

Assessment of patients with lower urinary tract symptoms where an undiagnosed neurological disease is suspected; 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 specialist input is needed to avoid bad LUTS outcomes, and to initiate suitable neurological management.

Methods

The International Continence Society (ICS) established a neurological working group to consider;

1. Which neurological conditions may include LUTS as an early feature
2. 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 (INUS) held in Istanbul in January 2020 -urological

Society meeting. A multidisciplinary working group then generated recommendations for identifying clinical features and management.

Results

The neurological panel identified the relevant conditions as multiple sclerosis (MS), multiple system atrophy (MSA), normal pressure hydrocephalus (NPH), 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 features which are atypical for a LUTS presentation; new onset severe LUTS (excluding infection), unusual aspects (e.g. enuresis without chronic retention) or "suspicious" symptoms (e.g. 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 (CNS) 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.

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 aetiology are risks of deterioration and of poor outcomes for LUTS treatment. 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 minimise disease progression through early treatment (especially for MS)
- For the maintenance of a patient centred approach to management
- 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. In order 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.

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 (NGT) was utilised to generate initial content (key relevant conditions) in response to the remit. 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 finalise the list. The list was then presented for open discussion at the annual congress of the International Neurourology Society (INUS) International Neuro-urological Society meeting (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.

Results

Neurological conditions where LUTS are an early feature

The following conditions may present for LUTS assessment before a neurological condition has been recognised, because LUTS are potentially an early feature in the disease course.

Multiple sclerosis (MS) and other neuroinflammatory disorders. The most common progressive neurological disease affecting younger people, it can impair function of any part of the central nervous system by demyelination (Table 1). Onset peaks at around 30 to 40 years, and it is more common in women than men. It is a progressive condition, but the rate and pattern of progression varies (the progression pattern only becoming evident with subsequent follow up after diagnosis). Commonly, there can be an abrupt deterioration (relapse) as a new demyelination event starts, and subsequently there is often (incomplete) improvement. Because any part of the neuraxis may be affected, the exact pattern of LUTS and the associated non-urological features are potentially diverse. 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 follow up**. (citation- Vivien Li, Prasad Malladi, Sara Simeoni, Mahreen Pakzad, Rosie Everett, Chanjira Satukijchai, Maria Isabel Leite, Jacqueline Palace, and Jalesh N Panicker. A clinico-neurophysiological study of urogenital dysfunction in MOG-antibody transverse myelitis. Accepted in Neurology; 2020.)

Multiple system atrophy (MSA). 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 55–60 years. The mean life expectancy is 6–10 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 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 (3, 4). For men, erectile dysfunction (ED) (5) is commonly an earlier feature than LUTS; the reviewing HCP considering this possibility needs to enquire about ED, since men commonly do not report the symptom unless the topic is raised.

Parkinson's disease (PD). A neurodegenerative condition with the key motor symptoms of tremor, rigidity and bradykinesia affecting motor control, which is also associated with prominent non-motor 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), with a frequency a little lower than in more established cases of PD (frequency approximately 2Hz, compared with typical PD tremor frequency of 3 Hz). 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 (6, 7). Voiding dysfunction increases with neurological disability (for men and women), correlating with the extent of dopamine depletion (8, 9). 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.

Normal pressure hydrocephalus (NPH). NPH is characterised 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. Since 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) (10). 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.

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 (11). 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 (12).

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, e.g. by causing lumbar spinal stenosis. There may be little in the way of localising 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 tumour of the spinal cord or vertebral column
- 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 (e.g. 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.

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.

History and Examination. All consultations on LUTS involve a basic assessment undertaken according to the relevant guidelines (5, 13, 14). 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, e.g. 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 bladder sensations
 - d) Dysuria in the absence of urinary tract infection (this may indicate detrusor sphincter dyssynergia)
2. Unusual urological symptoms or examination findings
 - a) Enuresis
 - b) Voiding dysregulation i.e. 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 (15)
 - c) Involuntary voiding i.e. sporadic bladder emptying when awake, without intention to void (15)
3. Indicators of lower urinary tract muscle weakness
 - a) Abdominal straining for voiding
 - b) Stress urinary incontinence (and possibly faecal 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, e.g. gastroparesis, constipation, reduced anal tone
 - b) Cardiovascular e.g. orthostatic hypotension
 - c) Musculoskeletal
 - d) Autonomic, e.g. 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
 - a) 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
 - c) NPH; gait disturbance, urinary incontinence, cognitive impairment
 - d) Dementia; memory and personality changes
 - e) 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 neurological referral. Essential tremor typically has a frequency of 8Hz, affects the head and voice, has a family history, and improves with beta blockers or alcohol.

