

Neurogenic lower urinary tract dysfunction: Evaluation and management

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Abstract

The lower urinary tract (LUT) in health is regulated by coordinated multi-level neurological inputs which require an intact central and peripheral nervous system. Lower urinary tract dysfunction is therefore a common sequelae of neurological disease and the patterns of bladder storage and voiding dysfunction depend upon the level of neurological lesion. Evaluation includes history taking, bladder diary, urological examination when relevant, ultrasonography and urodynamic testing when indicated. Antimuscarinic agents are the first line treatment for patients with storage dysfunction. Alternative treatments include intradetrusor injection of onabotulinumtoxinA, which has been shown to be of benefit in patients with neurogenic detrusor overactivity (NDO), and neuromodulation. Intermittent catheterization remains the option of choice in patients with significant voiding dysfunction resulting in high post-void residual volumes.

Introduction

Lower urinary tract (LUT) dysfunction commonly occurs following a variety of neurological diseases. Symptoms are often under-reported, yet have a significant impact on the quality of life of the patient and carer. The comprehensive assessment of neurological patients reporting LUT symptoms involves a multidisciplinary team including the treating neurologist, urologist, rehabilitation specialist, primary care physician, nurses and therapists. This review aims to provide an overview of the neural control of the LUT in health, patterns of LUT dysfunction following neurological disease and principles of management.

Neurological control of the lower urinary tract

The two functions of the LUT- storage of urine and periodic emptying- depend upon coordinated activity of the detrusor and urethral sphincters, and is under the control of a complex neural network distributed across the central and peripheral nervous system (1). In health, the LUT remains in the storage phase 99.8 % of the time and this is due to inhibitory signals from higher brain centers (2). The bladder holds between 400 to 600 mL, and micturition occurs every three to four hours (3, 4). The conscious decision to void is influenced by several factors including sensory input from the bladder, social environment, learned behaviors and an individual's emotional state (5, 6). Functional brain imaging studies in humans have demonstrated the role of several structures in the control of LUT functions including the insula, anterior cingulate cortex, prefrontal cortex and the periaqueductal grey (PAG) during storage, and medial prefrontal cortex, hypothalamus, the PAG and the pontine micturition center (PMC) during voiding (3, 7, 8).

A complex network of peripheral nerves innervates the LUT. Axons emerging from sympathetic preganglionic neurons in the intermediolateral horn of the thoracic 12th and lumbar 1st and 2nd spinal cord travel through the hypogastric plexus innervating the bladder dome, bladder neck and urethra, releasing noradrenaline at beta-adrenergic receptors predominantly on the bladder dome and alpha-adrenergic receptors on the bladder neck and

urethra (9, 10). Axons from parasympathetic neurons of the sacral 2, 3 and 4 spinal cord release acetylcholine at muscarinic receptors of the bladder wall and contraction involves direct contraction via M3 receptors and indirect 'recontraction' via M2 receptors through reduction in adenylate cyclase activity (11, 12). The somatic innervation of the striated external urethral sphincter is derived from the ventrolateral division of the Onuf's nucleus in the anterior horn of the sacral 2, 3 and 4 levels of the spinal cord and axons travel through the pudendal nerve (3, 13, 14). Motor neurons more medially placed in the Onuf's nucleus innervate the pelvic floor musculature. Afferent signals from the bladder and urethra are conveyed through the pudendal, sympathetic and parasympathetic nerves (14, 15). Thinly myelinated A δ fibres convey afferent signals from the LUT in health, and dormant unmyelinated C fibers become activated following noxious stimuli to the bladder or following neurological disease (16).

Urinary tract dysfunction following neurological disease

Considering the intricate neural networks that regulate the LUT in health, it is not surprising that LUT dysfunction occurs following neurological disease.

The pattern of LUT dysfunction is influenced by the level of neurological lesion (Table 1) (17-22).

