**Uncommon neurologic diseases for the neuro-urologist: Guidance on rare degenerative brain disorders, autoimmune diseases of the brain and spinal cord, and peripheral neuropathies from the International Continence Society Neurourology Promotion Committee**

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**Abstract**

The management of patients with neurogenic lower urinary tract dysfunction has been well-described, however this is most frequently discussed for more common conditions such as spinal cord injury or multiple sclerosis. Our objective was to review uncommon neurologic disorders and summarize both the underlying disease process (which are often not well known to urologists), and the relevant literature reviewing the disease-specific research on the conditions impact on the lower urinary tract. Among the degenerative brain disorders, we have reviewed the literature on frontotemporal dementia (which has a lower risk of incontinence compared to Lewy body or vascular dementia), Amyotrophic lateral sclerosis (which has increasing storage symptoms with disease progression), Huntington’s Disease (where urinary symptoms usually present late in the disease course), Progressive supranuclear palsy and Corticobasal degeneration (where beta-3 agonists may be the preferable treatment modality), and Multiple system atrophy (which can evolve from urinary urgency to urinary retention over the disease course). Among the autoimmune disorders, we reviewed transverse myelitis (which often results in persistent urinary symptoms even after motor recovery), Neuromyelitis Optica spectrum disorders (which often have detrusor-sphincter dyssynergia and detrusor overactivity on urodynamics), and Meningitis-retention syndrome (a form of aseptic meningitis that presents with urinary retention) in addition to others. Hereditary Spastic Paraplegia (a spinal cord disorder which is often associated with significant urodynamic dysfunction including detrusor overactivity and detrusor-sphincter dyssynergia (DSD)) and Wolfram syndrome spectrum disorder (a progressive peripheral neuropathy disorder with early onset diabetes, optic atrophy and megacystis in the early stage) are reviewed.

**Introduction**

The extensive regulation of the lower urinary tract (LUT) at all levels of the neuraxis1,2 makes neurological disease a substantial part of functional urology practice. The large number of neurological diseases can appear daunting, but understanding of fundamental LUT regulation provides some general themes which facilitate anticipation of potential relevant effects of most such conditions.3 When starting to consider how neurological disease might affect the LUT, the basic functions include:

1. Motor; nerves make muscles contract
2. Sensory; nerves carry information that underpins reflexes in the spine and brainstem (subconscious) and perceived sensations (conscious)
3. Reflex; Specific processes coordinated by particular nerve groups and connections
4. Higher order; Cerebral functions that ensure LUT regulation is suitable for daily life, for example social appropriateness and planning ahead

Structurally, the nerve cell bodies are grouped in centres (sometimes called nuclei) while their processes extend in the white matter or peripheral nerves Some key structures for the LUT are:

1. Motor
2. The detrusor nucleus in the intermediolateral horn of the sacral spinal cord. Damage to this nucleus or its peripheral nerves causes detrusor areflexia
3. Onuf's nucleus in the anterior horn of the sacral spinal cord. Damage here leads to sphincter weakness, hence stress urinary incontinence and faecal incontinence
4. The sympathetic nucleus in the intermediolateral horn of the thoracolumbar spinal cord. Damage here affects blood pressure regulation. In men, it impairs bladder neck control, so the bladder neck is seen to be open during the filling phase in videourodynamics.
5. Sensory
6. The bladder has nerves responsible for the ordinary filling sensations which travel via the sacral part of the spinal cord
7. The bladder also has noxious/pain sensory nerves which are triggered by stimuli such as overdistension or inflammation. These go to the thoracolumbar part of the spinal cord
8. The sensory nerves of the urethra travel via the pudendal nerve, delivering information important for voiding4, and generating the sensation of urine flow.
9. The sensory nerves congregate on the periaqueductal grey (PAG), which is a key midbrain centre vital in numerous sensory and reflex functions, including determining what sensory information progresses to become consciously perceived sensation
10. For reflexes affecting the LUT, by far the most important location is the pontine micturition centre (PMC) in the brainstem. It functions to keep the spinal nuclei in the appropriate configuration for the LUT functions. By default, the LUT is held in storage mode by the PMC, with the detrusor nucleus actively inhibited and Onuf's nucleus activated to keep the sphincter contracted
11. Higher order functions are complex and not easily mapped onto specific parts of the brain, Functions such as conscious perception of sensation, planning and social appropriateness are underpinned by multiple cerebral centres and their interconnections. However, a clear importance can be ascribed to the prefrontal cortex (PFC), which has a strong input to the brainstem and regulates whether the PMC can transition from storage mode to voiding.

A sound knowledge of the above basics enables anticipation of the likely LUT consequences for most neurological conditions, including unfamiliar ones. Damage to either the cell body or its process leads to loss of function, so a lesion can affect functions of the centres located there, but also fibres transiting through that area. Hence the location and severity of the neurological lesion determines how badly the function is affected:

1. For motor nerves, partial lesions cause weakness, while complete lesions cause paralysis. For the detrusor, partial or complete intermediolateral horn lesions may manifest as underactivity or areflexia, respectively. For the sphincter, partial or complete Onuf’s lesions may manifest as stress incontinence or continuous leakage, respectively. Since there is an Onuf’s nucleus and an intermediolateral horn on each side of the spinal cord, a unilateral lesion causes partial loss of function.
2. For sensory nerves, there can be partial or complete loss of sensation, since there is a lack of information reaching the PAG. This can lead to areflexia, since reflexes require sensory input. Partial loss of sensor information can lead to a post-void residual (PVR) emerging, since the reduced information wrongly suggests complete emptying has been achieved. Because of the different routes taken in the periphery by different sensory nerves there can be partial preservation of LUT sensory reporting. For example, it is fairly common for people with loss of the normal filling sensations to experience the noxious feelings of bladder overdistension, since the hypogastric nerves conveying the latter enter the spinal cord at a higher level, potentially above a lesion affecting the other bladder nerves.
3. Damage to the brainstem or midbrain (PMC and PAG) is not commonly seen, due to their roles in vital functions such as breathing. However, these centres may be impaired in early stages of some conditions, like multiple system atrophy. Much more likely is impairment of the tracts related to these structures, which can occur at a spinal level. The result is likely to include detrusor overactivity (since storage function includes active inhibition of the detrusor nucleus), and may also include DSD.
4. The higher order functions are at risk in diseases of the cerebral cortex. Detrusor overactivity is common, again due to the importance of detrusor inhibition in the default storage mode. Less well recognised are aspects such as urinary retention (if impaired function of the frontal lobe prevents the signal permitting the PMC to switch to voiding mode). Alternatively voiding dysregulation, involuntary voiding5 or enuresis can occur, if cortical impairment affects its role in ensuring situational appropriateness of behaviour.

