Management of Lower Urinary Tract Dysfunction in Patients with Neurological Disorders

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The proper performance of the lower urinary tract is dependent on an intact neural innervation of the individual structures involved. Therefore, any congenital neurological anomalies, diseases, or lesions of the central, peripheral, or autonomic nervous systems can result in lower urinary tract symptoms. Lower urinary tract dysfunction (LUTD) secondary to neurological disorders can significantly reduce quality of life (QoL) and may also give rise to serious complications and psychological and social sequelae. The goals of management of LUTD in patients with neurological disorders are to prevent serious complications and to improve the patient’s QoL. Understanding the physiology and pathophysiology of micturition is critical to selecting appropriate treatment options. This article provides an overview of the clinical characteristics, diagnosis, and management of LUTD in patients with certain central and peripheral neuropathies and common lesions.

Key Words: Clean intermittent catheterization; Lower urinary tract symptoms; Nervous system diseases; Neurogenic urinary bladder; Urodynamics

INTRODUCTION

The lower urinary tract consists of the bladder, bladder outlet, and urethra. It serves two major functions: 1) storage of urine at low pressure with normal sensation and perfect continence, and 2) periodic and complete voluntary elimination of urine [1,2]. The proper performance of these functions is dependent on an intact neural innervation of the involved individual structures of the lower urinary tract, including the peripheral nerves of the autonomic and somatic nervous system and various neural pathways and transition points in the spinal cord, which is under the control of a complex neural network at or above the brainstem. Therefore, any neurological diseases or lesions of the brain, spinal cord, or peripheral nerves can lead to lower urinary tract symptoms (LUTS), including storage, voiding, and postmicturition symptoms [3].

Lower urinary tract dysfunction (LUTD) secondary to neurological disorders can significantly reduce quality of life (QoL) and may also give rise to serious complications such as urinary tract infection (UTI), upper and lower urinary tract calculi, sepsis, vesicoureteral reflux (VUR), hydronephrosis, and renal failure [4,5]. The primary aims for the management of LUTD in patients with neurological disorders should consist of preventing serious complications and improving the patient’s QoL. If these goals are not met, complications can occur and cause significant morbidity and mortality. This article provides an overview of the clinical characteristics, diagnosis, and management of LUTD in patients with certain central and peripheral neuropathies that are commonly seen in our daily urological practice.

CLINICAL CHARACTERISTICS OF LUTD WITH NEUROLOGICAL DISORDERS

In general, LUTD secondary to disease or lesions at or above the brainstem and peripheral neuropathies primar-
ily negatively affect patients’ QoL. In contrast, a subset of LUTDs occurring after spinal cord injury (SCI) or disease results in a detrimental impact on patients’ QoL and can also lead to life-threatening complications.

1. Cerebrovascular accident

Stroke is frequently associated with LUTD, and the most common expression of urinary symptoms is different in the distinct stages (acute and chronic) and types (ischemic and hemorrhagic) of strokes. After the initial acute stroke (within 72 hours from the onset), urinary retention and overflow incontinence occur in 47% of patients, mainly due to emptying failure (75%), especially in hemorrhagic infarcts as compared with ischemic infarcts (85% vs. 10%) [6]. The prevalence of urinary retention has been reported to be 29% in stroke patients within 4 weeks [7]. Over a few weeks or months, a variable degree of recovery can be achieved and the symptoms are mainly characterized by frequency, urgency, and urge incontinence. These symptoms are generally due to detrusor overactivity (DO) [8]. Bladder sensation in this period of stroke is variable but is generally intact. Therefore, when the urgency and frequency due to DO occur, most patients try to inhibit the involuntary bladder contraction by voluntary contraction of the striated sphincter. If this cannot be accomplished, urgency with incontinence may occur. Urge incontinence has been reported in 29% of stroke patients at the 3-month follow-up [9] and in 19% at the 6-month follow-up [10]. In contrast to the acute stage, DO occurs in 68% of patients within 4 to 48 months of follow-up [9].

