Neurogenic bladder in multiple sclerosis

Athanasios Dellis³, Iraklis Mitsogiannis², Dimos D. Mitsikostas³

¹2nd Department of Surgery, Aretaieion Academic Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece
²2nd Department of Urology, Sismanoglion General Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece
³A Department of Neurology, Aeginition Academic Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

Abstract

Multiple sclerosis is the commonest progressive neurological disorder in young people, with lower urinary tract dysfunction suggesting a common and morbid component, affecting the vast majority of patients. Although urinary symptoms are very common, there are no prospective trials to date regarding management options for bladder dysfunction in multiple sclerosis patients. Additionally, it was only recently when well designed attempts regarding detailed evaluation and management came up, with validated questionnaires and new kinds of medication. In the present study we try to show up the urologic aspects of this progressive debilitating neurological disorder as well as we review current treatment strategies of neurogenic lower urinary tract dysfunction in multiple sclerosis patients.

Introduction

Multiple sclerosis (MS) is the commonest progressive neurological disorder in young people, whose pathological hallmark is the disruption of myelin sheaths. A relapse–remitting course is most commonly reported, in 85% of patients with MS. Chronic autoimmune T cell-mediated inflammation of the central nervous system (CNS), results in the appearance of new and active focal inflammatory demyelinating lesions in the white matter or diffuse injury of normal-appearing white matter, cortical demyelination and axonal loss¹.

Lower urinary tract dysfunction (LUTD) is a common and morbid component of MS. The prevalence and severity of urinary system involvement closely correlates with the severity of the underlying disease², duration of disease and extent of spinal cord involvement³. Between 32% and 97% of patients with MS report urinary tract symptoms, with the wide fluctuation in prevalence reflect-
The healthy adult bladder in an asymptomatic person is the regular and efficient bladder emptying. The primary principle in order to achieve the aforementioned minimization of urinary tract complications in general is the prevention of urolithiasis, achievement of social continence and minimization of urinary tract infections (UTIs), preventing the use of catheters or invasive surgical reconstruction of the urinary tract. Apart from urinary tract per se, effective bowel management is crucial to effective bladder management. Regular, efficient emptying of the rectum minimizes the risk of UTIs, facilitates bladder emptying, and improves quality of life (QoL). Finally, there are sex differences in neurogenic bladder management. Although the urinary tract physiology is the same in both sexes, there are considerable anatomic differences that cause severe practical considerations when determining an optimal bladder management plan: Women who perform clean intermittent self-catheterization (CISC) must be able to catheterize themselves without being able to visualize their urethras, whereas men, especially older ones, may have an enlarged prostate incommmoding CISC.

**Pathophysiology**

The NLUTD observed in patients with MS is a direct result of lesions in the spinal cord or brain. Practically, lesions above the S2-S4 cord level, or upper motor neuron lesions, manifest as an overactive bladder, while lesions of the peripheral nerves to the bladder (such as sacral cord demyelination among others), or lower motor neuron lesions, manifest as an acontractile or hypotonic bladder. In urodynamic studies (UDS) of MS patients, cord lesions above the S2-S4 level are more common and present as neurogenic detrusor overactivity (NDO). NDO is irrespective of bladder urine volume leading to increased bladder pressure, urgency, frequency, and urgency urinary incontinence (UI). In cases of suprapontine lesions, urgency UI is the result of the micturition reflex disinhibition, whereas in combined both upper motor neuron and peripheral lesions, detrusor-sphincter dysynergia (DSD) is present. The latter disco-ordination between detrusor and sphincter can lead to urinary retention, elevated post-v oid residual (PVR) volumes, and vesicoureteral reflux (VUR) which is the substantial cause of renal failure in MS patients. Storage symptoms and voiding dysfunction can be present simultaneously or independently changing NLUTD clinical manifestations.