An online search will usually reveal the likely distribution of deficit, so that potential consequences can be derived for the LUT. Clinical acumen is then needed to match the effects to the symptoms the patient is describing. For complete lesions, this is usually fairly clear-cut. However, for partial lesions and progressive diseases, careful attention is needed to establish the current situation, with a view to deciding therapy and follow up (surveillance) requirements. The objective of this report is to summarise selected uncommon neuro-urologic diseases (listed in table 1) and review the available literature relevant to the associated voiding dysfunction.

**Degenerative disorders of the brain**

*Frontotemporal dementia (FTD)*

Dementia is an overarching term that includes memory loss, problems with communication, reasoning and mood changes. Alzheimer’s disease is the most common cause of dementia; it occurs when physical disease causes death of the brain cells. Vascular dementia is the second most common cause of dementia and is caused by problems with the brain’s blood supply. Lewy body dementia is a Parkinsonian disorder which often leads to lower urinary tract symptoms (LUTS), especially overactive bladder syndrome (OAB). In this type of dementia there is interruption of neuronal signalling, and Lewy bodies are found in the brain. It is progressive and can lead to disorientation of mental activities. FTD is one of the less common forms of dementia. It can affect the frontal or the temporal lobes. Damage to these areas can lead to difficulty in controlling behaviour and emotions.

It is estimated that 1.3% of the population can be affected with dementia. The prevalence is set to rise with advancing age with 7.1% above 65 years.6 There is an increased risk of developing incontinence in people with dementia. it is estimated that between 53 and 90% can be affected with urinary symptoms.7 The main predictors of incontinence in dementia are degree of immobility and severity of cognitive impairment**.** A combination of declining cognitive function, polypharmacy, reduced mobility and decreased bladder capacity contribute to urinary incontinence.8 It has been suggested that impaired mobility has a stronger correlation with incontinence than cognitive decline in patients with dementia. Among people with FTD, NLUTD can be both psychogenic and neurogenic (due to neurogenic detrusor overactivity from a lack of inhibition of the spinobulbospinal micturition reflex).9 The proportion of FTD patients with incontinence is between 19-26% in two prior case series.10,11 A small case series of five patients found that neurogenic detrusor overactivity was the most common finding (4/5 patients), and two patients had evidence of voiding dysfunction (one with a large PVR, and one with detrusor overactivity).9 FTD and Alzheimer’s disease have lower rates of incontinence (25-40%) compared to Lewy body and vascular dementia (80-90%).9

Management Pearls:

1. Assessment should include the usual urologic assessment, plus an assessment of mobility and dexterity including the level of care assistance.
2. There are no specific protocols to manage incontinence in patients with dementia. The reversible causes should be explored and treated where possible.12 The treatment is generally conservative with emphasis on understanding the cognitive and functional aspects.
3. Bladder retraining and pelvic floor exercises have a limited role in the setting of cognitive impairment or behavioural disturbances and dementia. Timed voiding might be helpful if caregivers are able to provide consistent support.
4. The use of both a Cholinesterase Inhibitor and OAB anticholinergic medication in dementia does not seem to worsen cognitive function, and may improve LUTS.13,14

*Amyotrophic lateral sclerosis (ALS)*

ALS is an idiopathic, progressive neurodegenerative disease of the motor system that leads to death. ALS can be familial, with a Mendelian pattern of inheritance disease in 5–10%, while the majority (90% of the cases) are sporadic. The ALS Syndrome usually appears with a focal clinical onset in a muscle group. During the disease progression, signs and symptoms of involvement of both upper (UMN) and lower motor neuron (LMN) in the brainstem and spinal cord develop. The entire clinical and neuropathological spectrum of ALS includes progressive muscular atrophy, primary lateral sclerosis, progressive bulbar palsy and pseudobulbar palsy.15,16 In most cases, there is a relative sparing of neurons innervating the extraocular muscles and sphincters.17

Although neurogenic lower urinary tract dysfunction (NLUTD) is considered rare, there is some evidence that inverts this thought. In a cohort study of 43 ALS patients, there was an increased prevalence of urgency incontinence and a high burden of LUTS, especially in patients aged more than 60 years.18 In another similar cross-sectional study with 54 ALS patients, 41% of them reported LUTS and 35% had a PVR > 50 ml. Storage LUTS were reported in 27% of patients; voiding and post micturition LUTS were reported in 59%.19 In a recent cohort study with 30 patients, LUTS increased from 24% before to 76% after the ALS diagnosis. A second cohort study with 66 ALS patients found the prevalence of storage symptoms increased from 3% before, to 25% after the diagnosis of ALS.20 The clinical profile of the disease does not seem to impact the development of LUTS, as there was no difference in patients with classical ALS compared to progressive muscular atrophy or primary lateral sclerosis.21

There is little urodynamic data available, however a study of 55 ALS found that 24 of them experienced significant LUTS, and of the 10 that underwent UDS the most frequent finding was detrusor overactivity with obstruction due to an overactive sphincter.22

*Huntington’s Disease (HD)*

HD is a degenerative disease with autosomal dominant inheritance that often presents in middle adulthood. The pathophysiology of the disease consists of a progressive neuronal loss in the basal ganglia, especially in the caudate nucleus and cerebral cortex.23,24 Clinically, HD is characterized by progressive motor, cognitive, and emotional symptoms. Later onset of the disease is usually associated with slower progression.