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;

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.
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, in order 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 e.g. (1, 16). If negative, standard LUTS pathways can be followed, but this should be reconsidered if new symptoms subsequently emerge

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) (17) 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 co-morbidities such as affective disorders (e.g. 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 (17)
2. Centrally active medications may cause urinary retention (e.g. opioids, antipsychotics, antidepressant agents, anticholinergic respiratory agents, alpha-adrenoceptor agonists and benzodiazepines (18)) or enuresis (e.g. choline esterase inhibitors (such as rivastigmine or, donepezil) and antipsychotics (19))
3. Scrutiny of past medical history and current medication, to consider conditions that may already be diagnosed in this patient, but whose implication for LUTS has not been recognised. Potentially relevant conditions include (list not complete);
 - a) Previous pelvic or retroperitoneal surgery (in case of damage to peripheral lower urinary tract nerves)
 - b) Delayed second stage of labour (pudendal nerve damage)
 - c) Previous traumatic brain injury
 - d) Neuropathies e.g. 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
 - e) Herpes zoster infection of sacral dermatomes with shingles (this is very rare)
 - f) 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

Conclusions

There is a large catalogue of neurological diseases, but relatively few affect urinary tract function early in their course. MS, MSA, PD, NPH, some types of dementia or a spinal cord problem are particularly relevant. Thus an HCP seeing a patient with LUTS should remain alert to features indicating the possibility of an underlying neurological mechanism. If suspected, specialist input should be sought prior to requesting diagnostic imaging, and the LUTS management pathway should be adapted.

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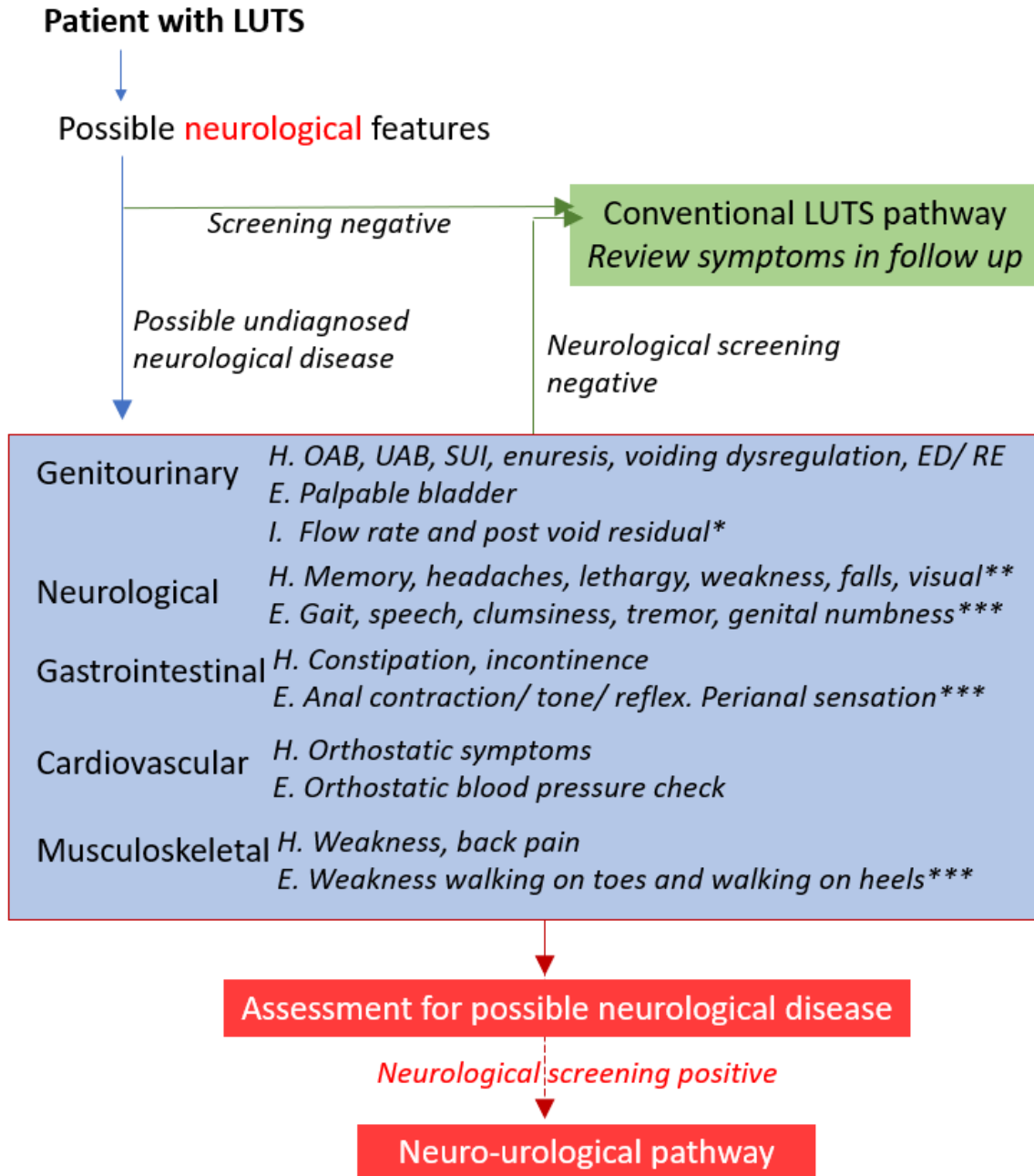
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Figure 1. Summary of key clinical evaluations in LUTS clinic in the event of a possible undiagnosed neurological disease. E: Examination; ED: Erectile dysfunction; H: History; I: Investigation; RE: Retrograde ejaculation. * Flow rate test may suggest straining/ post void residual. **Double vision/ loss of acuity. MS 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



