbances) may predict the future presense of NDO, while cerebellar signs may indicate DSD.[26] Pyramidial impairment of the lower limbs reflects the extent of spinal involvment and correlates with LUTS severity.[27] Digital rectal examination, pelvic measurements, and stress incontinence maneuvers may be needed to ascertain benign prostatic enlargement, malignancy, constipation, pelvic organ prolapse, and SUI.[1,28]

PVR volume should be evaluated, either by catheterization or preferably by bladder scan. MS patients have larger PVR volumes than their control counterparts,[29,30] and mean PVR is greater in MS patients with recurrent UTIs than in those without.[31]

Other important evaluation tools are three-day voiding or catheterization diaries, urine analysis, and culture.

Advanced testing

Advanced testing is not indicated for all patients. Generally, such assessment is reserved for cases where the chosen therapy could be changed based on the results.

Imaging

There is no consensus on imaging as a screening tool or confined to symptomatic patients at risk of UUT detrioration. Most guidelines recommend ultrasound in which hydronephrosis, cystolithiasis, and bladder diverticulum are considered to be UUT risk factors.[15,17,20]

Multichannel UDS and especially video-UDS are highly recommended by the EAU for neurogenic-related LUTS assessment (Grade A recommendation),[13] as repeated measurements can influence clinical decision-making (Grade C recommendation). However, these recommendations are not MS-specific.

In recent years, recommendations on UDS for LUTS evaluation in MS patients have changed drastically. de Sèze et al[18] proposed UDS for all symptomatic patients. However, more recent recommendations[15-17,19,20] and the fifth ICI[12] propose limits to UDS, suggesting urodynamic evaluation only in patients at risk of UUT deterioration or failure of initial, conservative treatment. However, UDSs are still recommended before any intravesical or surgical intervention. Although Blaivas et al[32] showed that 73% of MS patients without UDS were treated inappropriately, it remains an evaluation tool mainly employed by neurourologists. Wiedemann et al[33] tried to define risk profiling necessitating UDS. EDSS ≥6.5 MS subtypes other than relapsing-remitting and the use of more than one incontinence pad per day were found to increase the likelihood of abnormal UDS findings.

Five major urodynamic patterns can be seen in MS:[34]

- NDO without DSD
- NDO with DSD
- NDO with impaired contractility
- Detrusor underactivity (DU)
- Normal function

In a meta-analysis by Litwiller et al,[1] 62% had NDO, 25% had signs of DSD, 20% had DU, and 10% were normal on examination. Comparing MS patients with signs of NDO on UDS to patients with idiopathic DO revealed significant changes. MS patients had smaller bladder capacity with higher PVR volume and increased DO amplitude. Whether it is due to heightened bladder outlet resistance (DESD, for example) or is neurogenically mediated is still debatable.[30] Later work by the same authors[35] focused on the role of DSD in urinary dysfunction among women with MS. In a four-year followup period, no signs of UUT deterioration were documented in 143 patients. The authors concluded that the lack of significant detrusor pressure elevation in the DESD group accounts for the relatively low incidence of UUT damage in MS patients compared to SCI cases. More than that, no linkage was confirmed between MS subtype, time since diagnosis, patient age, and the presence of DESD. As MS is a fluctuating disease with exacerbations and remissions, UDS depicts urinary tract function at certain time points. Although improvement may occur, DSD is rarely resolved.[1]

Cystoscopy is not mentioned routinely in the above guidelines. It is usually reserved for the evaluation of recurrent UTIs, cystolithiasis, bladder outlet obstruction, and incontinence.

Conclusion

Most of the management consensuses (Grade D recommendations) discussed above are intended for urologists and general practitioners. Proposed diagnosis and followup algorithms differ as well, reflecting the diversity of clinicians' opinions on MS treatments, with variance between healthcare systems and the availability of different specialists. Urologists would be wise to adopt this consensus, as no one optimal management protocol suits all. They need to tailor specific evaluation protocols based on their experience and armamentarium to make the exact diagnosis and propose the best possible treatment.

Competing interests: Dr. Corcos has been an advisor for Allergan, Astellas, and Pfizer; a speaker for Allergan and Duchesnay; has received payment and honoraria from Astellas; and has participated in clinical trials for Allergan and Ipsen. The remaining authors report no competing personal or financial interests.

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