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Historical and Current Concepts Regarding Urodynamics in Multiple Sclerosis Patients

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Abstract

Purpose of Review In this review, current literature on management of neurogenic bladder in patients with multiple sclerosis (MS) is summarized. Topics include a review of MS, a brief overview of general treatment options, the effects of MS may manifest on lower urinary tract symptoms (LUTS), and clinical assessment of these patients. The utility of urodynamic evaluation in this patient population and the use of antibiotic prophylaxis in patients with MS on immunomodulatory medications are reviewed.

Recent Findings Unlike neurogenic bladder in spinal cord patients, lower urinary tract dysfunction in MS patients rarely leads to upper urinary tract deterioration. Currently there is no consensus on imaging as a screening tool to assess renal deterioration in this patient population. Internationally, there are differing opinions on the necessity of performing invasive urodynamic (UDS) investigation in MS patients during initial assessment. However, UDS evaluation can be useful in the guidance of treatment options and patient counseling and prior to more invasive interventions.

Summary Depending on the severity of MS, lower urinary tract symptoms are common and can evolve with progression of the disease. Although individual guidelines exist for management of patients with MS and select aspects of neurogenic LUTS, an optimal guideline for initial evaluation and surveillance is not available. The evaluation of patients with MS reporting LUTS should be uniquely tailored and take into consideration individual symptoms, disease course, comorbidities, and medications. Additionally, MS patients on immunomodulation medications that undergo UDS should be considered for prophylactic antibiotics.

Keywords Lower urinary tract symptoms · Neurogenic bladder · Urinary retention · Overactive bladder · Urinary incontinence · Multiple sclerosis · Urodynamic evaluation

Introduction

Depending on the varying symptoms and severity of multiple sclerosis (MS), lower urinary tract symptoms (LUTS) are common and can evolve with progression of disease. Management of dysfunction of the lower urinary tract in MS requires coordination of care across medical specialties. Management strategies can range from conservative, medical, self-catheterization, minimally invasive procedures, and reconstructive surgery. MS may be a progressive disease; therefore, patients with concomitant LUTS require routine evaluation and individually tailored treatment plans. Debate exists regarding the utility of UDS in the initial assessment of patients with MS, however, for those at-risk patients or those with changes of their urinary symptoms, invasive urodynamic studies may be beneficial.

In order to address urologic impact of MS, it is important to first understand the general clinical course of the disease. In most situations, MS is a progressive disease, and there is variability in the time of patient presentation to a urologist. Therefore, the role of a treating urologist will fluctuate as the patients' MS symptoms evolve. It is important to not only establish a urologist-patient relationship and discuss treatment goals acutely, but also establish future expectations of the

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patients' MS disease as it may progress. It is also imperative as a treating urologist to understand the potential pharmaceutical modalities utilized in MS as they can be immune modulating and therefore considered prior to invasive studies such as urodynamic evaluation or surgical interventions.

Review of Multiple Sclerosis and its Treatments

Multiple sclerosis is a demyelinating neurological disease, targeting the central nervous system (CNS). MS affects from 250,000 to 350,000 patients in the USA; approximately twice as many women than men, with the majority of European descent [1]. MS typically presents in adults ages 20–45, although occasionally it's onset is in adolescents and the elderly [2]. The exact cause of MS is unknown, although it is commonly theorized that the etiology is an inflammatory autoimmune-mediated process involving autoreactive lymphocytes [3]. There are genetic and environmental factors that predispose individuals to MS, including certain class I and class II major histocompatibility complexes and specific viral infections [4, 5].

MS is divided into several subtypes: relapsing-remitting, primary progressive (PPMS), and secondary progressive (SPMS). Relapsing-remitting MS (RRMS) is the most common type, characterized by distinct attacks with subsequent full or incomplete recovery. There is minimal disease progression between attacks [6]. Both types of progressive MS exhibit gradually worsening disability, most often involving motor impairment. For example, approximately 50% of patient will need assistance with walking within 15 years [7–9]. Onset of progression normally occurs at age 40–50 years old for both types, while secondary progressive MS exhibits an initial relapsing-remitting phase lasting typically 10–15 years [10]. There are reports regarding the complex association between disease severity, urologic symptoms, and urodynamic findings; a positive correlation has been shown between the expanded disability status score (EDSS) and neurogenic lower urinary tract symptoms [11, 12]. Using the EDSS, a significant relationship has been found between urologic symptoms, such as detrusor overactivity, and neurologic complaints [11, 12].