The literature regarding the NLUTD in patients with HD is extremely limited. In a case series study of 6 subjects, there were 4 patients with detrusor overactivity and normal sphincter function.25 Their symptoms (urinary frequency, urgency, nocturia, and incontinence), appeared 6 years after the onset of HD.25 A survey of 1283 symptomatic HD patients found that LUTS usually arise in the late stage of the disease, typically more than 10 years after onset.26 In a cohort study of 54 HD patients and 10 asymptomatic HD gene carriers27, the authors reported OAB (women/men: 40%/54%), urgency urinary incontinence (women/men: 43%/29%), and voiding symptoms (women/men: 40%/25%). In another study with 63 HD pts and 21 pre-manifest mutation carriers, autonomic dysfunction including urinary symptoms, and erectile and ejaculatory dysfunction in men, were significantly more prevalent in HD pts compared to the control group.28

Urodynamics were performed on 12 patients with HD and revealed detrusor overactivity in 2 pts (17%), DSD in 5 pts (42%), and reduced detrusor contractility in 2 pts (17%).27

*Progressive supranuclear palsy (PSP)*

PSP primarily affects the brain, particularly the substantia nigra, globus pallidus subthalamic nucleus (basal ganglia, gait pathway), dorsal midbrain (eye movement pathway), dentate nucleus, cerebellum, frontal lobe, limbic system (cognitive pathway), and to a much lesser extent, the spinal cord. In these areas, affected neurons show neurofibrillary tangles that are 4-repeat tau positive. Tau imaging helps diagnosing PSP. Clinically PSP shows several subtypes: PSP-Richardson syndrome (common, supranuclear gaze palsy, parkinsonism, dementia; MRI shows midbrain atrophy called ‘hummingbird’ or ‘emperor penguin’ sign), PSP-parkinsonism (parkinsonism without tremor/laterality with axial [neck, trunk] rigidity; and parkinsonism presenting pure akinesia), PSP-cortical (overlap symptoms with frontotemporal lobar degeneration) and PSP-cerebellar (C).

PSP causes significant NLUTD;29–32 most commonly this includes OAB symptoms that are often more severe compared to Parkinson’s disease. This is probably a reflection of PSP’s more severe and diffuse brain lesions in areas relevant to micturition control compared to Parkinson’s disease. Other autonomic disorders (gastrointestinal dysfunction, orthostatic hypotension, etc., reflecting mostly peripheral lesion) are not as severe in PSP compared to Parkinson’s Disease.

Common urodynamic abnormalities in PSP are detrusor overactivity with reduced bladder capacity; and to a lesser extent, PVR and neurogenic sphincter electromyogram presumably reflecting sacral spinal cord lesion in this disease.33,34

Management pearls:

1. Although a treatment strategy that is specific for PSP is not available, patient’s older age and susceptibility to cognitive decline means it is preferable to start with a beta3 adrenergic agonists or antimuscarinics that do not easily penetrate the blood-brain barrier.35,36

*Corticobasal degeneration (CBD)*

CBD affects the brain, particularly the cerebral cortex (cognitive and higher function pathway), subcortical white matter, substantia nigra, striatum, globus pallidus (basal ganglia, gait pathway), thalamus, subthalamic nucleus, basal nucleus of Meynert, locus ceruleus and other brainstem nuclei. The areas overlap with PSP, but the distinct feature of CBD is cortical involvement with laterality. The affected areas show ballooned neurons and threads/coiled bodies that are 4-repeat tau positive. Therefore, CBD and PSP are both referred to as 4-repeat tauopathies. Tau imaging also helps diagnosing CBD. Clinically, CBD patients show cortical signs, such as ‘alien limb’ syndrome (arms or legs may seem to move independently), apraxia (loss of coordinated movement in one hand), aphasia and other focal cognitive problem; and basal ganglia signs, such as unilateral limb dystonia/rigidity.

NLUTD in CBD is mostly OAB (from urinary urgency and increased voiding frequency, to urgency urinary incontinence), the severity of which is almost the same with that in Parkinson’s Disease.37 This is probably a reflection of CBD’s cortical and basal ganglia lesions, which are relevant to micturition control. In contrast to multiple system atrophy, PVR and neurogenic sphincter electromyogram is not observed in CBD.37

Management pearls:

1. Like PSP, it is recommended to start with a beta3 adrenergic agonists or antimuscarinics that do not easily penetrate the blood-brain barrier.36,37

*Multiple system atrophy (MSA)*

MSA is defined as a combination of a) motor (parkinsonian MSA [MSA-P] and/or cerebellar MSA [MSA-C]) and b) autonomic (orthostatic hypotension and/or bladder dysfunction) disorders.38 Pathologically, MSA affects both the brain (basal ganglia, cerebellum, brainstem pontine nuclei, locus ceruleus, raphe, cardiovascular and respiratory nuclei; on imaging it typically shows as ‘hot cross bun’ sign) and the spinal cord (intermediolateral nucleus innervating the arteries and the internal sphincter, and sacral Onuf’s nucleus innervating the external sphincter). The affected areas show glial cytoplasmic inclusion that are alpha-synuclein positive.