Condition	Classification, mechanism	Early urological features	Early neurological features	Epidemiology	Similar conditions
Multiple sclerosis	<i>Demyelinating disorder;</i> Focal CNS white matter demyelination	Urinary urgency (62-65%), frequency (50%), UUI (45%), nocturia (33%) (20, 21). SUI 31%. ED 53%. UDS; DO with DSD, detrusor underactivity. Fecal incontinence and/or constipation (40%) (22)	May report unilateral painful loss of vision, paraesthesias or motor deficit (23)	Peak onset: 30-40 years. Rare before puberty and in the elderly. Male: female ratio: 2:1 (Manji et al). Estimated incidence (Europe) <20 - >200/ 100,000 (24) Median time to death 30 years from onset depending on subtype (23)	Transverse myelitis. Neuromyelitis optica.
Multiple system atrophy	<i>Neuro-degenerative disorder;</i> Extrapyramidal, autonomic and cerebellar progressive degeneration	Difficulty voiding/ nocturia are most common, also urgency and UUI (25) ED is an early feature. In cerebellar MSA, 83% have ED at diagnosis, 58% have urinary incontinence and 50% have OAB.	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 years, with survival 7-9 years. UK prevalence 4.4/ 100,000 (26) Slight male preponderance	Alzheimer's dementia. Parkinson's disease. Progressive supranuclear palsy.
Occult spinal dysraphism, including SBO and tethered cord	<i>Developmental disorder;</i> Defective closure of the neural groove	Variable features. SBO; OAB (27), incontinence, enuresis. With tethered cord, urgency and UUI are common. UDS; DO 42%, low compliance 67% (28). DSD and sensory abnormalities can occur (29)	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 (30)	Congenital, reducing prevalence (31). Unlikely to influence survival.	Syringomyelia (developmental or acquired)

Table 1; Archetypal neurological conditions which may include lower urinary tract symptoms as an early feature. DO: detrusor overactivity; DSD: detrusor sphincter dyssynergia; ED: erectile dysfunction; NPH: Normal pressure hydrocephalus; SBO: spina bifida occulta; SUI: stress urinary incontinence; UDS: Urodynamics; UUI: urgency urinary incontinence