Neurogenic lower urinary tract dysfunction: Evaluation and management

Katarina Ivana Tudor[1], Ryuji Sakakibara[2], Jalesh N. Panicker[3]

1 Department of Neurology, University Hospital Center Zagreb, Zagreb, Croatia

2 Neurology Division, Department of Internal Medicine, Sakura Medical Center, Toho University, Sakura, Japan

3 Department of Uro-Neurology, The National Hospital for Neurology and Neurosurgery, University College London (UCL), Institute of Neurology, Queen Square, London, United Kingdom

Corresponding author:

Katarina Ivana Tudor

Department of Neurology

University Hospital Center Zagreb

Kispaticeva 12

10 000 Zagreb

Croatia

E-mail: tudorkatarinaivana@gmail.com

Word count: 3217

Number of tables: 3

Number of figures: 1

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 Aδ 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

7

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 videourodyamic 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 asses 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.

Acknowledgement

Bibliography

1.   Fowler CJ. Autonomic disorders of the urogenital system. CONTINUUM: Lifelong Learning in Neurology. 2007;December 13(6, Autonomic Disorders):165-81.
2.   Panicker JN, Fowler CJ. The bare essentials: uro-neurology. Practical neurology. 2010;10(3):178-85.
3.   Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. Nature reviews Neuroscience. 2008;9(6):453-66.
4.   Fowler CJ. Integrated control of lower urinary tract--clinical perspective. British journal of pharmacology. 2006;147 Suppl 2:S14-24.
5.   Pardo JV, Fox PT, Raichle ME. Localization of a human system for sustained attention by positron emission tomography. Nature. 1991;349(6304):61-4.
6.   Panicker JN, Fowler CJ, Kessler TM. Lower urinary tract dysfunction in the neurological patient: clinical assessment and management. The Lancet Neurology. 2015;14(7):720-32.
7.   Blok BF, Willemsen AT, Holstege G. A PET study on brain control of micturition in humans. Brain : a journal of neurology. 1997;120 (Pt 1):111-21.
8.   Blok BF, Sturms LM, Holstege G. Brain activation during micturition in women. Brain : a journal of neurology. 1998;121 (Pt 11):2033-42.
9.   Andersson KE, Arner A. Urinary bladder contraction and relaxation: physiology and pathophysiology. Physiological reviews. 2004;84(3):935-86.
10.   De Groat WC, Boothe AM. Nervous Control of the Urogenital System (Autonomic Nervous System). Maggi CA, editor. London1993.
11.   Matsui M, Motomura D, Fujikawa T, Jiang J, Takahashi S, Manabe T, et al. Mice lacking M2 and M3 muscarinic acetylcholine receptors are devoid of cholinergic smooth muscle contractions but still viable. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2002;22(24):10627-32.
12.   Chess-Williams R. Muscarinic receptors of the urinary bladder: detrusor, urothelial and prejunctional. Autonomic & autacoid pharmacology. 2002;22(3):133-45.
13.   Fry CHea. Incontinence. Abrams P, Cardozo L, Khoury S, Wein A, editors. Jersey: Health Publications Ltd; 2005.
14.   Morrison J. Incontinence. Abraham P, Cardozo L, Khoury S, Wein A, editors. Jersey: Health Publications Ltd.; 2005.
15.   Janig W, Morrison JF. Functional properties of spinal visceral afferents supplying abdominal and pelvic organs, with special emphasis on visceral nociception. Progress in brain research. 1986;67:87-114.
16.   de Groat WC, Kawatani M, Hisamitsu T, Cheng CL, Ma CP, Thor K, et al. Mechanisms underlying the recovery of urinary bladder function following spinal cord injury. Journal of the autonomic nervous system. 1990;30 Suppl:S71-7.
17.   Sakakibara R. Lower urinary tract dysfunction in patients with brain lesions. Handbook of clinical neurology. 2015;130:269-87.
18.   Walter U, Kleinschmidt S, Rimmele F, Wunderlich C, Gemende I, Benecke R, et al. Potential impact of self-perceived prodromal symptoms on the early diagnosis of Parkinson's disease. Journal of neurology. 2013;260(12):3077-85.
19.   Araki I, Matsui M, Ozawa K, Nishimura M, Kuno S, Saida T. Relationship between urinary symptoms and disease-related parameters in multiple sclerosis. Journal of neurology. 2002;249(8):1010-5.
20.   Bloch F, Pichon B, Bonnet AM, Pichon J, Vidailhet M, Roze E, et al. Urodynamic analysis in multiple system atrophy: characterisation of detrusor-sphincter dyssynergia. Journal of neurology. 2010;257(12):1986-91.
21.   Podnar S, Trsinar B, Vodusek DB. Bladder dysfunction in patients with cauda equina lesions. Neurourology and urodynamics. 2006;25(1):23-31.