NLUTD occurs in up to 90-100% of MSA patients, ranging from OAB to large PVR/ urinary retention.31,39

Urodynamics typically demonstrate detrusor overactivity (during filling), detrusor underactivity (on voiding), or their combination (so called DHIC, detrusor overactivity with impaired contraction), with or without DSD, and neurogenic sphincter electromyography (EMG) is specific for differentially diagnosing MSA from Parkinson’s disease.40 On video urodynamics, an open bladder neck early in filling with detrusor overactivity is sometimes observed in MSA.31

Management pearls:

1. Up to 18% MSA may present with bladder dysfunction alone.41 Such patients may visit a urologist before the correct diagnosis is made; therefore collaboration of neurologists and urologists is highly recommended. Urodynamics, sphincter EMG and neuroimaging will help with making the diagnosis.
2. NLUTD might change from OAB to urinary retention during the course of MSA; therefore, for those with initial urge incontinence, beta3 antagonists or antimuscarinics can be used but the patient’s PVR should be monitored for changes over time.
3. Elevated PVRs (>100ml) can start in the second year of MSA41; therefore, the specialist continence nurse has an important role to teach clean, intermittent self-catheterization (CISC) in this group of patients with symptomatic PVRs.
4. Transurethral resection of the prostate should be avoided because their retention is mostly caused by detrusor underactivity, and there is an increased risk of urinary incontinence.42–44

**Traumatic Brain Injury (TBI)**

TBI results principally from vehicular accidents, falls, acts of violence and sports injuries. It causes a physiological disruption of brain function which may be temporary or may lead to permanent disability. NLUTD following TBI may result from a direct consequence of brain damage, cognitive, language, motor, or coordination deficits, associated spinal cord injury, pelvic/bladder injury, or any combination of the above.

Although urinary dysfunction is common post TBI, literature on the subject is sparse. Giannantoni et al, reported that 86% of severe TBI patients complained of urinary symptoms, with 61% reporting symptoms of OAB alone, 14% reporting voiding symptoms alone and 25% reporting both OAB and voiding phase symptoms.45 Symptoms may be influenced by the increased secretion of brain natriuretic peptide and resulting polyuria during the early injury period.46 The incidence of urgency incontinence correlates with frontal lesions and with TBI severity, with patients having diffuse/bilateral injuries, aphasia, a longer acute length of stay and a poor functional status being more likely to develop urinary incontinence.47,48 Chua et al reported urinary incontinence in 62% patients during the early phase, which improved with time, with 18% having persistent urinary incontinence at 6 months.47 Resolution rates of urinary incontinence appear to be related to TBI severity, and impaired cognition/mobility may contribute to urinary incontinence. Urinary retention is relatively uncommon, being seen in 8% patients during the early phase, with only 2% requiring intermittent catheterisation at the time of discharge from rehabilitation.47

Urodynamic studies have demonstrated detrusor overactivity and impaired bladder contractility in 49-66% and 32% of patients, respectively. Right hemisphere injuries have been found to correlate with detrusor overactivity and left hemisphere injuries with impaired bladder contractility. Detrusor sphincter synergia is the norm.45,48

**Autoimmune and inflammatory disorders of the central nervous system**

*Transverse Myelitis (TM)*

TM is a clinical syndrome caused by an immune-mediated process disrupting the spinal cord. It is characterized by a varying degree of general weakness to paralysis, sensory alterations and autonomic dysfunction.49 Although general weakness might vary between individuals, nearly all patients have NLUTD, and bladder dysfunction may outlast general motor and sensory deficit and recovery.50 Symptoms related to NLUTD range from urinary urgency and incontinence to incomplete bladder emptying and urinary retention. Since transverse myelitis is an immune-mediated process, treatment of the neurologic symptoms usually consists of corticoids and or plasma exchange.51 Urinary symptoms occur in almost all patients with TM, and only approximately 1/3 patients will have complete resolution with time (usually among those with mild motor, sensory and bladder symptoms at presentation).50,52,53

Symptoms and consequences are similar to patients with traumatic SCI. Video-urodynamic evaluation is warranted, since detrusor overactivity and DSD have often been reported, which can jeopardize the upper urinary tract.54 TM extending over a significant length of the spinal cord is significantly predictive of NDO.55 Since lower urinary tract dysfunction might be the only sequel, long-term and individualized follow up is necessary.

Treatment of NLUTD is based upon the urodynamic results and consists of clean intermittent catheterization and or treatment for detrusor overactivity by means of anticholinergics and botulinum toxin injection, although beneficial effects of sacral neuromodulation have also been reported.56 Patients should be carefully monitored, as upper tract deterioration can occur, and persistent urodynamic abnormalities despite motor improvement are common.50,52,53

*Neuromyelitis Optica spectrum disorders (NMOSD)*

NMOSD are inflammatory diseases of the central nervous system that preferentially affect the optic nerves and the spinal cord. They frequently follow a relapsing course, with disabling episodes of Optic Neuritis and Longitudinally Extensive Transverse Myelitis (LETM).57 A serum reactivity that targets aquaporin-4 (AQP-4), a water channel in the CNS, has been described in patients with NMO and distinguishes NMO from other demyelinating disorders. It is termed AQP-4 immunoglobulin G (AQP4-IgG) and is detectable in 60–90% of patients with NMO and, with lower frequency, in patients with limited forms such as those with a first episode of LETM.57–59 NMOSD unifies all clinical variants, and is further stratified by serologic testing (NMOSD with or without AQP4-IgG). The basic characteristics required for patients with NMOSD with AQP4-IgG include clinical syndromes or MRI findings related to optic nerve, spinal cord, brainstem, diencephalic, or cerebral presentations. More stringent clinical criteria are required for diagnosis of NMOSD without AQP4-IgG or when serologic testing is unavailable.57

The prevalence of NMOSD varies throughout the world, and in most regions, NMOSD is less prevalent than MS.60 NLUTD is present in 78-83% of the patients and has a significant negative impact on quality of life.61,62 A combination of storage and voiding symptoms including urgency, nocturia, frequency, weak urinary stream and incomplete emptying is common. A high prevalence (87%) of bowel dysfunction has also been reported.62 In one cross-sectional study with 30 patients none had upper urinary tract abnormalities and 7/30 (23%) had bladder wall thickening.