To diagnose MS, McDonald's criteria must be fulfilled which involves a combination of history of clinical attacks, radiological evidence (brain and possible spinal cord MRI), and sometimes demonstration of CSF oligoclonal bands [13]. Acute attacks are defined by 2017 McDonald's criteria as an episode of patient-reported symptoms and objective findings reflecting an inflammatory demyelinating event in the CNS lasting at least 24 h, with or without recovery, and in the absence of fever or infection. There may be resulting disability from the attack which may persist for weeks or months, which may be shortened with medical treatment [14, 15]. Complicating the decision to start treatment is that during the remission period the patient may not be symptom-free. There may be fluctuations in symptoms associated with fatigue, stress or sleep deprivation which may be mistaken for an acute attack [16]. If a true relapse is suspected, treatment may be started with corticosteroids. A typical course may involve 3–5 days of intravenous methylprednisolone with or without an oral taper, or a high-dose oral steroid [16]. If unresponsive, other treatments for the acute phase include adrenocorticotrophic hormone, intravenous immunoglobulin, and plasma exchange [17].

For chronic management of active MS, disease-modifying therapy (DMT) is recommended with immunomodulation [18•]. There are a number of immunomodulatory agents that may be given via intravenous infusion, injection therapy, or oral therapy. These agents include alemtuzumab, dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta preparations, natalizumab, ocrelizumab, and teriflunomide. None of these therapies are curative, but some observational studies have found evidence suggesting use of DMTs is associated with lower longer-term risk of disease progression in MS patients [19–21]. Response to therapy is monitored by clinical follow-up with attention to frequency and severity of relapses, new radiologic lesions, or progression of disability [22•]. Should patient become refractory to DMT therapy, they may be switched to other individual or combination therapies. There only select few immunomodulatory agents available for the treatment of PPMS and SPMS. Only ocrelizumab and siponimod have been found to provide consistent benefits for patients with progressive MS [23].

Treatment of MS can be complex given the multitude of symptoms combined with the often insufficient clinical response to immunotherapy alone. MS symptoms can span multiple organ systems and include motor weakness, constipation, LUTS, depression, neuropathy, tremor, and spasticity. A multidisciplinary approach to treatment of MS is crucial for symptomatic management. Specialists including neurologists, psychiatrists, urologists, orthopedists, ophthalmologists, speech therapists, and occupational therapists collaborate to manage the symptoms with pharmacotherapy, rehabilitation, exercise therapy, and possibly surgery.

Multiple Sclerosis and Lower Urinary Tract Symptoms

Specific to the urologist, it is important to understand how MS can effect the function of the urinary system. LUT symptoms can be the reason for a patient's initial presentation, however urinary symptoms usually appear 6–8 years after initial diagnosis [24, 25]. Patients can present for a variety of reasons which can include localized genitourinary causes such as bladder outlet obstruction, urinary tract infections, or urinary

incontinence. Interestingly, there is a higher prevalence of voiding symptoms in men over 50 years old [26]. Other causes of LUTS could be due to cognitive deficits such as memory loss, functional retention, or incontinence due to limited mobility or debilitation, or medication side effects, including opioids, or tricyclic antidepressants [27•].

Depending on the location of the CNS lesion, there could be unique features of lower urinary tract dysfunction [28•]. Intracranial lesions may impact areas associated with urinary tract regulation including the prefrontal cortex, insula, and pons and are thought to contribute to detrusor overactivity (DO) [28•]. Suprasacral spinal cord lesions occur predominantly in the lateral corticospinal and reticulospinal tracts. Suprasacral defects may lead to DO or detrusor-sphincter-dyssynergia (DSD), depending on the tract affected [29]. Sacral spinal cord lesions can affect either the efferent or afferent pathways and may lead to detrusor hypo-contractility or rarely, complete bladder areflexia [30]. Common LUTS in MS include frequency, urgency, and nocturia; incontinence and retention are more rare [28•].