Lesions damaging the suprapontine or suprasacral spinal pathways result in involuntary contractions of the detrusor muscle, called detrusor overactivity (DO). A suprapontine lesion results in a loss of tonic inhibition of the PMC and uninhibited detrusor contractions, whereas following spinal cord injury, the emergence of a spinal segmental reflex mediated by previously dormant C fibers drives the micturition reflex and results in DO. Additionally, lesions of the spinal cord may result in a situation of simultaneous contraction of the detrusor and sphincters during attempted voiding, known as detrusor sphincter dyssynergia (DSD). This results in incomplete bladder emptying and high intravesical pressures which increases the risk for upper urinary tract damage. Lesions of the sacral spinal cord or infrasacrally, ie. the cauda equine, peripheral nerves, usually result in an underactive detrusor and various degrees of voiding dysfunction (2).

Detrusor overactivity, poor bladder wall compliance and/or DSD result in raised intravesical pressures that may lead to morphological changes in the

bladder wall such as trabeculations and diverticula. Sustained raised pressures may also result in upper urinary tract changes such as vesico-ureteric reflux, hydronephrosis, renal impairment and, in some situations, even end-stage renal disease (6, 16, 23). For reasons that are not entirely clear, patients with conditions such as spinal cord injury and spina bifida are at greater risk for developing upper urinary tract damage compared to patients with slowly progressive conditions such as Multiple sclerosis and Parkinson's disease, where the reported prevalence of complications is much lower (24-26).

Multiple sclerosis

Lower urinary tract dysfunction is present in 75 - 80 % of patients with MS and urinary incontinence in more than 50 %, and this is influenced by the duration and extent of disease (27-29). Patients reporting LUT symptoms usually have associated finding of pyramidal signs in the lower limbs, suggesting that spinal cord dysfunction is the cause for LUT dysfunction (6, 30-34). Patients most commonly report OAB symptoms of urinary urgency, incontinence and frequency, as well as the inability to initiate voiding voluntarily. Patients often describe an interrupted urinary flow may not empty their bladder completely and resort to voiding a second time soon afterwards, known as double voiding. Typical findings on urodynamics include the presence of DO, DSD and detrusor hypocontractility. Lower urinary tract dysfunction deteriorates with worsening of MS and one study that examined

urodynamic pattern changes in this group of patients demonstrated that 43 % with no new symptoms and 75 % with new symptoms had significant changes on follow-up urodynamic testing (35). Febrile episodes such as urinary tract infections (UTI) are particularly a concern as they are associated with deterioration of neurological status (36).

Parkinson's disease and related disorders

Non-motor symptoms (NMS) commonly accompany the motor complaints of Parkinson's disease (PD) and LUT dysfunction is reported in 27 - 63.9 %, and urinary incontinence in 33 % of patients with Parkinson's disease (PD) (27).

In PD, diminished dopaminergic input to the striatum resulting in a loss of tonic inhibition on the micturition reflex has been postulated as a mechanism for DO. Deterioration in bladder functions correlates with degree of neurological disease. The most frequently reported symptoms are nighttime frequency, urgency and difficulty voiding. Nocturnal polyuria, characterized by the excessive rate of urine production only at night with normal 24-hour urine output, is reported in PD (37).

Lower urinary tract symptoms often predate other neurological symptoms in patients with Multiple system atrophy (MSA) and patients report urogenital symptoms on average 4 – 5 years before the diagnosis is made, and 2 years before other neurological symptoms appear. In this disorder, neuronal degeneration occurs in several regions responsible for LUT control and the

cause for incontinence is therefore multifactorial- due to DO, overflow incontinence consequent to urinary retention and stress incontinence. An open bladder neck may be seen in videourodynamic studies, reflecting denervation of the external urethral sphincter due to degeneration at the level of the Onuf's nucleus in the sacral spinal cord (38, 39).

Stroke

Urinary incontinence is reported in 24 % of stroke patients (27). LUT symptoms are more commonly reported in patients with lesions that are anteriorly placed such as the anterior and medial surface of the frontal lobe, paraventricular white matter anteriorly, genu of the internal capsule, putamen and thalamus, compared to patients with posteriorly sited lesions (40). Lesion size may also influence the risk for micturitional disturbances (41-43). The commonest LUT dysfunction reported is DO, however patients with hemorrhagic strokes may report urinary retention due to detrusor underactivity (44). Patients with white matter lesions due to small vessel disease (leukoaraiosis) may also present with LUT symptoms, most commonly urgency incontinence (40, 45, 46). Urinary incontinence persisting seven days after stroke is associated with poor survival, disability and institutionalization (47, 48).