Video-urodynamics show DSD and detrusor overactivity in most patients.61 These findings are consistent with disease affecting the cervical and/or thoracic spinal cord level, which is present in most patients with NMOSD. The severity of neurological disability seems to be a predictive factor for the occurrence of NLUTD symptoms.

*Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)*

MOGAD is a recently described inflammatory disease of the central nervous system driven by antibodies that target myelin oligodendrocyte glycoproteinon myelin sheaths, causing oligodendrocyte damage and primary demyelination.63 Clinical manifestations include acute disseminated encephalomyelitis (ADEM), mostly in young children, and an opticospinal presentation in adults. Although MOGAD has clinical and radiological similarities with NMOSD and MS, these conditions have distinct demographics and are immunologically and pathologically different.58,59 Studies indicate that 40% of NMOSD AQP4-IgG negative patients are MOG antibody positive. In addition, MOG antibodies can be present in 10–20% of idiopathic atypical demyelinating diseases not meeting NMOSD criteria. MOGAD has distinct clinical and radiological characteristics compared to NMOSD and MS, and a recent study showed that a combination of MRI and clinical measures could achieve an accuracy of 85% and 93% for the classification of MOGAD versus AQP4+ NMOSD and MOGAD versus MS, respectively.59

MOGAD is considered milder and less relapsing than NMOSD, but clinical outcomes and predictors of relapses remain unknown.58,59,64,65 MOGAD can present at any age, with a slight female preponderance and no apparent ethnic bias.64 It typically has a favorable outcome and early diagnosis is important since prompt immunotherapy improves the prognosis.

In a study with 75 patients, permanent LUTD affected 21 (28%) patients and was more common than motor disability (7%).64 All patients with NLUTD had TM affecting the thoracic cord or conus and 13/21 (62%) required long-term catheterization. Overall bladder outcome was not affected by age of onset, disease duration or gender. In other studies, the prevalence of long-term LUTD was 55-59%, and up to 20% required long-term catheterization. The presence of a conus lesion is a risk factor for the need of long-term catheterization.65,66

Urodynamic findings in patients with a history of TM predominantly showed detrusor overactivity and/or DSD, consistent with a supraconal lesion.66

*Glial fibrillary acidic protein (GFAP) astrocytopathy*

GFAP (an intracellular astrocytic intermediate filament) astrocytopathy is an autoimmune inflammatory CNS disease first defined in 2016.67 Most patients have a meningoencephalomyelitis and can rarely manifest with isolated myelitis. Preceding flu-like symptoms are present in 40–66%.68 The disorder is confirmed by detection of IgG reactive with GFAP in the cerebrospinal fluid (CSF). Some patients may also have GFAP-IgG detected in serum.69 Coexisting autoimmune diseases such as diabetes mellitus, autoimmune thyroid disease and rheumatoid arthritis are present in approximately 20% of the patients.70 A characteristic MRI hallmark has recently been described, consisting of a linear perivascular enhancement radially oriented around the ventricles (radial enhancement), while the myelitis component is generally associated with a longitudinally extensive T2 lesion on spinal cord MRI, similar to that typically encountered in aquaporin-4-IgG (AQP4-IgG) related myelitis. Most patients with GFAP have a monophasic course, but about 20% may have a relapsing course. Approximately one in four patients have a coexisting neoplasm, most commonly ovarian teratoma. Occasional patients may have coexisting AQP4-IgG or MOG-IgG and their neurological phenotypes are indistinguishable from those positive for GFAP-IgG alone.69

Lower urinary tract symptoms have not been characterized in patients with GFAP but studies mention a rate of 21-28% of autonomic dysfunction.

*Meningitis-retention syndrome (MRS)*

MRS is a newly-recognized inflammatory neurological condition.71–74 Clinically MRS is defined as a combination of a) aseptic meningitis (increased reflexes without leg weakness might be seen; abnormal cerebrospinal fluid (CSF) alone may also be found75) and b) acute urinary retention. Aseptic meningitis is a common condition, which is caused by many viruses but also from autoimmune etiologies. MRS occurs in 8% of aseptic meningitis cases. Average latencies from the onset of meningeal irritation to urinary symptoms is 0-8 days. However, in some cases, urinary retention precedes fever and headache, and in such cases patients with MRS may be seen by urologists first before the correct diagnosis is made. The duration of urinary retention in MRS is mostly 7-14 days, but can last up to 10 weeks. Mild acute disseminated encephalomyelitis (ADEM) is considered an underlying mechanism of MRS, because some patients show elevated myelin basic protein in the CSF and a reversible splenial lesion on brain MRI. As it is observed in ADEM, antecedent/comorbid infections or conditions with MRS include Epstein‒Barr virus, herpes simplex virus, varicella-zoster virus, West Nile virus, listeria, etc. In addition to these, elevated CSF adenosine deaminase levels or decreased cerebrospinal fluid/serum glucose ratio may be predictive factors for MRS development.73 It is not known whether steroid pulse therapy can shorten the period of urinary retention.

Urodynamics show that all patients had detrusor underactivity during their period of urinary retention. Repeated urodynamics showed that the underactive detrusor changed to an overactive detrusor after a 4-month period. While urinary retention in MRS resolves in most cases, care must be taken to prevent bladder injury from chronic overdistension by performing intermittent catheterization.

The term “Elsberg syndrome” is occasionally assigned to urinary retention of diverse etiologies. Kennedy, Elsberg, and Lambert (1913) reported five cases of pathology-demonstrated cauda equina radiculitis.76 Their clinical/pathological features were: rare CSF abnormalities; no clinical meningitis; a subacute/chronic course; presentation with typical cauda equina motor-sensory-autonomic syndrome; Wallerian degeneration of the spinal afferent tracts; and mild upper motor neuron signs. All these are different from those of MRS.

