



Roy, H. A., Nettleton, J., Blain, C., Dalton, C., Farhan, B., Fernandes, A., Georgopoulos, P., Klepsch, S., Lavelle, J., Martinelli, E., Panicker, J. N., Radoja, I., Rapidi, C-A., Silva, R. P. E., Tudor, K., Wagg, A. S., & Drake, M. J. (2020). Assessment of patients with lower urinary tract symptoms where an undiagnosed neurological disease is suspected: report from an International Continence Society consensus working group. *Neurourology and Urodynamics*.
<https://doi.org/10.1002/nau.24469>

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**SOUNDING BOARD**

Assessment of patients with lower urinary tract symptoms where an undiagnosed neurological disease is suspected: A report from an International Continence Society consensus working group

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Abstract

Aim: Lower urinary tract symptoms (LUTS) are a common urological referral, which sometimes can have a neurological basis in a patient with no formally diagnosed neurological disease ("occult neurology"). Early identification and

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specialist input is needed to avoid bad LUTS outcomes, and to initiate suitable neurological management.

Methods: The International Continence Society established a neurological working group to consider: Which neurological conditions may include LUTS as an early feature? What diagnostic evaluations should be undertaken in the LUTS clinic? A shortlist of conditions was drawn up by expert consensus and discussed at the annual congress of the International Neurourology Society. A multidisciplinary working group then generated recommendations for identifying clinical features and management.

Results: The relevant conditions are multiple sclerosis, multiple system atrophy, normal pressure hydrocephalus, early dementia, Parkinsonian syndromes (including early Parkinson's Disease and Multiple System Atrophy) and spinal cord disorders (including spina bifida occulta with tethered cord, and spinal stenosis). In LUTS clinics, the need is to identify additional atypical features; new onset severe LUTS (excluding infection), unusual aspects (eg, enuresis without chronic retention) or "suspicious" symptoms (eg, numbness, weakness, speech disturbance, gait disturbance, memory loss/cognitive impairment, and autonomic symptoms). Where occult neurology is suspected, healthcare professionals need to undertake early appropriate referral; central nervous system imaging booked from LUTS clinic is not recommended.

Conclusions: Occult neurology is an uncommon underlying cause of LUTS, but it is essential to intervene promptly if suspected, and to establish suitable management pathways.

KEYWORDS

incontinence, lower urinary tract symptoms, neurology, neurourology, overactive bladder, overactive bladder

1 | INTRODUCTION

Lower urinary tract symptoms (LUTS) are highly prevalent and a major cause of urological referral. The majority reflect uncomplicated presentations, such as overactive bladder (OAB) or benign prostate enlargement. LUTS are also a significant feature in neurological disease.¹ Notably, there are some neurological conditions where LUTS can be an early symptom in the presentation of the disease. Consequently, a situation can arise where LUTS assessment might be requested and the underlying neurological disease is still undiagnosed. Two major dangers inherent in failing to identify an undiagnosed neurological etiology are risks of deterioration of the neurological conditions, and of poor outcomes for LUTS treatment, potentially due to inappropriate surgery or symptom deterioration. Suitable neurological management for the underlying condition is needed

- to establish a correct diagnosis and prognosis,

- to actively manage the neurological condition by obtaining early specialist input,
- to minimize disease progression through early treatment (especially for multiple sclerosis [MS]),
- to avoid predictable adverse events during invasive diagnostics and after surgical therapy,
- for the maintenance of a patient-centered approach to management, and
- for patients to adapt their life according to prognosis.

Healthcare professionals (HCPs) from various disciplines, notably doctors, nurses, continence advisors, and physiotherapists, may be responsible for initial assessment of these patients. Accordingly, these HCPs need to remain alert to patients with subtle symptoms and clinical signs that should be further explored and who might need an additional referral to exclude or identify an, as yet, undiagnosed neurological condition. For this to be effective, they must be aware of potential pathways

of evaluation, to ensure the possibility is appropriately addressed.

This consensus considers situations where LUTS could be a presenting complaint preceding the identification of an underlying neurological disease,² hereafter referred to as “occult neurology.” This consensus document gives brief outlines of neurological conditions in which LUTS arise relatively early in the disease course, and presents an approach to assessment of a patient where the receiving clinician suspects there could be an undiagnosed neurological condition.