Dementia

Incontinence is a cardinal feature of normal-pressure hydrocephalus, and improvement in LUT symptoms and urodynamic parameters may be demonstrated following lumbar puncture. Takashi et al. found that white matter lesions are a more significant contributor to overactive bladder symptoms (OAB) and incontinence, than Alzheimer's disease (AD) pathology in elderly adults with dementia. Incontinence presents earlier in the course of patients with Dementia with Lewy bodies compared to AD (49).

Spinal cord injury

Lower urinary tract dysfunction is found in 85 % of spinal cord injury (SCI) patients and urinary incontinence reported in 52 % (50). Patients in the acute stage of supraconal injury may present initially with urinary retention due to an acontractile bladder for the first 6 - 12 weeks of spinal shock, and subsequently develop the typical pattern of LUT dysfunction characterised by DO and DSD (51, 52). Voiding dysfunction is a prominent finding in patients with a lesion of the conus medullaris or cauda equina, due to poorly sustained detrusor contractions and, less often, non-relaxing urethral sphincters (53).

Spina bifida

Lower urinary tract symptoms are reported in 90% of patients and usually present in childhood, but may occasionally present for the first time in adulthood. Urodynamics show evidence for DO, detrusor underactivity and DSD (54, 55).

Autonomic disorders

Voiding difficulty with incomplete bladder emptying have been described in autoimmune autonomic ganglionopathy, a condition characterised by a myriad of autonomic complaints including orthostatic intolerance, anhidrosis, constipation, urinary dysfunction, sicca syndrome and pupillary dysfunction, and significantly raised antibody titers towards ganglionic acetylcholine receptors (AChR) (56).

In patients with acute idiopathic autonomic neuropathy, urinary retention and voiding difficulty are common initial presentations presumably due to pre- and postganglionic cholinergic dysfunction with preserved function of the somatic innervation to the sphincter (57).

Nocturia and voiding dysfunction have been described in pure autonomic failure (PAF), a degenerative postganglionic autonomic disorder, in addition to other pelvic organ complaints such as erectile dysfunction and constipation (58).

Postural tachycardia syndrome (PoTS) is a disorder characterized by sympathetically mediated vasoconstriction, excessive sympathetic drive, volume dysregulation and deconditioning. Chronic symptoms reported in this disorder include orthostatic palpitations, dizziness and fatigue, as well as LUT dysfunction including DO (59-61).

Peripheral neuropathy

Small fiber neuropathy affecting the innervation of the LUT is often associated with impaired sensations of bladder fullness and poor detrusor contractility. This results in reduced or absent bladder contractions, chronic low pressure urinary retention, bladder distension and overflow incontinence (23).

Overactive bladder symptoms and impaired bladder contractility are reported in diabetes mellitus and are associated with the presence of peripheral neuropathy, nephropathy, and the metabolic syndrome (62, 63). Lower urinary tract dysfunction is reported in amyloid neuropathy, presenting with difficulty in bladder emptying and incontinence usually within 3 years of disease onset. Urodynamic studies may demonstrate reduced bladder sensation, underactive detrusor, poor urinary flow and opening of the bladder neck, whilst ultrasound may show thickening of the bladder wall (64-67).

Approximately 25% of patients with Guillain-Barre syndrome report LUT symptoms (50) and both detrusor areflexia and DO have been described (68).

Myotonic dystrophy

Lower urinary tract symptoms range from voiding difficulties to urinary frequency, urgency and stress incontinence, with varying findings on urodynamics (69, 70).

Fowler's syndrome

Fowler's syndrome typically presents in young women with urinary retention and is due to a nonrelaxing external urethral sphincter, and often associated with polycystic ovaries (71, 72).