**Spinal cord disorders**

*Hereditary Spastic Paraplegia (HSP)*

HSP is a rare group of genetic disorders that lead to degeneration of the long tracts of the corticospinal tract and dorsal column of the spinal cord; it is most commonly inherited as an autosomal dominant condition, although it can also be autosomal recessive, and up to 40% can be sporadic. Clinically, patients present with gait problems that progress to leg spasticity. A minority of patients present with “complex HSP” which has additional features such as peripheral neuropathy epilepsy, ataxia, retinopathy, cognitive problems, hearing loss, and impaired speech/swallowing.77 This is a disease that can present in childhood and throughout adulthood.

Small case series have supported significant urinary symptoms in the majority of patients: urgency/ frequency, incontinence, and voiding symptoms such as poor stream and hesitancy.78–81 In the largest case series (49 patients from Estonia), storage symptoms were most common, incontinence was reported by the majority of patients, and a PVR >100mL was found in only 10%.78 Other reports have noted a significant PVR in more than 50% of patients.81 There was a high frequency of coexisting detrusor overactivity with detrusor underactivity.79,80 Up to 2/3 patients may have DSD.79,81 Risk of renal deterioration are conflicting. Renal Ultrasound assessment of 29 HSP patients (after a mean of 22 years of HSP followup) did not find any significant hydronephrosis or renal atrophy.79 Conversely, a series of 33 HSP people found that 8% had hydronephrosis, 20% had stone disease, and 17% had chronic renal failure.81 Some of these differences in urinary disease presentation is likely a result of either case series recruited from neurourology practises (with a higher rate of LUTS) as opposed to neurologic practices. It is possible that the spinothalamic pathways are partially impacted, or that pelvic floor spasticity results in secondary bladder changes over time.

Management pearls:

1. Given the potential for renal deterioration, patients should probably have neurourological monitoring if there are significant risk factors at presentation.
2. If patients are using botulinum toxin for leg spasticity, any intravesical doses should be administered with a significant time interval from the skeletal muscle treatments; total botulinum dose that the patient is receiving should be monitored.82

*VATER Syndrome/VACTERL association*

VATER is an acronym to describe an association of congenital malformation including vertebral abnormalities (V), anal atresia (A), trachea-esophageal fistula (T), esophageal atresia (E), renal dysplasia (R). Because of the occurrence of further non-random abnormalities described in literature, the acronym was extended as VACTERL, to include Cardiac and Limb malformations. There is no consensus regarding the criteria for the definitive diagnosis. Some authors proposed that at least three of the above-mentioned features should be present.83 Vertebral abnormalities are one of the most common defects, occurring in about 65-95% of patients;84 this can include missing vertebrae, vertebral malformations (fusions, clefts and hemivertebrae), sacral agenesis and tethered spinal cord. Therefore, these abnormalities may cause NLUTD mainly secondary to a cauda equina/ sacral lesion. The surgical correction of pelvic abnormalities (such as imperforate anus) may lead to peripheral nerve damage.

Symptomatic urinary infections are often an early urologic manifestation, due to the co-existence of hydronephrosis and vesico-ureteral reflux. This is related to congenital abnormalities of the upper urinary tract, although it may also be associated with concomitant high pressure from reduced bladder compliance.85 Patients having VATER/VACTERL disease should be always be referred to a neuro-urologist and a nephrologist to evaluate the bladder and kidneys, and to prevent kidney failure and/or further renal deterioration.86

**Peripheral Neuropathies**

*Guillain-Barre syndrome (GBS)*

GBS is a group of acute demyelinating and axonal autoimmune polyneuropathies, triggered by a bacterial or viral infection, and characterized by rapidly evolving limb weakness and loss of tendon reflexes, with or without sensory and autonomic disturbances. Despite available treatment, GBS is associated with significant mortality (3-10% of patients die), and 20% of patients may have residual permanent severe disability. The form and severity of the disease is possibly determined by the type of preceding infection and patient factors.87

Among 65 of patients with GBS, 28% had NLUTD. The most prevalent symptom was voiding dysfunction (9% had urinary retention), 8% had urgency symptoms and none of the patients were incontinent.88 An Australian study reported the prevalence and long-term impact of NLUTD in patients in the chronic phase of GBS. Of the 66 patients, with a mean of 6 years since the diagnosis, more than half reported nocturia and one-third reported urgency and frequency. In addition, nearly one-half of the patients reported interference in their daily life due to urinary problems.89

Urodynamic studies were performed in 9 patients within 8 weeks of diagnosis, with variable results: 3 patients had a significant PVR, 1 had decreased bladder sensation, 8 had detrusor overactivity (of which 5 also showed detrusor underactivity), 1 patient had low compliance and 2 had a non-relaxing sphincter.90 In another report, 10 of 38 patients had urinary symptoms (all voiding difficulty), and in 50% urinary retention was present at some point of the illness. Urodynamic abnormalities were seen in 23 patients, mostly detrusor underactivity (15 patients).88

Management pearls:

1. Post-void ultrasonography is recommended in patients with a higher Hughs motor grade, higher age and defecation dysfunction. The management of urinary symptoms is mainly supportive.90

*Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)*

CIPD is a group of acquired immune-mediated disorders that affect the peripheral nerves. They are, by definition, chronically progressive or relapsing for over 8 weeks.91 The management is supportive.92

The literature regarding the relation of LUTS and CIPD is scarce. A series of 32 patients with CIPD showed that 8 of the 32 (25%) patients had LUTS.92 Four patients had voiding difficulties, four urinary urgency (one had associated urgency incontinence), and several had increased day- and night-time frequency. None of the patients had urinary retention. Figueroa and colleagues reported genitourinary symptoms in 8/47 patients (17%). However, these symptoms were retrospectively derived from a standardized chart review and were not further specified.93