22.   Burakgazi AZ, Alsowaity B, Burakgazi ZA, Unal D, Kelly JJ. Bladder dysfunction in peripheral neuropathies. Muscle & nerve. 2012;45(1):2-8.

23.   Panicker JN, de Seze M, Fowler CJ. Rehabilitation in practice: neurogenic lower urinary tract dysfunction and its management. Clinical rehabilitation. 2010;24(7):579-89.

24.   Lawrenson R, Wyndaele JJ, Vlachonikolis I, Farmer C, Glickman S. Renal failure in patients with neurogenic lower urinary tract dysfunction. Neuroepidemiology. 2001;20(2):138-43.

25.   Castel-Lacanal E, Game X, Clanet M, Gasq D, De Boissezon X, Guillotreau J, et al. Urinary complications and risk factors in symptomatic multiple sclerosis patients. Study of a cohort of 328 patients. Neurourology and urodynamics. 2015;34(1):32-6.

26.   Urinary Incontinence in Neurological Disease: Management of Lower Urinary Tract Dysfunction in Neurological Disease. National Institute for Health and Clinical Excellence: Guidance. London2012.

27.   Ruffion A, Castro-Diaz D, Patel H, Khalaf K, Onyenwenyi A, Globe D, et al. Systematic review of the epidemiology of urinary incontinence and detrusor overactivity among patients with neurogenic overactive bladder. Neuroepidemiology. 2013;41(3-4):146-55.

28.   de Seze M, Ruffion A, Denys P, Joseph PA, Perrouin-Verbe B, Genulf. The neurogenic bladder in multiple sclerosis: review of the literature and proposal of management guidelines. Multiple sclerosis. 2007;13(7):915-28.

29.   Fowler CJ, Panicker JN, Drake M, Harris C, Harrison SC, Kirby M, et al. A UK consensus on the management of the bladder in multiple sclerosis. Journal of neurology, neurosurgery, and psychiatry. 2009;80(5):470-7.

30.   Chancellor MB, Anderson RU, Boone TB. Pharmacotherapy for neurogenic detrusor overactivity. American journal of physical medicine & rehabilitation / Association of Academic Physiatrists. 2006;85(6):536-45.

31.   De Ridder D, Van Der Aa F, Debruyne J, D'Hooghe M B, Dubois B, Guillaume D, et al. Consensus guidelines on the neurologist's role in the management of neurogenic lower urinary tract dysfunction in multiple sclerosis. Clinical neurology and neurosurgery. 2013;115(10):2033-40.

32.   Fowler CJ. Neurological disorders of micturition and their treatment. Brain : a journal of neurology. 1999;122 (Pt 7):1213-31.

33.   Panicker JN, De Seze M, Fowler CJ. Neurogenic lower urinary tract dysfunction. Handbook of clinical neurology. 2013;110:209-20.

34.   Panicker JN, Fowler CJ. Lower urinary tract dysfunction in patients with multiple sclerosis. Handbook of clinical neurology. 2015;130:371-81.

35.   Ciancio SJ, Mutchnik SE, Rivera VM, Boone TB. Urodynamic pattern changes in multiple sclerosis. Urology. 2001;57(2):239-45.