2. Neurodegenerative disease

Parkinson’s disease (PD) and multiple system atrophy (MSA) are the major neurodegenerative diseases that commonly induce LUTD. PD, which primarily affects adults over the age of 55 years by an unknown cause, is characterized by a loss of dopaminergic neurons in the substantia nigra pars compacta. The clinical symptoms of PD consist of tremor, skeletal rigidity, and bradykinesia, and the complex is often referred to as parkinsonism [11,12]. MSA is a progressive neurodegenerative disease that affects various areas of the central nervous system including the substantia nigra, striatum, cerebellum, and spinal cord [13]. The etiology of MSA is unknown; it usually begins in the sixth decade of life and is associated with a mean survival of 6 to 9 years. Clinically, MSA is characterized by any combination of dysautonomia (including urinary and erectile problems), parkinsonism, cerebellar ataxia, and pyramidal signs particularly distinguished by MSA-P (parkinsonian features predominate) and MSA-C (cerebellar ataxia features predominate) [13]. Similar to PD, tremor, rigidity, and bradykinesia occur in MSA-P patients as common clinical symptoms, and it is particularly difficult to make a differential diagnosis between the early stage of MSA-P and idiopathic PD. However, careful distinction between PD and the early stage of MSA-P is critical for the management of LUTD in patients with these disorders because the treatment principles are quite different between the individual diseases. Some characteristics may be useful for differential diagnosis. Earlier erectile dysfunction in men, urinary incontinence, and micturition disorders occur concurrently or before the onset of symptoms of parkinsonism, which suggests this is more rapidly progressive in the running towards MSA [14,15]. Assessment of bladder function is very important and provides critical evidence for distinguishing MSA from other neurodegenerative diseases, including PD [16,17].

In patients with PD, DO-induced storage disorders (urinary urgency/incontinence) are the most common urinary symptoms, whereas voiding symptoms (incomplete emptying/urinary retention) induced by detrusor underactivity or detrusor sphincter dyssnergia (DSD) are less common. The rate of DO in patients with PD is 58% in an average 23.6 months of disease duration [18]; however, detrusor underactivity was observed in 16% and 26.7% of patients with PD of an average 10.9 years and 23.6 months of disease duration, respectively [18,19]. The postvoid residual urine volume (PVR) was generally lower than 100 ml in a disease duration of 23.6 months [18].

In contrast, patients with MSA generally have both storage symptoms and voiding symptoms simultaneously. The initial urinary symptoms of MSA are frequency, urgency, and urgency incontinence due to DO, which occurs significantly earlier in MSA patients than in patients with PD (<2 years vs. >5 years) [17,20]. As the disease progresses, difficulty in initiating and maintaining voiding due to detrusor underactivity may occur. In MSA, detrusor underactivity was observed in 58% and 76% of patients with a relatively short (<4 years) and later disease duration (>4 years), respectively [17]. The combination of DO and incomplete bladder emptying contributes to the urinary incontinence and large PVR. In addition, the pathology of MSA induces denervation of both smooth sphincter (bladder neck) and striated urethral sphincter, resulting in an open bladder neck and dysfunction of the striated urethral sphincter [21,22]. These conditions cause incontinence during the filling phase and DSD and further incomplete emptying during the voiding phase. A videourodynamic study has shown that an open bladder neck at the start and during bladder filling, even when not accompanied by DO, was noted in 0% and 31% of patients with PD but occurred in 53% and 87% of patients with MSA, respectively. This study also found that DSD in the voiding phase occurred less commonly in PD (0%) than in MSA (47%) [20]. These findings suggest that denervation occurs much earlier and more frequently in MSA than in PD [21,22]. Moreover, the subsequent open bladder neck at the start and during bladder filling and neurogenic changes in motor unit potentials of the sphincter muscle are features suggestive of MSA when comparing these two disorders [20,22].

3. Diseases or lesions primarily affecting the spinal cord

SCI-induced neurogenic bladder is the most severe form of LUTD; accordingly, mortality and morbidity are higher
than in patients with other neurologic abnormalities. Approximately 12,000 patients sustain traumatic SCI every year in the United States, although there are no accurate data on overall incidence [23,24]. Since 2005, the main causes of SCI were motor vehicle accidents (40.4%), falls (27.97%), and violence (15.0%) [24]. Patients with a spinal injury, depending on the level and severity of the lesion, will have different kinds of voiding dysfunction and are at increased risk of developing renal failure, urolithiasis, bladder cancer, UTI, and VUR [23,25].

Generally, lower urinary tract function after SCI is divided into three phases: the spinal shock, recovery, and stable phases, although the actual mechanisms of spinal shock and its recovery remain poorly understood [26]. Immediately after a significant SCI, swelling and bleeding shock and its recovery remain poorly understood [26].