2 | METHODS

The International Continence Society (ICS) established a working group whose remit was to consider:

1. Which neurological conditions may include LUTS as an early feature?
2. What diagnostic evaluations should be undertaken in the LUTS clinic, and which should be left to specialist expertise?

The qualitative method of nominal group technique was utilized to generate initial content (key relevant conditions) in response to the remit. An iterative group dialogue for a panel of neurological and neurosurgical specialists was used to draw up a shortlist of conditions, with two rounds of blind voting to finalize the list. The list was then presented for open discussion at the annual congress of the International Neurourology Society, Istanbul, 2020. The ICS then established a multidisciplinary working group to generate recommendations for identifying clinical features and management, which worked remotely due to the widely dispersed international representation.

3 | RESULTS

3.1 | Neurological conditions where LUTS can be an early feature

The following conditions may present for LUTS assessment before a neurological condition has been recognized, because LUTS are potentially an early feature in the disease course. The underlying processes commonly involve demyelination, neurodegeneration, or developmental abnormality, for which some archetypal conditions are listed in Table 1. The main conditions responsible include the following.

3.1.1 | MS and related neuroinflammatory disorders

The most common progressive neurological disease affecting younger people with onset around 20 to 40 years of age. It is more common in women than men. It can impair function of any part of the central nervous system by demyelination and axonal loss (Table 1). It is a progressive condition, but the rate and pattern of progression varies (the progressive clinical course usually becoming evident after 10-20 years after diagnosis). Commonly, there is abrupt deterioration (relapse) lasting days to weeks as a new demyelination event starts, followed by (often incomplete) improvement. Neurological symptoms are typically monocular loss of vision, double vision, sensory loss, weakness, and ataxia. A variety of disease-modifying medications are available. The exact pattern of LUTS is diverse, while severe incontinence is mainly seen in the late stages of the disease.

Transverse myelitis due to other inflammatory causes can occasionally present as urinary retention with few neurological signs because of predilection for conus involvement, particularly when associated with antibodies against Myelin oligodendrocyte glycoprotein (MOG antibody transverse myelitis); persisting urogenital and bowel dysfunction is common despite motor recovery at followup.¹⁵

3.1.2 | Multiple system atrophy

A progressive sporadic adult-onset neurodegenerative disorder (Table 1). Prevalence is 8 per 100 000 among people older than 40 years of age. It affects men and women equally and has an average age onset of approximately 55 to 60 years. The mean life expectancy is 6 to 10 years following diagnosis. Clinical symptoms are subdivided into extrapyramidal, pyramidal, cerebellar, and autonomic symptoms (notably postural hypotension). Extrapyramidal symptoms include bradykinesia, rigidity, and postural instability, resembling Parkinson's disease (PD). Nonmotor symptoms, such as sleep and cognitive disorders, respiratory problems, and emotional/behavioral symptoms, might also occur during disease development. The different symptoms can be used to categorize multiple system atrophy (MSA) into the Parkinsonian subtype (MSA-P) and the cerebellar subtype (MSA-C). MSA-P predominates in Western countries, while MSA-C is more common in Japan. The condition may initially present with bladder dysfunction, particularly urinary retention.^{16,17} For men, erectile dysfunction (ED)¹⁸ is commonly an earlier feature than LUTS; the

TABLE 1 Archetypal neurological conditions, which may include lower urinary tract symptoms as an early feature