36.   Buljevac D, Flach HZ, Hop WC, Hijdra D, Laman JD, Savelkoul HF, et al. Prospective study on the relationship between infections and multiple sclerosis exacerbations. Brain : a journal of neurology. 2002;125(Pt 5):952-60.

37.   Smith M, Seth J, Batla A, Hofereiter J, Bhatia KP, Panicker JN. Nocturia in Patients With Parkinson˙s Disease. Movmnt Disords Clncl Practice. 2015.

38.   Ito T, Sakakibara R, Yasuda K, Yamamoto T, Uchiyama T, Liu Z, et al. Incomplete emptying and urinary retention in multiple-system atrophy: when does it occur and how do we manage it? Movement disorders : official journal of the Movement Disorder Society. 2006;21(6):816-23.

39.   Sakakibara R, Hattori T, Uchiyama T, Yamanishi T. Videourodynamic and sphincter motor unit potential analyses in Parkinson's disease and multiple system atrophy. Journal of neurology, neurosurgery, and psychiatry. 2001;71(5):600-6.

40.   Sakakibara R, Hattori T, Yasuda K, Yamanishi T. Micturitional disturbance after acute hemispheric stroke: analysis of the lesion site by CT and MRI. Journal of the neurological sciences. 1996;137(1):47-56.

41.   Feder M, Heller L, Tadmor R, Snir D, Solzi P, Ring H. Urinary continence after stroke: association with cystometric profile and computerised tomography findings. European neurology. 1987;27(2):101-5.

42.   Gelber DA, Good DC, Laven LJ, Verhulst SJ. Causes of urinary incontinence after acute hemispheric stroke. Stroke; a journal of cerebral circulation. 1993;24(3):378-82.

43.   Reding MJ, McDowell F. Stroke rehabilitation. Neurologic clinics. 1987;5(4):601-30.

44.   Han KS, Heo SH, Lee SJ, Jeon SH, Yoo KH. Comparison of urodynamics between ischemic and hemorrhagic stroke patients; can we suggest the category of urinary dysfunction in patients with cerebrovascular accident according to type of stroke? Neurourology and urodynamics. 2010;29(3):387-90.

45.   Tadic SD, Griffiths D, Murrin A, Schaefer W, Aizenstein HJ, Resnick NM. Brain activity during bladder filling is related to white matter structural changes in older women with urinary incontinence. NeuroImage. 2010;51(4):1294-302.

46.   Kuchel GA, Moscufo N, Guttmann CR, Zeevi N, Wakefield D, Schmidt J, et al. Localization of brain white matter hyperintensities and urinary incontinence in community-dwelling older adults. The journals of gerontology Series A, Biological sciences and medical sciences. 2009;64(8):902-9.

47.   Brittain KR, Peet SM, Castleden CM. Stroke and incontinence. Stroke; a journal of cerebral circulation. 1998;29(2):524-8.

48.   Rotar M, Blagus R, Jeromel M, Skrbec M, Trsinar B, Vodusek DB. Stroke patients who regain urinary continence in the first week after acute first-ever stroke have better prognosis than patients with persistent lower urinary tract dysfunction. Neurourology and urodynamics. 2011;30(7):1315-8.

49.   Ransmayr GN, Holliger S, Schletterer K, Heidler H, Deibl M, Poewe W, et al. Lower urinary tract symptoms in dementia with Lewy bodies, Parkinson disease, and Alzheimer disease. Neurology. 2008;70(4):299-303.

50.   Ruffion A, Castro-Diaz D, Patel H, Khalaf K, Onyenwenyi A, Globe D, et al. Systematic Review of the Epidemiology of Urinary Incontinence and Detrusor Overactivity among Patients with Neurogenic Overactive Bladder. Neuroepidemiology. 2013;41(3-4):146-55.

51.   de Groat WC. A neurologic basis for the overactive bladder. Urology. 1997;50(6A Suppl):36-52; discussion 3-6.