Evaluation

The clinical assessment begins with history taking assessing both storage and voiding symptoms, and physical examination. A properly completed bladder diary provides real-time prospective information about patient-reported LUT symptoms and ideally should be recorded for a minimum of two days (26, 29). Urinalysis using combined reagent strips, known as the dipstick test, provides a rapid method of screening for urinary tract infections. If abnormal, a urine sample should be sent to the lab for culture to confirm infection and to guide antibiotic use (73).

The post-void residual urine volume (PVR) is measured by ultrasonography or “in-out” catheterization and is an essential investigation to assess voiding functions, as often patients may not be aware that their bladder has emptied only incompletely (2, 23). Ultrasonography also provides information about upper tract changes such as hydronephrosis and renal scarring, and may be repeated periodically in patients deemed to be at greater risk for developing upper urinary tract damage.

Urodynamics provides information about LUT functions. Uroflowmetry is a valuable non - invasive test of the urinary flow for detecting voiding

dysfunction. Patients should void volumes greater than 150 ml for the results to be properly interpreted (2, 6).

Invasive urodynamics including filling cystometry and pressure flow study help to assess pressure - volume relationships during nonphysiological bladder filling and emptying. Videocystometry uses simultaneous fluoroscopic monitoring while the bladder is filled with contrast agent, and provides further information such as vesico-ureteric reflux and structural abnormalities, eg. diverticula, bladder neck incompetence (2). Urodynamic tests help not only to prognosticate the risk for upper tract damage, but also to guide appropriate treatment for LUT dysfunction. Due to the invasive nature of these tests however, the place for cystometry in the routine assessment of LUT symptoms reporting neurological symptoms is a topic of debate. For instance, in the United Kingdom the first-line management of LUT symptoms in early MS follows a simple algorithm involving testing for UTIs and measuring the PVR (Figure 1) without invasive urodynamics, whereas French guidelines recommend urodynamics (26, 29). The decision to perform urodynamics should ultimately reflect the clinical scenario as well as regional recommendations.

Pelvic neurophysiology may be useful in specific situations. Concentric needle EMG of the urethral sphincter is useful in diagnosing DSD during conventional cystometry, however since the advent of videocystometry this is less often being performed for this indication. Anal sphincter EMG is useful to

assess the integrity of the sacral (S2, 3, 4) roots when a cauda equina lesion is suspected, or in a patient presenting with a parkinsonian disorder where MSA is suspected. Urethral sphincter EMG is characteristically abnormal in women with urinary retention due to Fowler's syndrome (74-76). Recording the penilo-cavernosus reflex (previously known as "bulbo-cavernosus" reflex) serves to assess sacral root afferent and efferent pathways in patients with a suspected cauda equina lesion (77).

Management

The goals when managing LUT dysfunction in the neurological patient are to achieve continence, improve quality of life, prevent UTIs and preserve renal functions (26, 78). A multidisciplinary team should be involved in the care of patients including the patient and their carer, continence advisor, general practitioner, neurologists, urologist, physiatrist and therapists, and should be tailored to the specific needs of the given patient (23, 78). Figure 1 presents an algorithm for the evaluation and first line management of neurological patients reporting LUT symptoms. There are a few situations where early onward referral to a specialist urology unit is warranted (Table 2).

Management of storage dysfunction

Optimizing fluid intake and conservative measures such as bladder training and timed voiding, should be explored (79-81). Antimuscarinic agents are the mainstay of treatment for OAB symptoms (Table 3). Common adverse events include dry mouth and eyes, blurred vision, constipation, tachycardia, and increasing PVR (79, 82-84) and, in general, as low as only 18% of patients are found to be continuing with antimuscarinic therapy after 6 months of treatment (85). Of concern as well are the central side effects, as an increasing anticholinergic burden is associated with greater risk for cognitive

impairment, falls and mortality (86, 87). The currently available antimuscarinic agents have differing physicochemical properties, and an antimuscarinic that is relatively impermeable to the blood brain barrier, such as trospium chloride, or that is highly selective for the M3 receptor (rather than the M1 receptor), such as darifenacin, theoretically have less effects on cognitive functions (88, 89).

Mirabegron is an agonist of the beta 3 receptor and has been shown to improve OAB symptoms and is currently licensed in several countries and may be efficacious in neurological patients (90). Side effects include palpitations, rise in blood pressure, and rarely atrial fibrillation (91).