**Therapeutic goals**

There are several principles in bladder management that guide our decision making: Renal preservation, minimization of urinary tract infections (UTIs), preventing of urolithiasis, achievement of social continence and minimization of urinary tract complications in general. The primary principle in order to achieve the aforementioned, is the regular and efficient bladder emptying. The healthy adult bladder in an asymptomatic person empties completely approximately 4 to 8 times every 24 hours (h), depending on fluid intake. Ineffective bladder emptying results in LUTS, UTIs and UI, while it further negatively affects renal function. In such patients, the use of catheters can overcome bladder emptying failure. However, bladder management should proceed from the least invasive to most invasive techniques, and from the least complicated to most complicated. Methodology to manage the neurogenic bladder ranges from simple behavioral modifications to extensive surgical reconstruction of the urinary tract. Apart from urinary tract per se, effective bowel management is crucial to effective bladder management. Regular, efficient emptying of the rectum minimizes the risk of UTIs, facilitates bladder emptying, and improves quality of life (QoL). Finally, there are sex differences in neurogenic bladder management. Although the urinary tract physiology is the same in both sexes, there are considerable anatomic differences that cause severe practical considerations when determining an optimal bladder management plan: Women who perform clean intermittent self-catheterization (CISC) must be able to catheterize themselves without being able to visualize their urethras, whereas men, especially older ones, may have an enlarged prostate incommmoding CISC.

**Evaluation of Symptoms**

There are several screening tools and instruments used to evaluate patients with bladder symptoms, however most of them are not MS specific. Recently, two new questionnaires have been developed and validated in order to efficiently and appropriately screen this population. The Actionable Bladder Symptom and Screening Tool (ABSST) is a 17-item tool consisted of three domains-Bladder Symptoms, Coping Strategies, and Impact of Bladder Symptoms, which is a validated screening tool in order to identify MS patients with symptomatic NDO. There is an 8-item short form of ABSST, which maintained the integrity of the long version and has an additional direct question asking if the patient would like help for their bladder problems. In this short version, a score of 3 or greater (from 0-8) indicates the need for further evaluation. Along with its ease of use in the clinical setting, the ABSST leads to a referral when appropriate. The Neurogenic Bladder Symptom Score (NBSS), is a 22-item tool consisted of three major domains-Incontinence, Storage and Voiding Symptoms,
and Urinary Complications along with two additional questions regarding bladder management and QoL, which is the first patient reported outcome measure designed to objectively assess signs and symptoms related to neurogenic bladder dysfunction of several neurological disorders, such as spinal cord injury, spina bifida, and MS. Over time, this can be used as a tool to objectively measure changes in bladder symptoms.

In patients with NLUTD, apart from history, physical and neurological exam, voiding diaries can be helpful as well as history of bowel or sexual dysfunction. For patients with new bladder symptoms, urine testing to exclude hematuria or UTI and measurement of a PVR volume and renal ultrasound are both advisable, while cystoscopy is reserved for selected patients.

Treatment
There are several treatment options for the MS patient with NLUTD, ranging from simple behavioral modifications to the complex urinary tract reconstruction.

Behavioral modifications
Behavioral modifications suggest the first-line options in managing NLUTD. Patients are encouraged to carry out a diary of their fluid intake and voiding output. Using an hourly chart, patients document volume of fluid consumed and volume voided, evacuated in cases of CISC, or their combination. Preferably three consecutive or nonconsecutive days of a diary is generally representative of the patient's schedule.

Fluid restriction
It is suggested in order to minimize urine production. Furthermore, it includes the restriction of certain types of beverages (e.g., caffeinated or carbohydrate-containing beverages, alcohol) to limit irritative voiding symptoms.

Biofeedback and physical therapy
They should be used as an attempt to strengthen pelvic floor muscles that have been weakened from previous surgery or traumatic delivery. Kegel exercises are the most recognized of the physical therapy maneuvers. The efficacy of biofeedback in treating bladder symptoms due to MS is mixed, while yoga has been anecdotally reported as well. Aforementioned therapeutic options seem to be efficacious in persons with only mild NLUTD.

Valsalva and Crede maneuver
Although with these maneuvers urinary bladder is forcefully evacuated by the concomitant intra-abdominal pressure increase, they should be both avoided since they may cause pelvic organ prolapse or inguinal hernias.

External urine collection devices
They include condom-like devices, diapers or pads. External urine collection devices allow patients to void spontaneously, even if they are unable to toilet themselves. However, since skin irritation is usual especially in patients using diapers or pads, meticulous care is of high importance.