The incidence of LUT symptoms is reported in 80% of MS patient [31, 32]. Due to the wide variety of symptoms, a convenient categorization is to determine if the LUTS involve either the storage phase or the emptying phase, or both. Storage phase signs include overactive bladder symptoms such as urgency (38–99% of patients), frequency (26–82%), urgency, stress, and mixed urinary incontinence (27–56%) [26, 33–35]. Voiding phase symptoms are less frequent (prevalence 6–49%) and can present as DSD, detrusor hypo-contractility, or bladder areflexia [33, 36, 37]. Patients can also have both storage and voiding problems, and these have been determined to coexist in 50% of patients [38, 39].

Urodynamic investigations provide urologists with a more precise evaluation of both storage and voiding phases of bladder function. DO and underactivity can be readily diagnosed by UDS as well as evaluation of DSD and bladder compliance. DO is the most common UDS finding in MS, however additional UDS findings often coexist. Interestingly, patients may be asymptomatic while demonstrating abnormal UDS findings [26]. Importantly, patients' LUTS and UDS findings can change over time along with patient's MS progression of neurologic disease. Repeat UDS should be considered in established patients whose symptoms change, for example in those patients who may experience worse urinary incontinence or more frequent urinary tract infections. For patients with abnormal storage such as decreased compliance, consideration should be given to repeat UDS evaluation even in the absence of worsening symptoms. Additionally, patients with changing neurologic complaints related to multiple sclerosis, studies have shown that there is a significant relationship between UDS findings, urologic symptoms, and disease severity [12]. For example, a positive correlation has been shown between the EDSS and UDS abnormalities such as detrusor overactivity, detrusor acontractility, altered compliance, and detrusor external sphincter dyssynergia [12].

Assessment of Patients with Multiple Sclerosis and Lower Urinary Tract Symptoms and the Value of Urodynamic Evaluation

The evaluation of patients with multiple sclerosis reporting LUT symptoms should be uniquely tailored for every patient, taking into consideration symptoms, disease course, comorbidities, and medications. In addition to a complete history and physical examination, the International Continence Society recommends the use of a bladder diary in all patients with LUTS [40••]. Further investigations can include a uroflow, post-void residual volume (PVR) measurement, and urinalysis and culture if indicated. There is debate as to the necessity of obtaining a renal ultrasound to assess upper tract anatomy or doing an initial urodynamic evaluation.

Unlike neurogenic bladder in spinal cord injury patients, the lower urinary tract dysfunction in MS patients rarely lead to upper urinary tract deterioration [41]. Lawrenson et al. observed that age-standardized relative risk for renal failure was no different for MS patients compared with general population [42]. In comparison, traumatic and congenital spinal cord injury patients are 5 and 8 times more likely to develop severe renal failure, respectively [42]. Interestingly, unlike spinal cord injured patients, MS patients with DSD and neurogenic detrusor overactivity (NDO) typically manifest minimal renal deterioration [26, 43]. Currently there is no consensus on imaging as a screening tool to assess for upper urinary tract deterioration; however, most recommend renal ultrasound for patients with prior diagnosis and known risk such as hydronephrosis, cystolithiasis, and bladder diverticulum [44, 45].

Urodynamic evaluation includes filling cystometry to monitor the storage phase and pressure flow study to evaluate the emptying phase of bladder function. This dynamic evaluation assesses pressure–volume relationships during non-physiological bladder filling and emptying. Fluoroscopic video cystometry can be added to simultaneously monitor the bladder and upper tracts while the bladder is filled with contrast agent. It can provide information on the presence of vesico-ureteric reflux or structural abnormalities like bladder diverticula or bladder neck incompetence [46]. Due to the invasive nature of these tests and the possibility that lower urinary tract dysfunction in MS patients rarely lead to upper urinary tract deterioration, the need for UDS in the routine assessment of patients with MS is a topic of international discussion [41].

Indeed, there are discordant opinions on the necessity of performing invasive UDS investigation in all patients with MS during their initial assessment [46, 47••, 48••]. The United Kingdom Guidelines and Turkish consensus statements on the management of urinary incontinence due to neurologic diseases, both recommend not to offer UDS routinely to low-risk neurologic patients and to monitor with urinalysis and PVR, without the use of invasive UDS [47••, 49••]. The French guidelines recommend UDS in the assessment of patients with early MS [50••]. UDS are highly recommended by the EAU for neurogenic lower urinary tract assessment; however, these are not specific to MS patients [51].