Desmopressin is a synthetic analogue of arginine vasopressin and is most commonly used for managing nocturia and nocturnal polyuria (92). Caution should be exercised when used in patients over the age of 65, or with signs of fluid overload such as ankle oedema, and prescribed no more than once in 24 hours for fear of developing hyponatremia (92).

Neuromodulation either through electrical stimulation of the tibial nerve (tibial nerve stimulation) or sacral root (sacral neuromodulation) has been shown to be effective in managing OAB symptoms (93). A multicentric randomized controlled double blinded SUMiT Trial compared the efficacy of once weekly 30 minute stimulations of tibial nerve stimulation delivered percutaneously (PTNS) against a sham treatment for 12 weeks (94, 95) and demonstrated

efficacy and safety in patients reporting OAB symptoms. Tibial nerve stimulation delivered transcutaneously (TTNS) may be used at home and has been shown to be safe and efficacious in managing urgency incontinence in patients with MS and after stroke (96, 97).

Sacral neuromodulation has been found to be of benefit for managing DO, however it is unclear which neurological patients are suitable for this treatment (98). This is the treatment of choice in managing non-obstructive urinary retention in women with Fowler's Syndrome (99).

Intradetrusor injections of onabotulinumtoxinA have proven to be an effective treatment for the management of DO in neurological patients where first line treatments are either ineffective or intolerable, and are licensed in several countries throughout the world. The duration of effect lasts usually between 9 – 13 months, with significant improvements in storage symptoms and quality of life. Patients should be cautioned about the potential need to catheterize after treatment (100, 101).

Management of voiding dysfunction

Incomplete bladder emptying with a raised PVR may provoke DO, and impair the efficacy of antimuscarinic agents and botulinum toxin. Intermittent catheterization is advocated if a patient retains a significant volume of urine. The PVR at which to commence catheterization depends upon the overall

bladder capacity and in neurological patients, a PVR of greater than 100 mL is generally advocated (6, 29). Experienced health-care professionals, for example continence advisers, should be involved in teaching the technique. The frequency of intermittent catheterization depends upon the degree of voiding dysfunction, between one to three times per 24 h in patients with incomplete bladder emptying, and four to six times a day in patients in complete urinary retention (29). Neurological lesions that result in poor dexterity, truncal stability, lower limb spasticity, cognitive impairment and/or impaired visual acuity may prove to be barriers to intermittent self catheterization and should be reviewed at the time of assessing suitability for intermittent catheterisation (29, 81).

Suprapubic tapping and thigh scratching may trigger the reflex voiding and were found beneficial in patients with suprasacral spinal cord lesions (102). Performing Credes manoeuvre is not recommended as this may be associated with a rise in detrusor pressures, and possible vesico-ureteric reflux (102). α -Adrenoreceptor blockers have been shown to be of benefit in men with MS reporting voiding dysfunction, however in clinical practice their use is mostly of benefit in men where an additional pathology of bladder outlet obstruction due to benign prostate enlargement is suspected . (29). Botulinum toxin injections into the external urethral sphincter was found to be of benefit in patients with DSD due to SCI, and has shown promising results in women with Fowler's Syndrome (76, 103).

Conclusion

Lower urinary tract dysfunction is common following neurological lesion. Depending on the site of the lesion patients may report LUT symptoms reflecting underlying bladder dysfunction. It is important to consider this, because of possible upper urinary tract damage that may long-term lead to renal failure. In this review we discuss diagnostic approach and possible treatment options for patients with lower urinary tract symptoms due to different neurological conditions.

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Table 2 Situations where early referral to a specialist urology service is indicated

Table 3 Commonly used antimuscarinic agents presented in alphabetical order

Figure 1 Algorithm for management of neurogenic lower urinary tract dysfunction in patients with progressive neurological disorders

Requires permission from the BMJ Publishing Group (*J Neurol Neurosurg Psychiatry* 2009; 80:470-7). CISC, clean intermittent self-catheterisation; PVR, postvoid residual volume; UTI, urinary tract infection.