Immediately after a significant SCI, swelling and bleeding shock and its recovery remain poorly understood [26]. Spinal shock lasts from 6 to 12 weeks in complete suprasacral SCI but may extend to 1 or 2 years. In incomplete suprasacral lesions, the period of spinal shock is shorter, sometimes lasting for a few days [24]. During the period of spinal shock the bladder is accontractile. The smooth sphincter appears to be functional and sphincter tone exists and thus the bladder neck is generally competent and closed. Therefore, urinary retention can commonly occur, and urinary incontinence does not generally occur unless overdistention with overflow exists [24]. Clean intermittent catheterization (CIC) or transurethral or suprapubic indwelling catheterization is the optimal management in this period [27,28].

When spinal shock resolves, recovery of detrusor contractility is possible and is often heralded by the presence of incontinence [24]. In this period, the pattern of LUTD varies with the level and severity of the injury.

With SCI above the S1 level, cortical inhibition of the voiding reflex and detrusor-sphincter coordination are interrupted but the integrity of the parasympathetic (S2 through S4) and somatic (S1 through S4) nerves is not disturbed. Injury at this region results in involuntary detrusor contraction and DSD. Therefore, it usually causes incontinence owing to the involuntary detrusor contraction, and if DSD coexists, it will result in higher detrusor pressure and PVR. Urodynamic patterns of lower thoracic and upper lumbar SCI, especially at the level of T10 to L2, include a wide variety of presentations, including accontractile detrusor, overactivity, and DSD. Because the pelvic nerves are involved in detrusor muscle contractility and the pudendal nerves are responsible for contraction of the striated sphincter, injury at the S2-S4 level is significantly correlated with storage and emptying failure. Injury at the S2-S4 level can cause sphincter denervation owing to malfunction of pudendal nerves resulting in reduced tone of the urethral sphincter in the storage phase and incomplete relaxation of the urethral sphincter during the voiding phase [24].

The most common complications of SCI are autonomic dysreflexia symptoms, UTI, and VUR. Autonomic dysreflexia especially occurs in patients with SCI at or above the T5/6 levels and is more common in tetraplegia with complete lesions (91%) than incomplete tetraplegia (27%) [29,30]. It is often triggered by painful somatic or distension of pelvic viscera (bladder and bowel) and is characterized by acute elevations of arterial blood pressure (increase in blood pressure higher than 20 to 30 mmHg), bradycardia, or tachycardia [29,30]. Because autonomic dysreflexia can cause serious consequences including intracranial hemorrhage, retinal detachment, seizures, and death, any bladder procedures including urodynamic evaluations or cystoscopy should be done under careful monitoring or general anesthesia [29].

Spina bifida is a developmental birth defect due to the incomplete closing of the embryonic neural tube. Some vertebrae overlying the spinal cord are not fully formed and remain open. A portion of the spinal cord protrudes through the opening in the bones. Spina bifida malformations fall into three categories: spina bifida occulta, meningocoele, and myelomeningocele [31]. The incidence of spina bifida ranges from 0.3 to 4.5 per 1000 births, and the lumbar and sacral areas are the most common locations of the malformations [31,32]. Although spina bifida can be closed surgically, more than 90% of patients with spina bifida have neurogenic bladder dysfunction including DO, elevated detrusor leak point pressure (DLPP), VUR, sphincteric incompetence, and DSD [31,33]. Renal damage by high bladder pressure and UTI is the leading cause of death among infants and children, and urinary incontinence is the main problem adversely affecting QoL in adulthood. Therefore, the goals of management should be to preserve renal function by maintaining lower bladder storage pressures and to promote urinary continence by increasing bladder capacity [33].

4. Peripheral neuropathy

Diabetes mellitus is the most common metabolic disease and affects lower urinary tract function. Although the exact incidence of diabetes-induced voiding dysfunction is unclear, more than 80% of patients with diabetes suffer from diabetic bladder dysfunction (DBD), which has been reported to be a more common complication of diabetes than neuropathy (60%) and nephropathy (50%), the widely recognized diabetic complications [34].

The pathophysiology of DBD is multifactorial and includes neuronal, smooth muscle, and urothelial dysfunction [35]. A temporal hypothesis on the time-dependent pathophysiology of DBD provides a potential unifying theory on the complex interaction among seemingly confusing bladder dysfunctions. In the early phase, compensatory bladder hypertrophy can occur by polyuria, the main mechanistic factor, which causes myogenic and neurogenic alterations; in the later phase, excessive oxidative stress results in decoupling of bladder tissue and function [36]. Previously, we found oxidative stress-induced increase in bladder apoptosis as a pathophysiological mecha-
nism significantly related to DBD [37,38].