Urodynamic data was available for 4 patients and it showed abnormal bladder sensation in two, “bladder areflexia” in one and neurogenic changes of the external sphincter in one.92

*Autoimmune autonomic ganglionopathy (AAG)*

AAG, was formerly known as subacute autonomic neuropathy or autoimmune autonomic neuropathy. It is a rare disease with an unknown prevalence and is difficult to diagnose. It is an immune-mediated disorder of the autonomic nervous system that mostly spares the motor and sensory nerves. Autoantibodies to the ganglionic acetylcholine receptor (nAChR) can be measured in a subset of patients.94 These nicotine acetylcholine receptors are present in the entire nervous system. In the peripheral autonomic nervous system, the ganglionic nAChR mediates fast synaptic transmission in sympathetic, parasympathetic and enteric ganglia. So autoantibodies to the ganglionic acetylcholine receptor can potentially disrupt the entire autonomic nervous system. Patients with high levels of ganglionic nAChR antibodies, usually at the extreme end of disease severity, present with severe autonomic failure and NLUTD.95 Immunotherapy can be considered as a treatment, with potentially significant side effects

Koay and colleagues conducted a study in patients with ganglionic nAChR positive neuropathy, and 9/13 patients had urinary retention. Eight patients performed a uroflowmetry, six of whom had an abnormal flow with prolonged voiding times, intermittent flow and evidence of straining, and two had a normal flow after immunotherapy. In addition, erectile disfunction and ejaculatory disfunction were also common.96

*Wolfram syndrome spectrum disorder (WSSD)*

Wolfram syndrome spectrum disorder (WSSD) is a progressive neurodegenerative disorder characterized by the onset of diabetes mellitus (DM) and optic atrophy (OA) by the age of 16, and typically associated with other endocrine abnormalities, sensorineural hearing loss, and progressive neurologic abnormalities (cerebellar ataxia, peripheral neuropathy, dementia, psychiatric illness, and urinary tract atony).97,98 WSSD is also known as a DIDMOAD (diabetes insipidus, early-onset diabetes mellitus, optic nerve atrophy and deafness) and two subtypes of this syndrome have been described, each associated with a specific gene, wolframin (WFS1) and CISD2 (WFS2). These genes encode a transmembrane protein and an endoplasmic reticulum intermembrane protein, respectively.97 They are detected in different organs and account for the pleiotropic features of this syndrome. Wolfram syndrome type 1 (WFS1) is the most frequent and best characterized disorder. In a patient with suggestive clinical features and family history, the diagnosis is confirmed by molecular genetic testing.98

NLUTD affects up to 90% of the patients with WSSD and may lead to end-stage renal disease.98,99 Marked dilation of the bladder, often labeled megacystis, has been described as a common finding in patients with WSSD but other clinical presentations are common, including small and non-compliant bladder and DSD.98–100 The megacystis has been attributed to polyuria from diabetes insipidus, but it has been shown that the NLUTD in WSSD is also from progressive neurodegeneration.99,100 Studies have shown that brain volume is decreased in patients with WSSD and decreased pons volume is associated with worse NLUTD.100 Bowel dysfunction is also common in WSSD and deserves proper attention.98

Treatment of NLUTD in patients with WSSD follows the same principles of those with other etiologies. Periodical evaluation is strongly recommended based on the potential severity of LUTD.98,100

*Charcot Marie Tooth Disease (CMT)*

First described in 1886, CMT is the commonest form of hereditary neuromuscular disease and includes a large number of different genetic mutations which result in a common clinical phenotype.101 The disease usually presents in early in life with a classical clinical appearance that includes muscle wasting and deformities- firstly of the lower limbs (callosities, high arch, foot deformities), and later involving the upper limbs (main en griffe, claw hand). The disease can present in different forms, classified as demyelinating, axonal, X-linked and various combinations of sensory and motor neuropathies. Initially distal in onset, there is progressive involvement of more proximal neural structures. Many genetic defects have now been identified which usually (but not always) involve autosomal dominant transmission.101

The prevalence of NLUTD in CMT is uncertain. In a series of 58 patients (36 women; mean age 52.8 ± 13.4 years), LUTS were more common than in age-matched controls. Symptoms included a sense of incomplete evacuation and urgency incontinence in men and nocturia, urgency, hesitancy, straining and interrupted stream in women. Urinary symptoms had an impact on quality of life. Bowel symptoms and sexual dysfunction were also common in both sexes.102,103

In a small series of 9 patients, 7 patients (3 men) were evaluated by urodynamics. Findings included neurogenic acontractility (2 patients), underactivity (1 patient), neurogenic detrusor overactivity (1 patient), delayed opening time (1 patient) and normal urodynamics (1 patient). Bladder outlet obstruction was not seen in any patient. One of the nine patients presented with end stage kidney disease, but it is unclear whether this was causally related to the diagnosis of CMT disease.104

In view of the varied presentation, treatment needs to be individualized based on the patient’s presentation.

*Amyloid Neuropathy (AN)*

Amyloidosis refers to a heterogenous group of conditions involving mis-folding of protein molecules, and resulting in deposition of sheets of insoluble beta configuration amyloid fibrils that can be either localized or systemic. The condition can be acquired (AL, the commonest), genetic (ATTR hereditary variant), or result from chronic inflammation (AA).105 There are 18 different proteins identified in systemic amyloidosis and 22 proteins identified in localized form. Nomenclature consists of the capital letter ‘A’ followed by a letter(s) identifying the protein involved and small case suffix for additional qualifiers (such as ‘wt’, wild type).106 AL (light immunoglobulin chain) and ATTRv (hereditary transthyretin variant) amyloidosis commonly involve the nervous system. Deposition of amyloid can also be a part of other disease processes not generally recognized currently as ‘amyloidosis’, such as Alzheimer’s or Parkinson’s disease.106 The absence of any unique pathognomonic feature makes the condition elusive (the “great mimicker”). Diagnosis requires a high index of suspicion and is confirmed by tissue biopsy.105