Classification (mechanism)	Archetypal condition	Early urological features	Early neurological features	Epidemiology	Similar conditions
Demyelinating disorder	Multiple sclerosis	Urinary urgency (62%-65%), frequency (50%), UUI (45%), nocturia (33%). ^{3,4} SUI 31%. ED 53%. UDS; DO with DSD, detrusor underactivity.	May report unilateral painful loss of vision, paraesthesias or motor deficit ⁶	Peak onset: 30-40 y. Rare before puberty and in the elderly. Estimated incidence (Europe) <20 - >200/100 000 ⁷	Transverse myelitis. Neuromyelitis optica
Focal CNS white matter demyelination		Fecal incontinence and/or constipation (40%) ⁵		Median time to death 30 y from onset depending on subtype ⁶	
Neurodegenerative disorder	Multiple system atrophy	Difficulty voiding/nocturia are most common, also urgency and UUI ⁸ ED is an early feature	Postural hypotension and incoordination are common presenting symptoms. Slow movement, slurred speech, poor balance, and fainting (syncope) also commonly occur	Mean age of onset is 54 y, with survival 7-9 y. UK prevalence 4.4/100 000 ⁹	Alzheimer's dementia. Parkinson's disease. Progressive supranuclear palsy
Extrapyramidal, autonomic, and cerebellar progressive degeneration		In cerebellar MSA, 83% have ED at diagnosis, 58% have urinary incontinence and 50% have OAB			
Developmental disorder	Occult spinal dysraphism, including SBO and tethered cord	Variable features. SBO, OAB, ¹⁰ incontinence, enuresis. With tethered cord, urgency and UUI are common. UDS; DO 42%, low compliance 67%. ¹¹ DSD and sensory abnormalities can occur ¹²	SBO often asymptomatic. Dimple/hair tuft on the back. Maybe posture changes, with altered spinal curvature. Tethered cord can include impaired lower limb or bowel function ¹³	Congenital, reducing prevalence. ¹⁴ Unlikely to influence survival	Syringomyelia (developmental or acquired)

Abbreviations: CNS, central nervous system; DO, detrusor overactivity; DSD, detrusor sphincter dyssynergia; ED, erectile dysfunction; MSA, multiple system atrophy; NPH, normal pressure hydrocephalus; OAB, overactive bladder; SBO, spina bifida occulta; SUI, stress urinary incontinence; UDS, Urodynamics; UUI, urgency urinary incontinence.

reviewing HCP considering this possibility needs to enquire about ED, since men commonly do not report the symptom unless the topic is raised.

3.1.3 | Parkinson's disease

A neurodegenerative condition with the key motor symptoms of tremor, rigidity, and bradykinesia affecting motor control, which is also associated with prominent nonmotor symptoms. Early PD can cause storage LUTS, and motor symptoms may be mild. A useful feature to look out for is a unilateral low frequency pill-rolling tremor affecting the upper limb (or leg). Established PD manifests obvious motor features (shaking, rigidity, slowness of movement, and difficulty with walking); once it has reached this stage, PD will generally have been diagnosed.

PD patients usually report nocturia, urgency, and difficulty voiding and present with detrusor overactivity (DO) on urodynamics.^{19,20} Voiding dysfunction increases with neurological disability (for men and women), correlating with the extent of dopamine depletion.^{21,22} In some male patients, benign prostatic obstruction can occur concomitantly with PD, and therefore selection of patient for possible prostate surgery should be done with great care to avoid possible urinary incontinence.

3.1.4 | Normal pressure hydrocephalus

Normal pressure hydrocephalus (NPH) is characterized by communicating enlargement of cerebrospinal fluid (CSF) ventricles, with normal intraventricular pressures. The enlargement is associated with stretching of periventricular fibers of the corticospinal tract in the brain, which impairs bladder control. DO is a typical finding on urodynamics. As it is substantially underdiagnosed, the actual worldwide incidence and prevalence have not been defined; in Japan it was estimated at around 1% of older adults (over 65).²³ The classic triad is abnormal broad-based shuffling gait, urinary incontinence and dementia (short term memory impairment), but about half present with gait abnormality only as the initial feature. There may be only mild cognitive impairment at the time the patient starts to experience urinary symptoms. Treatment is with placement of a ventriculoperitoneal shunt by a neurosurgeon and can lead to symptom resolution/prevention of progression.

3.1.5 | Dementia

A group of neurodegenerative conditions (including Alzheimer's disease, vascular dementia, dementia with

Lewy bodies and frontotemporal dementia), with wide-ranging effects on memory, cognition, and personality. LUTS are more common in people living with dementia than those without dementia.²⁴ In certain forms of dementia, such as dementia with Lewy bodies, LUTS are more likely to be an early feature of the disease. LUTS tend to be a later feature in Alzheimer's disease.²⁵

3.1.6 | Spinal cord conditions

A range of situations may affect the spinal cord directly (Table 1), while degenerative spine conditions may affect the spinal cord secondarily, for example, by causing lumbar spinal stenosis or cervical myelopathy. There may be little in the way of localizing symptoms. The archetypal condition is spina bifida occulta (SBO) and tethered cord, in which a developmental abnormality fixes the lower part of the spinal cord, placing it at risk by stretching and distortion as the person grows. Affected patients are often asymptomatic until late childhood or adulthood, then presenting with back pain and LUTS. Syringomyelia is a problem with the central CSF canal in the spinal cord, which can lead to compression of the surrounding spinal cord tracts; this can occur in SBO.