Clinically, classic DBD is characterized by decreased sensation, increased capacity, impaired detrusor contractility, and increased residual urine. Smooth or striated sphincter dyssynergia is rarely seen in diabetes-induced LUTS. However, the pattern of DBD is not a predominant form of LUTD. Kaplan et al. [39] reported urodynamic findings showing that in 183 diabetic patients with LUTS, 55% of patients had involuntary bladder contractions, 23% had acontractile detrusor, 11% had indeterminate findings, 10% had detrusor areflexia, and 1% were normal. Bladder outlet obstruction occurred in 57% of men. In the patients with sacral cord signs, 50% had impaired detrusor contractility and 24% had detrusor areflexia. These data suggest that classic diabetic cystopathy is not the most common urodynamic finding or voiding dysfunction. These patients present with variable pathophysiological findings. In addition, large proportions of men with diabetes and LUTS have electrophysiological evidence of neuropathy, and thus may present with varied urodynamic findings [40]. Furthermore, most diabetic patients with LUTS have reported a lower incidence of bladder outlet obstruction (26 to 36%), even though they have prostate enlargement (46%) [40,41]. In these patients, the etiology of their symptoms is only determined by urodynamic evaluation and not by noninvasive tests such as the International Prostate Symptom Score, free uroflowmetry, or PVR, which have low sensitivity and specificity for diagnosis of bladder outlet obstruction [41]. Therefore, the performance of systematic urodynamic evaluation has been suggested to be a prerequisite for making critical decisions and especially before surgical management in diabetic patients with LUTS [40,41].

EVALUATION AND DIAGNOSIS

1. History
A careful medical history is a prerequisite for the assessment and classification of neurogenic bladder dysfunction. The medical history should focus on the type, degree, onset, and duration of symptoms (frequency, urgency, incontinence, dysuria, etc), voiding pattern (normal, voluntary evacuation, intermittent catheterization, increased abdominal pressure, etc), and prior investigations and treatments. In addition to the previous general surgical history, including pelvic, retroperitoneal, or spinal surgical procedures and genitourinary tract disorders, concomitant medication as a major factor should be recorded carefully. Many drugs may affect bladder function significantly, even though they do not have side effects. Histories about the bowel (ileus, constipation, fecal incontinence, etc) and sexual function (erection and ejaculation for males, sexuality and orgasm in both sexes, etc) must be also obtained [42]. Possible injury sites in the central or peripheral nervous system are often quite clear. In addition, because the choice of treatment, especially the surgical management, often depends on the patients’ QoL, its assessment is particularly important [43,44].

2. Physical examination
Physical examination is essential in the evaluation of all patients with LUTS. General appearance, health status, gait, manual ability, mobility, flexibility, muscular strength, psychomotor function, and cognitive function can be helpful in diagnosis and management. A complete examination of the abdomen, back, and buttocks (dimples, skin tags, hair patches, asymmetrically curving gluteal cleft), particularly a focused examination of genitalia, rectum, and perineum, is essential. In addition to the evaluation of the prostate in men, a digital rectal examination essential to assess the anal reflex and anal sphincter tone and stool in the rectal vault [42]. Furthermore, examination of the neurologic system, including cough reflex, perineal sensitivity to pain and temperature, pinprick sensation, bulbocavernous reflex, cremasteric reflexes, and urethral hypermobility, must be performed, because such examination is critical for elevation of the sacral nerve reflex arc (S2 to S4).

3. Laboratory evaluation
All patients with neurogenic bladder are at risk of developing a UTI, regardless of how they manage their bladder, especially in patients with PVR >150 ml or long-term indwelling catheters [4]. Therefore, a meaningful assessment of urinalysis under the microscope, by urine culture and sensitivity, are required before any invasive investigation or procedures. However, leukocyturia or bacteriuria alone without clinical symptoms does not yet require treatment in patients with neurogenic bladder dysfunction, especially in patients with indwelling urethral catheters or practicing intermittent catheterization [45,46]. In addition, serum blood urea nitrogen/creatinine, creatinine clearance, and electrolyte status should also be estimated.

4. Uroflowmetry and postvoid residual measurement
Uroflowmetry and PVR serve as noninvasive screening tests for selecting patients who should undergo more sophisticated urodynamic studies and for evaluating treatment effect during follow-up [47]. Although reduced urine flow rates indicate impaired voiding function, uroflowmetry alone is insufficient for distinguishing impaired detrusor contractility and urinary outlet obstruction because it is dependent on the contractile force of the bladder and urethral resistance and is affected by voided volume (should be greater than 150 ml).