Management of storage symptoms
Antimuscarinic drugs
Antimuscarinic or anticholinergic drugs suggested the cornerstone of NDO treatment for several years. Antimuscarinic drugs competitively antagonize muscarinic acetylcholine receptors, resulting in detrusor relaxation, lower intravesical pressures, and reduced storage symptoms. Although some of the drugs have a higher selectivity for the muscarinic receptor subgroups that are more prevalently expressed in the urinary bladder (M2: Functionally the most relevant subtype in the bladder and M3: Widely distributed throughout the detrusor, urothelium, and suburothelium), none of the available drugs is devoid of adverse events, which include dry mouth, constipation, cognitive impairment, dry eyes, nausea, and fatigue. There are several non-selective antimuscarinic agents such as oxybutinin, fesoterodine and tolterodine, as well as selective ones such as darifenacin and solifenacin.

Measurement of the PVR volume should be done preferably before antimuscarinic treatment is started.

Desmopressin
Desmopressin is a synthetic vasopressin analogue, first introduced for the treatment of polyuria in patients with diabetes insipidus, and it was also shown to be effective in the management of primary nocturnal enuresis and of nocturia in MS patients. Desmopressin has showed its efficacy in managing daytime frequency and urine
volume in MS patients, providing symptom relief for up to 6 h. However, desmopressin should be prescribed with caution in patients older than 65 years or with dependent leg oedema, and should not be used more than once in 24 h because of the risk of hyponatraemia or congestive heart failure.

**β3-Adrenoceptor agonists**

Mirabegron is the first available drug in this class. It is a potent agonist that targets the β3 adrenergic receptor found within urothelium and detrusor smooth muscle. Agonists of the receptor cause relaxation of the detrusor muscle during storage. It has been shown to inhibit detrusor overactivity and increase bladder capacity without any increase in residual volume or decrease in micturition pressure. There are currently no published randomized controlled trials assessing the efficacy of mirabegron in MS patients, however it may prove to be an advantageous alternative to anticholinergics/antimuscarinics in this population because of a more favorable side effect profile including less cognitive effects, impairment of bladder emptying, and gastrointestinal motility.

**Botulinum toxin**

Antimuscarinics and β3-adrenoceptor agonists are the pharmacological treatment of choice and suggest the first line treatment option for NDO. However, there are cases with limited treatment effectiveness and there are patients who have to discontinue their treatment because of side-effects. Onabotulinum toxin A (BoNT-A), which is commercially available as BOTOX® (Allergan, Irvine, California, USA) has been licensed since 2012 in several countries for use in patients with treatment-refractory NDO owing to MS or spinal cord injury. BoNT-A is the only type of botulinum toxin to be evaluated for the management of any LUTD in large, multicentre, randomized controlled trials, that have since revolutionised the management of neurogenic overactive bladder. There are seven serotypes of botulinum toxin, but it is type A that is generally used for urological indications. Intradetrusor injections of BoNT-A are highly effective in reducing the incidence of UI, in improving patients’ urodynamic parameters and, therefore, their QoL. Twenty to thirty injections are made into the bladder wall, requiring a cystoscopy (rigid or flexible), an intervention that can be done under local anaesthesia in most neurological patients. The effects of BoNT-A injections usually last for 6-9 months, therefore, repeated injections are often necessary. All patients with MS should have been taught, or agreed to learn to do CISC before being treated with BoNT-A injections as 88% of patients need to perform de novo CISC. However, the need for CISC did not affect quality of life outcomes.

**Neuromodulation**

Neuromodulation suggests a further therapy in patients with storage symptoms or even refractory urgency UI, although there are very limited data regarding its efficacy in patients with MS.

**Tibial nerve stimulation (TNS)**

It is a minimally invasive technique where the posterior tibial nerve is electrically stimulated either using a needle to deliver electrical stimulation (the percutaneous approach) or using an electrode patch (the transcutaneous approach). The first approach requires the insertion of a needle close to the tibial nerve by a healthcare professional, in comparison to the transcutaneous method, which has the advantage that it can be easily used at home, either by the patient or by their carer. By this stimulation, somatic afferent branches that pass through the L4–S3 spinal roots inhibit the central reflex pathways which may cause uninhibited detrusor contractions. Percutaneous TNS has been shown to be effective in managing storage symptoms and improving urodynamic parameters in patients with MS. Initial percutaneous stimulation is usually delivered during 30-min, weekly sessions, over a period of 10-12 weeks, and generally followed in responders by a period of maintenance therapy, of which the optimal characteristics are poorly defined. This therapy is safe, the patients’ reported subjective and objective cure rates are between 60-80%, patients’ treatment satisfaction is generally high (70%) and their overall quality of life is usually improved substantially. PTNS may be a promising therapy for MS patients since it has no metallic implant limiting Magnetic Resonance Imaging (MRI) use, and transcutaneous patches have been recently developed which may lead to home based therapies.