Other conditions include:

- a tumor of the spinal cord or vertebral column and
- spinal stenosis, leading to claudication and LUTS.

Prolapsed intervertebral disc (lumbar disc prolapse) is usually easily diagnosed from the association of urinary retention (painless) with severe back pain, nerve root pain (eg, sciatica), loss of range of movement, and bowel dysfunction. However, back pain is sometimes not prominent, notably where there is central disc prolapse with little impingement on the spinal roots.

3.2 | Evaluation where there is a possible occult neurological mechanism

For the HCP, the fundamental issue is to identify a situation where LUTS are present alongside other unexplained symptoms, which are atypical for a LUTS presentation. This must then trigger an onward referral to an appropriate specialist (neurology or neurosurgery), or an alert to the patient's primary care physician. HCPs in the LUTS clinic are not required to make the neurological diagnosis, but they must remain vigilant to the possibility of a neurological disorder and seek relevant expertise (neurological consultation) where needed.

Situations in which HCPs should suspect possible occult neurology:

- New onset severe LUTS not caused by urinary tract infection.
- Association with unusual features not typically seen in LUTS presentations.
- Presence of other “suspicious” symptoms, such as altered speech, vision, or balance.

3.2.1 | History and examination

All consultations on LUTS involve a basic assessment undertaken according to the relevant guidelines.^{18,26,27} The details of basic LUTS assessment are not given in detail here, but guidelines include assessment of:

- Evaluation of the severity and bother associated with each LUTS.
- Consideration of possible pathophysiology and differential diagnosis.

- Exclusion of features, which are possible indicators of serious underlying mechanism, for example, infection/inflammation, or malignancy.
- Concomitant bowel or sexual dysfunction.

Any neurological feature might, but not necessarily, have a similar time course to the LUTS. If the initial impression suggests there could be an occult neurological problem, the practitioner should evaluate key indicators that may increase the index of suspicion. A summary is presented in Figure 1. This assessment includes looking for:

1. Urological symptoms or findings
 - (a) Severe/rapid onset OAB maybe with urgency incontinence.
 - (b) Difficulty initiating voiding and prolonged duration. Flow rate test may suggest straining, and there may be a post void residual.
 - (c) Changes in bladder sensation, including reduced or absent bladder sensations.
 - (d) Dysuria in the absence of urinary tract infection (this may indicate detrusor sphincter dyssynergia).