If the flow rate is less than 10 ml/sec, a component of urodynamic study may be necessary [47]. PVR in the bladder immediately after voiding can be measured with ultrasound or transurethral catheterization and serves as a predictor of the ability of the bladder to empty completely. If patients have a large PVR, the pressure of the bladder may be elevated and may result in UTI, functional obstruction at the vesico-ureteric junction or VUR, further upper urinary tract dilatation, and ultimately renal failure [4].
However, the optimal PVR threshold for identifying inadequate bladder emptying has not been clearly established. In general, a range of 50 to 100 ml is considered the lower threshold for defining abnormal PVR [47], and a PVR volume > 150 ml or > 300 ml is a significant risk factor for the development of UTI, and upper urinary tract dilation and renal insufficiency, respectively [47,48].

5. Frequency-volume charts and voiding diaries
Frequency-volume charts and voiding diaries are primary tools for evaluating LUTS and cannot be replaced by any other method in clinical practice. Frequency-volume charts are used to record the volumes voided as well as the time of each micturition, day and night, for at least 24 hours, whereas a voiding diary is used to record the times of micturitions and voided volumes, incontinence episodes, pad usage, and other information such as the degree of urgency and incontinence [49]. These measures can provide important information on a patient’s voiding problem and are deemed to be noninvasive, inexpensive, and accurate. In particular, these records are of utmost importance for educating the patient about performing intermittent catheterization in accordance with the appropriate voiding volume and interval. For accuracy and reliability, numerous versions of voiding diaries have recommended durations of 1 to 14 days, and 7 days seems to be the most commonly recommended. However, long periods of time, such as 7 days, can result in poor patient compliance and burden; therefore, optimal diary duration should cover fewer days, such as 2 to 4 days, according to different diary parameters [50-52].

6. Urethrocystoscopy
Urethrocystoscopy is not absolutely necessary in the initial evaluation of neurogenic bladder, but urethrocystoscopic examination of the entire lower urinary tract can provide important information on making a diagnosis and treatment decisions by excluding intravesical or intraurethral anatomic anomalies or pathology that may be contributing to the patient’s symptoms. Major urethral lesions such as urethral strictures and false passages can be seen on urethrocystoscopy; this condition is very important for making a treatment decision in patients requiring intermittent catheterization. The degree of bladder neck incompetency cannot be adequately evaluated by urethrocystoscopy. If a patulous bladder neck can be seen, it often indicates that patients may have a higher degree of sympathetic denervation. Furthermore, the degree of the bladder neck obstruction due to benign prostatic hyperplasia in men and bladder neck contracture secondary to previous bladder neck surgeries for decreasing bladder neck resistance can be easily seen by urethrocystoscopy. In addition to observing time-dependent secondary complications such as trabeculations, stones, diverticula, and bladder tumors, the location, number, and shape of ureteral orifices also should be documented.

7. Upper urinary tract imaging
In cases of neurogenic bladder with a high risk of renal damage, upper urinary tract imaging is most important. In patients with neurogenic bladder, especially in the case of low bladder compliance; DO; DSD; or chronic retention with incontinence, the pressure of the bladder may be elevated and may cause hydronephrosis with or without VUR. When reflux occurs, it aggravates the development of hydronephrosis. Therefore, upper urinary tract imaging is important during baseline evaluation, treatment, and follow-up in all patients with a neurogenic bladder.

The most commonly used imaging modalities include ultrasonography and computed tomography (CT) scanning. Although ultrasonography is noninvasive and can evaluate many features of the renal anatomy, it cannot predict renal function or the degree of reflux. In some cases, the presence of excessive bowel gas or constipation may limit the use of ultrasonography or interfere with its results. Furthermore, it is highly examiner-dependent, subjective, and thus not accurately reliable. Therefore, ultrasonography is most frequently used for follow-up rather than initial evaluation in our practice.

Alternatively, non-enhanced CT scanning can give fast, accurate information on the presence of stones, bladder wall thickness, diverticula, and prostate size free from the risk of contrast dye and fasting that potentially affect patients who already have compromised renal function. Therefore, it is particularly useful in initial evaluation.

If impaired renal function is predicted by laboratory evaluation and routine scanning by non-enhanced CT or ultrasonography, diuresis renography or magnetic resonance urography may provide valuable information about renal function.