The 4th International Consultation on Incontinence generally recommends UDS evaluation in routine assessment of neurologic patients with risk factors predisposing them to upper urinary tract damage, in those whose symptoms are refractory to first-line treatment, or if surgery is being considered [27•, 40••]. The AUA/SUFU guidelines for UDS studies in adults state that clinicians should perform PVR assessment, either as part of complete UDS study or separately, during the initial urological evaluation of patients with relevant neurological conditions and as part of ongoing follow-up when appropriate [52]. Cystometrogram (CMG) is recommended at the time of initial consultation of patients for neurogenic bladder conditions thought to be at risk for developing renal complications. However, the utility of CMG in patient's with MS is less clear, specifically regarding prevention of renal complications but can remain an option for the evaluation of detrusor dysfunction in these patients [52]. Literature supports that significant proportion of patients with MS with and without new urinary symptoms can develop changes in their underlying UDS patterns and detrusor compliance as their disease progresses [53].

Clearly UDS evaluation can be useful in the guidance of ultimate application of therapeutic options to treat LUT symptoms in patients with MS. Most guidelines agree that urodynamic evaluation should be reserved for cases where the chosen therapy could be changed based on UDS results or for at-risk patients. UDS evaluation should also be considered prior to any intravesical or surgical intervention in this patient population.

Although different guidelines exist for the management of patients with neurogenic bladder, an optimal surveillance schedule has not been clearly provided. Some argue that the definition of neurogenic bladder does not give the clinician much information about the bladder disorder or its natural history, i.e. patients with MS have a different clinical course than a patient with spinal cord injury, both of which can be given the vague diagnosis of "neurogenic bladder." There are a few classification systems in the literature that try to stratify neurogenic bladder into more precise systems. For example, the Madersbacher classification system is based on the tone of the bladder and urinary sphincter [54]. The SALE (stratify by anatomic location and etiology) classification system was proposed to better define the bladder defect and prognosis; for example, patients would be classified as demyelinization disorders neurogenic bladder-multiple sclerosis [55].

Urodynamic Antibiotic Prophylaxis in Patients with Multiple Sclerosis on Immunomodulatory Medications

Invasive studies such as UDS evaluation does include known risks of the development of urinary tract infection or bacteriuria. However, this risk must be balanced with the known risk of the use of prophylactic antibiotics and the development of resistant microbes as well as the inherent risks of antibiotic use. The AUA best practice policy statement on Urologic Surgery Antimicrobial Prophylaxis recommends against the use of prophylactic antibiotics prior to UDS for patients without known UTI risk factors (e.g. "index" patients) [56]. Furthermore, the Infectious Disease Society of America has published guidelines that do not recommend treating asymptomatic bacteriuria unless a patient is undergoing an invasive surgical procedure [57]. In 2017, SUFU published a best practice policy panel of recommendations on antibiotic prophylaxis in the "non-index" patient, or those patients who have known risk factors for UTI. They recommend antibiotic prophylaxis for UDS studies in patients with immunosuppression from immunosuppressants, chronic steroids, or innate immunosuppression [58•]. Therefore, patients with MS on immunomodulation medications undergoing UDS should be given prophylactic antibiotics [58•].

Conclusion

MS is a progressive neurological disease that can contribute to significant LUTS. Treatment and management of MS can be complex, and a multidisciplinary approach is crucial. Patients with MS can present with LUTS at different stages of their MS disease with dysfunction of either or both the storage and voiding phases of the micturition cycle. Unlike neurogenic bladder in spinal cord patients, however, the lower urinary tract dysfunction in MS patients rarely leads to upper urinary tract deterioration. For this reason, there are differing opinions on performing an invasive UDS evaluation in all patients at initial consultation. However, UDS can be useful in the guidance of the application of treatment options and should also be reserved for at-risk patients or prior to surgical intervention. Patients on MS immunomodulatory medications undergoing UDS should also be considered for prophylactic antibiotics at the time of the procedure.

Compliance with Ethical Standards

Conflict of Interest The author declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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