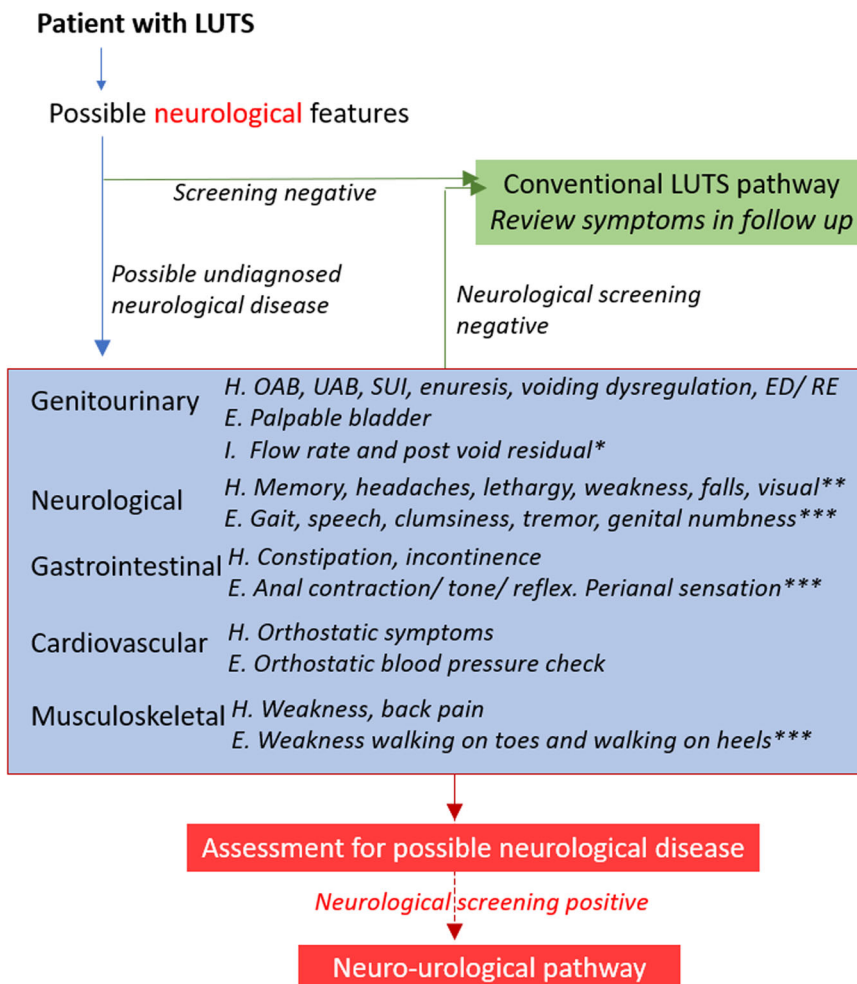


FIGURE 1 Summary of key clinical evaluations in LUTS clinic in the event of a possible undiagnosed neurological disease. E, examination; ED, erectile dysfunction; H, history; I, investigation; LUTS, Lower urinary tract symptoms; RE, retrograde ejaculation. *Flow rate test may suggest straining/post void residual. **Double vision/loss of acuity. Multiple sclerosis can cause transient unilateral loss of vision some years previously. ***Nerve supply is from the sacral spinal cord, and is a consequence of weak plantar flexion and dorsiflexion

2. Unusual urological symptoms or examination findings
 - (a) Enuresis.
 - (b) Voiding dysregulation, that is, urination in situations, which are generally regarded as socially inappropriate, such as while still fully dressed, or in a public setting away from toilet facilities.²⁸
 - (c) Involuntary voiding, that is, sporadic bladder emptying when awake, without intention to void.²⁸
3. Indicators of lower urinary tract muscle weakness
 - (a) Abdominal straining for voiding.
 - (b) Stress urinary incontinence (and possibly fecal incontinence), particularly in nulliparous women and younger men with no previous lower urinary tract surgery.
 - (c) Retrograde ejaculation.
4. Symptoms or findings in other organ systems, which are heavily dependent on neurological control or likely to be affected by a relevant condition
 - (a) Gastrointestinal, for example gastroparesis, constipation, reduced anal tone.
 - (b) Cardiovascular for example orthostatic hypotension.
 - (c) Musculoskeletal.
 - (d) Autonomic, for example loss of salivation, loss of sweating, and impaired thermoregulation. In PD and MSA there may be drooling (sialorrhoea).
5. Features of one of the neurological conditions listed above
 - (a) MS; motor or sensory deficit, transient unilateral visual disturbance (previous optic neuritis).
 - (b) MSA; ED, orthostatic hypotension, unilateral tremor, slow movement, postural instability.
 - (c) PD; Stooped posture, lack of facial expression, quiet and hoarse speech, slowness of movement especially visible during walking, and shaking (tremor)—more often seen unilaterally in the hand while walking or at rest and classically “pill-rolling” in nature.
 - (d) NPH; gait disturbance, urinary incontinence, cognitive impairment.
 - (e) Dementia; memory and personality changes.
 - (f) Spinal cord problem; limb weakness, sensory changes, back pain.

Observation of or assessment for gait, tremor, speech, and clumsiness can easily be made in clinic. It is worth noting any history of essential tremor, as this might be confused with a parkinsonian tremor, but does not need neurology referral. Essential tremor typically presents with bilateral postural hand tremor and can also affect the head and voice, has a family history, and improves with beta blockers or alcohol.

3.3 | Additional assessment for possible neurological disease

In the event that history and examination are consistent with the possibility of occult neurological disease, the responsible practitioner needs to consider the following.