8. Complete urodynamics
If the initial evaluation indicates patients with voiding dysfunction or neurological disorders, complete urodynamics including videourodynamics should be performed because entire lower urinary tract function can only be evaluated by complete urodynamics. The complete urodynamic evaluation consists of several components, including uroflowmetry, cystometrogram, electromyography, and pressure-flow studies. In addition to routine assessment of bladder sensation, detrusor stability, compliance, capacity, and the leak point pressure, especially DLPP, should be measured during the cystometrogram. DLPP directly reflects the bladder outlet resistance, which is defined as the lowest detrusor pressure at which urine leakage occurs in the absence of either a detrusor contraction or increased abdominal pressure [49]. If outlet resistance is too high, thus exceeding the “safe” pressure, the pressure in the bladder will continuously increase with the bladder filling and eventually be transmitted to the upper urinary tract, resulting in hydronephrosis or dilatation of the upper urinary tract. McGuire et al. [53] demonstrated the deleterious effects of high DLPP on the upper urinary tract; in their study, among myelodysplastic patients with DLPP of
more than 40 cmH2O, 68% showed VUR and 81% showed ureteral dilatation. During the voiding phase, in addition to urine flow and detrusor contractility, the coordination between the detrusor and striated sphincter should also be assessed. DSD is defined as a detrusor contraction concurrent with an involuntary contraction of the urethral or periurethral striated muscle. Occasionally, flow may be prevented altogether [49]. DSD more commonly occurs in the neurological abnormalities between the pontine micturition center and sacral spinal cord, including SCI, multiple sclerosis, and spina bifida [54]. If DSD is left untreated, over half of patients develop serious urological complications such as high bladder pressure, reduced bladder compliance, VUR, hydronephrosis, and renal failure [54]. DSD can be accurately diagnosed by using videourodynamic. Videourodynamic studies play a critical role in the evaluation and diagnosis of neurological disorders associated with LUTD, and their results are generally correct. However, the urodynamic findings do not always correlate with neurological disorders and voiding symptoms, especially in SCI patients [56-58]. This discrepancy may be attributed to the primarily involved neurological diseases and the extent and completeness of the lesion [57]. Therefore, management of the urinary tract in patients with LUTS and neurological disorders must be based on urodynamic findings rather than on inferences from the neurologic evaluation [56-58].

Urodynamic studies play a critical role in the evaluation and diagnosis of neurological disorders associated with LUTD, and their results are generally correct. However, the urodynamic findings do not always correlate with neurological disorders and voiding symptoms, especially in SCI patients [56-58]. This discrepancy may be attributed to the primarily involved neurological diseases and the extent and completeness of the lesion [57]. Therefore, management of the urinary tract in patients with LUTS and neurological disorders must be based on urodynamic findings rather than on inferences from the neurologic evaluation [56-58].

9. Consultation with other subspecialties

Through the above detailed and careful examination, initial diagnosis can be made in most patients. However, in some cases, a cooperation or consultation is needed with other departments such as neurology or rehabilitation if the patient's symptoms and bladder and urinary tract anatomical and urodynamic findings do not correlate with the physical examination. If necessary, more extensive neurological examinations such as electromyography are needed.

TREATMENT

Regardless of the cause, the goals of the management of LUTDs in patients with neurological disorders are the same. The goals are to 1) preserve renal function, 2) prevent bladder overdistension and achieve efficient bladder emptying, 3) achieve/maintain continence, and 4) minimize risk of UTI. There are a number of management options for these patients; however, a single, optimal treatment is not yet available. Currently, only combination treatment can achieve maximal therapeutic effects [27,59-61].

1. Nonpharmacological treatment

Lifestyle modifications and behavioral therapy: The first-line treatment consists of lifestyle modifications and behavioral therapy; in particular, the fluid intake schedule is important in patients requiring intermittent catheterization as part of their management [60,61]. Simply on the basis of bladder diaries regarding fluid intake, timing of voiding and a fluid schedule can often yield significant benefits in the prevention of bladder overdistension. The bladder diaries provide much important information for communication and education for patients performing intermittent catheterization in accordance with appropriate voiding volumes and intervals. Bladder diaries can also help patients to actively participate in their management. Therefore, we suggest recording bladder diaries in all patients with neurogenic bladder, especially at the initial stage of management. The recommended total fluid intake and urine formation per day are about 1,800 ml and 1,600 ml, respectively; a fluid schedule of 400 ml with meals; 200 ml at 10 am, 2 pm, and 4 pm; and only sips of fluid after the evening meal will meet these requirements [60].