**Sacral nerve stimulation (SNS)**

It is a minimally invasive treatment that can be used to treat patients with treatment-refractory LUTS ow-
ing to a range of different underlying neurological diseases. SNS is indicated for refractory OAB, non-obstructive urinary retention and fecal incontinence. Similar to TNS, there are limited data regarding efficacy and treatment outcomes of SNS in MS patients. SNS might exert its effect through activation of afferent pathways that modulate the activity of other neural pathways within the spinal cord and higher centres. In a meta-analysis based in studies with limited sample sizes, it has been shown that SNS might be effective (in terms of reduced incontinence and fewer voids per day) and safe in patients with neurogenic LUTD. It has been proposed that SNS should be used in patients with MS of a relapse-remitting course, who have not had a relapse for at least 2 years. Unfortunately, there are no data from randomized controlled trials available in this area, and the types of patients who are most suitable for SNS are also largely unknown.

Surgery

In cases of MS patients where aforementioned therapies have failed or in certain situations such as sepsis, severe UI or inability for CISC, surgical treatments are efficient options.

Augmentation cystoplasty is a recommended treatment option for selected patients who are capable for CISC in the long term, but their LUTS are refractory to conservative treatment. It is performed using a detubularized ileal segment in order to restore a low-pressure and compliant reservoir to augment the urinary bladder along with urinary continence maintenance. There are a few studies with MS patients reporting improvement in maximum mean detrusor capacity and maximum detrusor pressure, as well as in continence and patient satisfaction rates. Therefore, augmentation cystoplasty is an effective surgical approach for MS patients who also have treatment-refractory neurogenic bladder, provided that patients are able to self-catheterize, and this approach can improve patients’ LUT-specific quality of life. In cases where the patient is unable to perform CISC through the urethra, augmentation cystoplasty can also be performed concomitantly with a cutaneous continent urinary diversion, while for cosmetic reasons, the umbilicus is often used as the stoma site in these patients. However, there are cases such as quadriplegia, limited dexterity and/or devastating cognitive impairment that cause serious inability for CISC. In order to restore a low-pressure reservoir without the use of an indwelling urethral, or suprapubic catheter and to improve QoL, a non-continent cutaneous diversion using an ileal conduit and a urine collecting device can also be performed.

Management of voiding symptoms

CISC

CISC is the method of choice for the treatment of incomplete bladder emptying or urinary retention in patients with neurogenic bladder which was incidentally initially described in a MS patient. CISC has to be initiated in patients whose incomplete bladder emptying is reflected by the presence of a high residual volume, although the exact volume has not been defined yet and it depends upon the characteristics of each patient. Actually, no evidence-based cut off post-void residual value exists for the recommendation to start CISC in patients with MS-related LUTD. However, using data from NARCOMS survey, CISC are suggested in patients with residual urine volume >100 ml confirmed with several ultrasonographic evaluations, in patients with chronic retention and a very weak urine stream as well as in patients with residual urine and upper urinary tract dilatations. The average frequency of catheterization per day is 4-6 times. CISC are rarely necessary in the early stages of MS but becomes increasingly likely to be needed as patient’s mobility deteriorates. Proper use of CISC decreases the risk of UTIs and upper urinary tract damage, promotes urinary continence and improves patients’ QoL.

Indwelling catheterization

For patients with high residual volume unwilling or unable to perform CISC, a long-term indwelling transurethral or suprapubic catheter is often used to ensure that the bladder empties and to provide urinary continence, although it is accompanied by several complications, such as recurrent UTIs, catheter blockages, catheter bypassing, urethral destruction or bladder stones.

Epilogue

LUTD are common in MS patients and have a negative impact on patients’ QoL. First line treatment of storage symptoms are, apart from lifestyle modifications, antimuscarinics and β3 agonists, while further treatments
range from injections of botulinum toxin into the bladder wall and neuromodulation to more complex surgical procedures. Voiding symptoms can be effectively managed mainly with CISC. However, given the fact that MS is a progressive neurological disorder with potential changes in its clinical manifestations, long-term monitoring of patients is essential.

Conflicts of interest
The author declared no conflict of interest.