1. Steps to confirm or exclude the neurological diagnosis:
 - (a) The HCP treating LUTS should refer for a formal specialist opinion. Direct referral is preferable, for reliable and prompt assessment.
 - (b) The consensus panel does not recommend the use of MRI scanning or other imaging modality from the LUTS clinic. This is best arranged from the neurology clinic, in consultation between the neurology and neuroradiology services, because it is crucial that the correct part of the neuraxis is scanned and the appropriate settings are used.
 - (c) The referral should be made immediately, without waiting for the results of urodynamic testing (due to the potential delay). If urodynamics have already been done, the results can be included in the referral. Subsequent urodynamic tests can be forwarded when available.
 - (d) Neurological consultation and investigation following referral may not necessarily attain a confirmatory diagnosis; urological follow up is nonetheless appropriate, and re-referral to neurology may be needed in the event of subsequent change in symptoms or apparent deterioration.
2. Adaptations of the urological assessment pathway:
 - (a) The role of urodynamic testing should be re-evaluated; if not already done, they may be delayed pending receipt of the neurological evaluation, to decide how the test should be run. In this situation, it is appropriate that the test is directly overseen by the urologist.
 - (b) Definitive LUTS management should be delayed until the result of neurological assessment is available. If the neurological finding is positive, the patient should be moved to a neuro-urological care pathway for example.^{1,29} If negative, standard LUTS pathways can be followed, but this should be reconsidered if new symptoms subsequently emerge.

3.4 | Additional considerations

In several situations, factors affecting lower urinary tract function may be suggested by features in the medical history or physical examination:

1. Functional neurological disorder (FND)³⁰ is suggested by symptoms such as limb weakness and nonepileptic attacks, particularly in women with chronic idiopathic urinary retention. FNDs may be accompanied by psychological comorbidities such as affective disorders (eg, depression and anxiety) and other functional syndromes, such as fibromyalgia or irritable bowel syndrome. Screening tools are available for evaluating psychological/psychiatric morbidities in adults.³⁰
2. Centrally active medications may cause urinary retention (eg, opioids, antipsychotics, antidepressant agents, anticholinergic respiratory agents, alpha-adrenoceptor agonists and benzodiazepines³¹) or enuresis (eg, choline esterase inhibitors (such as rivastigmine or, donepezil) and antipsychotics³²).
3. Scrutiny of medical history and current medication, to consider conditions that may already be diagnosed in the patient, but whose implication for LUTS has not been recognized. Potentially relevant conditions include (list not complete):
 - (a) Previous pelvic or retroperitoneal surgery (in case of damage to peripheral lower urinary tract nerves). This may make the patient reliant on abdominal straining for bladder emptying.
 - (b) Delayed second stage of labor (pudendal nerve damage).
 - (c) Previous traumatic brain injury.
 - (d) Previous spine hyperextension without fracture.
 - (e) Neuropathies for example vitamin B₁₂ deficiency, diabetic neuropathy (but not uncomplicated diabetes mellitus), systemic lupus erythematosus, Sjogren's syndrome, amyloid, myasthenia gravis, or Guillain Barre syndrome. Severe peripheral neuropathies can cause gait disturbance with sensory ataxia.
 - (f) Herpes zoster infection of sacral dermatomes with shingles (this is very rare).
 - (g) Active genital herpes affecting sacral levels.

If any of these is identified, they should be considered in case they represent a contributory factor underlying LUTS. If they appear to be causative:

- The possibility of occult neurological disease is reduced, and the priority of neurological assessment should be reviewed accordingly.
- The urological assessment should be designed to reflect the complexity of the LUTS mechanisms.

4 | CONCLUSIONS

There is a large catalog of neurological diseases, but relatively few affect urinary tract function early in their

course. MS, MSA, PD, NPH, some types of dementia or specific spinal cord pathologies are particularly relevant. Thus, an HCP seeing a patient with LUTS should remain alert to features indicating the possibility of an underlying neurological condition. If suspected, specialist input should be sought before requesting diagnostic imaging, and the LUTS management pathway should be adapted.

ACKNOWLEDGMENTS

JNP is supported in part by funding from the United Kingdom's Department of Health NIHR Biomedical Research Centres funding scheme.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Roy HA, Nettleton J, Blain C, et al. Assessment of patients with lower urinary tract symptoms where an undiagnosed neurological disease is suspected: A report from an International Continence Society consensus working group. *Neurourology and Urodynamics*. 2020;1-9. <https://doi.org/10.1002/nau.24469>