52.   Van Rey FS, Heesakkers JP. Applications of neurostimulation for urinary storage and voiding dysfunction in neurological patients. Urologia internationalis. 2008;81(4):373-8.

53.   Podnar S, Fowler C. Pelvic organ dysfunction following cauda equina damage. Fowler CJ, Panicker JN, Emmanuel A, editors. Cambridge: Cambridge University Press; 2010. 266/77 p.

54.   Kessler TM, Lackner J, Kiss G, Rehder P, Madersbacher H. Predictive value of initial urodynamic pattern on urinary continence in patients with myelomeningocele. Neurourology and urodynamics. 2006;25(4):361-7.

55.   Veenboer PW, de Kort LM, Chrzan RJ, de Jong TP. Urinary considerations for adult patients with spinal dysraphism. Nature reviews Urology. 2015;12(6):331-9.

56.   Gibbons CH, Freeman R. Antibody titers predict clinical features of autoimmune autonomic ganglionopathy. Autonomic neuroscience : basic & clinical. 2009;146(1-2):8-12.

57.   Sakakibara R, Uchiyama T, Asahina M, Suzuki A, Yamanishi T, Hattori T. Micturition disturbance in acute idiopathic autonomic neuropathy. Journal of neurology, neurosurgery, and psychiatry. 2004;75(2):287-91.

58.   Sakakibara R, Hattori T, Uchiyama T, Asahina M, Yamanishi T. Micturitional disturbance in pure autonomic failure. Neurology. 2000;54(2):499-501.

59.   O'Leary ML, Smith CP, Erickson JR, Eidelman BH, Chancellor MB. Neurovesical dysfunction in postural tachycardia syndrome (POTS). International urogynecology journal and pelvic floor dysfunction. 2002;13(2):139-40.

60.   Benarroch EE. Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. Mayo Clinic proceedings. 2012;87(12):1214-25.

61.   Stewart JM, Glover JL, Medow MS. Increased plasma angiotensin II in postural tachycardia syndrome (POTS) is related to reduced blood flow and blood volume. Clinical science. 2006;110(2):255-63.

62.   Karoli R, Bhat S, Fatima J, Priya S. A study of bladder dysfunction in women with type 2 diabetes mellitus. Indian journal of endocrinology and metabolism. 2014;18(4):552-7.

63.   Bansal R, Agarwal MM, Modi M, Mandal AK, Singh SK. Urodynamic profile of diabetic patients with lower urinary tract symptoms: association of diabetic cystopathy with autonomic and peripheral neuropathy. Urology. 2011;77(3):699-705.

64.   Adams D, Samuel D, Goulon-Goeau C, Nakazato M, Costa PM, Feray C, et al. The course and prognostic factors of familial amyloid polyneuropathy after liver transplantation. Brain : a journal of neurology. 2000;123 (Pt 7):1495-504.

65. Andrade MJ. Lower urinary tract dysfunction in familial amyloidotic polyneuropathy, Portuguese type. Neurourology and urodynamics. 2009;28(1):26-32.

66. Lobato L. Portuguese-type amyloidosis (transthyretin amyloidosis, ATTR V30M). Journal of nephrology. 2003;16(3):438-42.

67. Ito T, Sakakibara R, Yamamoto T, Uchiyama T, Liu Z, Asahina M, et al. Urinary dysfunction and autonomic control in amyloid neuropathy. Clinical autonomic research : official journal of the Clinical Autonomic Research Society. 2006;16(1):66-71.

68. Sakakibara R, Hattori T, Kuwabara S, Yamanishi T, Yasuda K. Micturitional disturbance in patients with Guillain-Barre syndrome. Journal of neurology, neurosurgery, and psychiatry. 1997;63(5):649-53.

69. Sakakibara R, Hattori T, Tojo M, Yamanishi T, Yasuda K, Hirayama K. Micturitional disturbance in myotonic dystrophy. Journal of the autonomic nervous system. 1995;52(1):17-21.