Bladder retraining: Bladder training is a noninvasive strategy for bladder evacuation, and the goal is to increase bladder capacity and the time interval between voiding as well as to suppress involuntary bladder contractions. Bladder training consists of three components: education, scheduled voiding, and positive reinforcement [62]. Individualized patient education is important for increasing the efficiency of bladder training during neurogenic bladder management. An initial voiding interval can be selected on the basis of the bladder diaries and the ability of patients to void [61]. In patients with involuntary detrusor contraction and low PVR, the voiding interval can be gradually increased, with the aim of retraining the bladder to hold more urine and to inhibit inappropriate detrusor contractions during the filling phase. Timed voiding can be implemented in neurogenic bladder patients with significantly decreased bladder sensation such as diabetes. Although the Credé technique, tapping, and/or Valsalva maneuver are appropriate in some carefully selected patients, these are not generally recommended. These methods may increase the occurrence of VUR and cannot always promote complete bladder emptying, even though they can be performed.

Urinary drainage: Because PVR increases the risk of serious complications such as UTI, VUR, and the formation of urinary calculi, the frequency of voiding should be determined by the PVR rather than by the time interval between voiding. When patients have a PVR greater than 30% of bladder capacity, urinary drainage by catheterization is appropriate [63]. CIC is the preferred method of urinary drainage for patients with neurogenic bladder dysfunction with urinary retention. Individualized and spe-
cational education and training for patients are very important to the initial stage of CIC and during follow-up. We established a “centralized intensive education system” for instructing patients and providing them with continuous support and encouragement to perform clean intermittent self-catheterization and obtained good results compared with a conventional “individualized ward education system” [64]. However, despite the beneficial effects of CIC on urinary drainage, patients using CIC because of neurogenic bladder secondary to SCI generally exhibit a reduced QoL in all health domains as assessed by the Medical Outcomes Study Short Form 36 [44]. If patients have uncontrollable incontinence or intermittent catheterization is not suitable, indwelling Foley catheter placement or suprapubic catheters can also be considered [65-67].

UTI, especially asymptomatic bacteriuria, is the most frequent complication of catheterization. Because antimicrobial prophylaxis to prevent UTI will result in the development of drug-resistant microorganisms, its use should be avoided unless patients have febrile UTI. If patients on CIC have febrile UTI, in addition to treating the patient with appropriate antibiotics, the PVR and voiding interval should be checked. These are helpful for making sure the catheterization is performed in a correct and efficient way and to necessitate a change in order to achieve complete emptying [4,27,45,60].

2. Pharmacological treatment
Several oral and intravesical medications have been evaluated for the management of neurogenic patients with LUTS and improved long-term outcomes.

Antimuscarinic medications: Antimuscarinic medications are the first-line treatment strategy for neurogenic DO by binding to muscarinic receptors and thereby preventing acetylcholine release from parasympathetic nerves [59]. These drugs decrease DO, improve bladder compliance, increase bladder capacity, reduce bladder filling pressure, and thus help to prevent renal and bladder damage [68-71]. However, higher doses or 2 different antimuscarinic agents might be required in neurogenic patients than in non-neurogenic patients [71-73]. In addition, antimuscarinic medications are generally well tolerated by most patients, but the side effects may result in early discontinuation of therapy [70,74]. The most common side effects of antimuscarinic agents include dry mouth, constipation, blurred vision, drowsiness, and dry skin and mucosa [59]. Because the human detrusor contains only M2 and M3 muscarinic receptor subtypes [75], M2 and M3 receptor-specific antimuscarinics reduce the side effects of nonselective antimuscarinic drugs that bind to M1, M2, and M3 receptors [60]. In addition, oral sustained-release formulations, transdermal or intravesical instillation, and a combination of different antimuscarinic drugs have been found to be helpful to reduce antimuscarinic side effects [27,76-78].

Alpha-1-adrenergic antagonists: Alpha-1-adrenoceptors, particularly their α1A-subtype, are mainly expressed in the bladder neck, urethra, and prostate and promote bladder outlet contraction and enhancement of resistance [79]. Therefore, α-adrenergic receptor antagonists facilitate urine release in conditions of functionally increased urethral resistance and have been recommended as a possible treatment for neurogenic bladder [80]. Currently used α-adrenergic receptor blockers include phenoxybenzamine hydrochloride, terazosin, tamsulosin, alfuzosin, and doxazosin. Individual antagonists have also been shown to improve maximum detrusor pressure, bladder capacity, and autonomic dysreflexia symptoms [59]. The most common side effects of these drugs include fatigue, nasal congestion, abnormal ejaculation (especially with tamsulosin), and dizziness or postural hypotension (especially with doxazosin and terazosin) [59].

Botulinum toxin (BTX): Botulinum toxin is a potent neurotoxin produced by the bacterium Clostridium botulinum, which blocks signal transmission across the neuromuscular junction. Injection of BTX type A (BTX-A) into the bladder wall is now a well-established strategy for the treatment of neurogenic DO and produces long-lasting improvements in urgency, incontinence, and QoL in individuals [81]. BTX is postulated to contribute to the beneficial clinical effects in treating neurogenic bladder via several different mechanisms, including inhibiting the release of acetylcholine, adenosine triphosphate, and substance P from the urethral and/or parasympathetic nerve endings and thus blocking neuromuscular transmission leading to detrusor paralysis [60,82]. It also acts on sensory afferent neurons and prevents the transmission of a sensation of urgency to the central nervous system [60,82]. Although intravesical injection of BTX-A has been increasingly used to treat persistent neurogenic DO, the appropriate doses and means of administration as well as the long-term effects have not yet been clearly elucidated [83,84].

3. Surgical treatment
If patients have DO, a small-capacity bladder, or a poor filling-compliant bladder and all the conservative approaches have failed, surgical treatment can be considered to prevent upper tract damage by lowering bladder pressure and to improve QoL by restoring continence [85]. With the benefits of increasing bladder capacity while simultaneously lowering filling pressures, bladder augmentation by use of detubularized bowel segments is a widely accepted and effective surgical approach to achieving an adequate reservoir of urine [86]. The ileum is the most commonly used bowel segment, although other parts of the bowel such as the caecum, ascending and sigmoid colon, and stomach have been infrequently but successfully used [87,88].

The success rate of bladder augmentation has been reported to be higher than 90%, and overall, 77% of patients report a ‘good result’ [87]. Complications of bladder aug-
mentation include bladder stones, recurrent UTI and chronic bacteruria, metabolic disturbances, bowel disturbance, bladder perforation, and increased risk of bladder or bowel malignancy [85,86,88]. Surgical revision is required in about one third of patients and careful lifelong follow-up is necessary, because some of these complications can occur late [85]. Although some neurogenic bladder patients may be able to void spontaneously after bladder augmentation with abdominal straining and simultaneous relaxation of the pelvic floor, 10 to 75% of patients require intermittent catheterization [27,60,87]. Therefore, the evaluation of the patients’ ability to perform intermittent catheterization is necessary before performing bladder augmentation.

Depending on the state of the patient’s ability, motivation, urethral anatomy, and urinary sphincter function, primary or secondary forms of additional surgeries such as artificial urinary sphincter implantation and continent or incontinent urinary diversion combined with or without bladder augmentation may also required. In the case of neurogenic bladder patients with adequate bladder compliance and capacity, who have primary or remaining urinary incontinence after bladder augmentation alone owing to sphincter weakness, artificial urinary sphincter or bulbourethral sling procedures may be considered at the time of bladder augmentation or afterward [60,85]. Although these replacement procedures provide satisfactory success rates in carefully selected patients, the procedures may require sufficient hand function of the patients and a higher rate of revision and reoperation [60,85].

For patients who have abnormal urethral anatomy (such as stricture, false passages, and bladder neck obstruction) that does not allow a catheter to pass into the bladder, or patients who require closure of the bladder neck owing to irreparable sphincter defects, a continent urinary diversion can be considered on the abdominal wall combined with abdominal straining and simultaneous relaxation of the pelvic floor, 10 to 75% of patients require intermittent catheterization [27,60,87]. Therefore, the evaluation of the patients’ ability to perform intermittent catheterization is necessary before performing bladder augmentation.

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For patients who have abnormal urethral anatomy (such as stricture, false passages, and bladder neck obstruction) that does not allow a catheter to pass into the bladder, or patients who require closure of the bladder neck owing to irreparable sphincter defects, a continent urinary diversion can be created on the abdominal wall combined with bladder augmentation [27,60,80,85]. If the patients have no ability or motivation to perform self-catheterization, incontinent urinary diversion can be considered primarily or secondarily to bladder augmentation. Usually, an ileal segment is used to form an ileal conduit or ileo-vesicostomy [27,60,80,85].

**CONCLUSIONS**

LUTD have a significant effect on the QoL of patients with neurological disorders. They are also significantly associated with an increased risk of serious, life-threatening complications. Over the years, LUTD secondary to neurological disorders have been successfully treated by many treatment options. The conservative approaches are still the first-line treatment options, but more invasive treatments including surgical approaches may be required when conservative treatment fails. However, a group of patients are refractory to these treatments, and many neurological diseases are progressive and aggravate LUTD continually; therefore, further study is needed to develop new and novel treatments to improve patients’ symptoms and QoL.

**CONFLICTS OF INTEREST**
The authors have nothing to disclose.

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