70. Dickson MJ, Massiah N, Church E. Urinary stress incontinence as the presenting feature of myotonic dystrophy. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology. 2012;32(1):102.

71. Osman NI, Chapple CR. Fowler's syndrome--a cause of unexplained urinary retention in young women? Nature reviews Urology. 2014;11(2):87-98.

72. Swinn MJ, Wiseman OJ, Lowe E, Fowler CJ. The cause and natural history of isolated urinary retention in young women. The Journal of urology. 2002;167(1):151-6.

73. Fowlis GA, Waters J, Williams G. The cost effectiveness of combined rapid tests (Multistix) in screening for urinary tract infections. Journal of the Royal Society of Medicine. 1994;87(11):681-2.

74. Bacsu CD, Chan L, Tse V. Diagnosing detrusor sphincter dyssynergia in the neurological patient. BJU international. 2012;109 Suppl 3:31-4.

75. Vodusek DB. Sphincter EMG and differential diagnosis of multiple system atrophy. Movement disorders : official journal of the Movement Disorder Society. 2001;16(4):600-7.

76. Panicker JN, Seth JH, Khan S, Gonzales G, Haslam C, Kessler TM, et al. Open-label study evaluating outpatient urethral sphincter injections of onabotulinumtoxinA to treat women with urinary retention due to a primary disorder of sphincter relaxation (Fowler's syndrome). BJU international. 2015.

77. Podnar S. Predictive value of the penilo-cavernosus reflex. Neurourology and urodynamics. 2009;28(5):390-4.

78. Stohrer M, Blok B, Castro-Diaz D, Chartier-Kastler E, Del Popolo G, Kramer G, et al. EAU guidelines on neurogenic lower urinary tract dysfunction. European urology. 2009;56(1):81-8.

79. Madhuvrata P, Singh M, Hasafa Z, Abdel-Fattah M. Anticholinergic drugs for adult neurogenic detrusor overactivity: a systematic review and meta-analysis. European urology. 2012;62(5):816-30.

80. Giannantoni A, Proietti S, Costantini E, Gubbiotti M, Rossi De Vermandois J, Porena M. OnabotulinumtoxinA intravesical treatment in patients affected by overactive bladder syndrome: best practice in real-life management. Urologia. 2015;82(3):179-83.

81. Seth JH, Haslam C, Panicker JN. Ensuring patient adherence to clean intermittent self-catheterization. Patient preference and adherence. 2014;8:191-8.

82. Kessler TM, Bachmann LM, Minder C, Lohrer D, Umbehr M, Schunemann HJ, et al. Adverse event assessment of antimuscarinics for treating overactive bladder: a network meta-analytic approach. PloS one. 2011;6(2):e16718.

83. Yamaguchi O. Latest treatment for lower urinary tract dysfunction: therapeutic agents and mechanism of action. International journal of urology : official journal of the Japanese Urological Association. 2013;20(1):28-39.

84. Krause P, Fuhr U, Schnitker J, Albrecht U, Stein R, Rubenwolf P. Pharmacokinetics of intravesical versus oral oxybutynin in healthy adults: results of an open label, randomized, prospective clinical study. The Journal of urology. 2013;190(5):1791-7.

85. Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A medium-term analysis of the subjective efficacy of treatment for women with detrusor instability and low bladder compliance. British journal of obstetrics and gynaecology. 1997;104(9):988-93.

86. Zia A, Kamaruzzaman S, Myint PK, Tan MP. Anticholinergic burden is associated with recurrent and injurious falls in older individuals. Maturitas. 2016;84:32-7.

87.   Sakel M, Boukouvalas A, Buono R, Moten M, Mirza F, Chan WY, et al. Does anticholinergics drug burden relate to global neuro-disability outcome measures and length of hospital stay? Brain injury : [BI]. 2015;29(12):1426-30.

88.   Chancellor MB, Staskin DR, Kay GG, Sandage BW, Oefelein MG, Tsao JW. Blood-brain barrier permeation and efflux exclusion of anticholinergics used in the treatment of overactive bladder. Drugs & aging. 2012;29(4):259-73.

89.   Gaziev G, Topazio L, Iacovelli V, Asimakopoulos A, Di Santo A, De Nunzio C, et al. Percutaneous Tibial Nerve Stimulation (PTNS) efficacy in the treatment of lower urinary tract dysfunctions: a systematic review. BMC urology. 2013;13:61.

90.   Phe V, Mukhtar B, Couchman A, Grewal M, Hamid R, Ockrim J, et al. [In Process Citation]. Progres en urologie : journal de l'Association francaise d'urologie et de la Societe francaise d'urologie. 2015;25(13):845-6.

91.   Wu T, Duan X, Cao CX, Peng CD, Bu SY, Wang KJ. The role of mirabegron in overactive bladder: a systematic review and meta-analysis. Urologia internationalis. 2014;93(3):326-37.

92.   Bosma R, Wynia K, Havlikova E, De Keyser J, Middel B. Efficacy of desmopressin in patients with multiple sclerosis suffering from bladder dysfunction: a meta-analysis. Acta neurologica Scandinavica. 2005;112(1):1-5.

93.   Kabay SC, Yucel M, Kabay S. Acute effect of posterior tibial nerve stimulation on neurogenic detrusor overactivity in patients with multiple sclerosis: urodynamic study. Urology. 2008;71(4):641-5.

94.   Peters KM, Macdiarmid SA, Wooldridge LS, Leong FC, Shobeiri SA, Rovner ES, et al. Randomized trial of percutaneous tibial nerve stimulation versus extended-release tolterodine: results from the overactive bladder innovative therapy trial. J Urol. 2009;182(3):1055-61.

95.   Peters KM, Carrico DJ, Perez-Marrero RA, Khan AU, Wooldridge LS, Davis GL, et al. Randomized trial of percutaneous tibial nerve stimulation versus Sham efficacy in the treatment of overactive bladder syndrome: results from the SUmiT trial. J Urol. 2010;183(4):1438-43.

96.   de Seze M, Raibaut P, Gallien P, Even-Schneider A, Denys P, Bonniaud V, et al. Transcutaneous posterior tibial nerve stimulation for treatment of the overactive bladder syndrome in multiple sclerosis: results of a multicenter prospective study. Neurourology and urodynamics. 2011;30(3):306-11.

97.   Monteiro ES, de Carvalho LB, Fukujima MM, Lora MI, do Prado GF. Electrical stimulation of the posterior tibialis nerve improves symptoms of poststroke neurogenic overactive bladder in men: a randomized controlled trial. Urology. 2014;84(3):509-14.

98.   Kessler TM, La Framboise D, Trelle S, Fowler CJ, Kiss G, Pannek J, et al. Sacral neuromodulation for neurogenic lower urinary tract dysfunction: systematic review and meta-analysis. European urology. 2010;58(6):865-74.

99.   Datta SN, Chaliha C, Singh A, Gonzales G, Mishra VC, Kavia RB, et al. Sacral neurostimulation for urinary retention: 10-year experience from one UK centre. BJU international. 2008;101(2):192-6.

100.   Cruz F, Herschorn S, Aliotta P, Brin M, Thompson C, Lam W, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. European urology. 2011;60(4):742-50.

101.   Ginsberg D, Gousse A, Keppenne V, Sievert KD, Thompson C, Lam W, et al. Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. The Journal of urology. 2012;187(6):2131-9.

102.   Groen J, Pannek J, Castro Diaz D, Del Popolo G, Gross T, Hamid R, et al. Summary of European Association of Urology (EAU) Guidelines on Neuro-Urology. European urology. 2015.

103.   Naumann M, So Y, Argoff CE, Childers MK, Dykstra DD, Gronseth GS, et al. Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008;70(19):1707-14.

List of tables and figures

Table 1 Diagnostic evaluation of neurogenic lower urinary tract dysfunction
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.