Systemic amyloidosis commonly results in peripheral sensorimotor neuropathy, myopathy or autonomic dysfunction. There is axonal degeneration involving the small myelinated and unmyelinated nerve fibers. Autonomic dysfunction may be noted in 65%-75% of those with neuropathy and about 30% of these patients have urinary tract involvement.105,107 In patients with hereditary ATTR, a systematic review noted urinary symptoms in 83% patients.108 Onset was noted in the 4th decade (mean age 30 years in males and 34 years in females) with age-associated progression.109 LUTS include voiding difficulty, frequency, urgency, urinary incontinence and propensity for urinary tract infection.107,108 Ultrasonography often shows elevated PVR urine and may identify hydronephrosis (secondary to lower tract dysfunction) or an open bladder neck at rest (signifying autonomic dysfunction).108

On urodynamics, detrusor underactivity is a consistent finding and is noted in 78% of patients with familial amyloidotic polyneuropathy.107,109 Other findings are impaired sensation, poor compliance, urethral incompetence, failure of sphincteric relaxation and DSD.107,109,110 Timed voiding, use of alpha-adrenergic blockers (in men) and intermittent self-catheterization are key components of management.

Management pearls:

1. Alpha blockers must be used with caution since they might trigger or exacerbate postural hypotension that often co-exists with Amyloidosis.107

**Conclusions**

We selected neurologic diseases that may not all be familiar to physicians providing care for NLUTD. For each of these diseases, we have provided a brief review of the neurologic disease process, and the specific clinical and urodynamic data where available. The management of NLUTD is often complex, and must always follow the general principles of careful patient assessment and proper urodynamic investigation when appropriate. The final decision on bladder management and any potential interventions should be done in the context of the patient’s neurologic disease, prognosis, and their wishes.

Table 1. Characteristics of the selected degenerative brain disorders, autoimmune diseases of the brain and spinal cord, and peripheral neuropathiesreviewed in this report.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Disease** | **Estimated Frequency in the population** | **Usual Onset** | **Progressive?** | **Average lifespan of patient** | **Gene (if known)** | **Neurological site of lesion (if known)** |
| **Degenerative disorders of the brain** | *Frontotemporal dementia (FTD)* | 10-20% of dementia cases | 40-65 years of age | Yes | 6-8 years | 20-50% of cases are familial. Mutations in hexanucleotide expansion repeats in the open reading frame of chromosome 9 (C9ORF72), MAPT (microtubule-associated protein tau) or (granulin) GRN are found in 60% of these cases | Brain |
|  | *Amyotrophic Lateral Sclerosis (ALS)*  | 3-6 /100,000 | Very rare before 35, more common onset after 45 with maximum prevalence between 55 - 70 years. | Yes | 2.5 years without treatment. Multidisciplinary specialised care may reduce the risk of death by 45% at 5 years. | 90% sporadic, 5–10% familial. Of the known genes, mutations in SOD1 (encodes for copper/zinc ion-binding superoxide dismutase), TARDBP (also known as TDP-43; encodes for TAR DNA binding protein), FUS (encodes fusion in sarcoma), ANG (encodes angiogenin, ribonuclease, RNase A family, 5), and OPTN (encodes optineurin) cause a typical clinical phenotype.  | Upper (in the brainstem and the spinal cord) and Lower Motor Neuron involvement |
|  | *Huntington's disease (HD)* | 0.4–7.3/100,000 | Childhood to middle adulthood age (average onset age: 40 years) | Yes | Survival from onset to death averages 17–20 years (later onset is associated with slower progression) | HD gene located on chromosome 4p16.32. The genetic alteration which causes the disease is associated with the number of repetitions of three nucleic acids (C, A, and G) in the coding region of the first exon of the HD gene | Suprapontine and pontine lesions - basal ganglia pathology |
|  | *Progressive supranuclear palsy (PSP)* | 6-10/100,000 | 60-70 years | Yes | 6-7 years | Heredity (MAPT gene) is extremely uncommon | Basal ganglia including pallidum, cerebellum, midbrain tegmentum |
|  | *Corticobasal degeneration (CBD)* | <5/100,000 | 50-70 years | Yes | 7-8 years | Heredity (MAPT gene) is extremely uncommon | Cerebral cortex with laterality in addition to pathology of PSP |
|  | *Multiple system atrophy (MSA)* | 0.6-3.3/100,000 | 40-60 years | Yes | 7-10 years | Rarely hereditary. | basal ganglia, cerebellum, brainstem, spinal cord (intermediolateral nuclei, Onuf's nucleus) |
| **Traumatic Brain Injury (TBI)** |  | Mean 258/100,000 per year | Children: 0-4 years, Adolescents 15-19 years, Older Adults >75 years  | Possibly. Neurodegenerative processes may occur post injury  | Average life expectancy reduced by 9 years  | NA | Brain |
| **Autoimmune and inflammatory disorders of the central nervous system** | *Transverse myelitis (TM)* | 1-4/100,0000 | Adolescents, 30-39year | No | Normal | NA | Spinal cord |
|  | *Neuromyelitis optica spectrum disorder (NMOSD)* | 1-10/100,000 (greater frequency in individuals of Asian and African descent; Female:male ratio is 9:1) | Adulthood | Yes | May be shortened based on neurological disabilities | Genetic role not clear | Spinal cord and optic nerve |
|  | *Myelin oligodendrocyte glycoprotein (MOG) myelitis* | 1.6-3.4/100,000 | Childhood to early adulthood | Usually not | Normal for most patients; varies with neurological disabilities | Genetic role not clear | Spinal cord and optic nerve |
|  | *Glial fibrillary acidic protein (GFAP) astrocytopathy* | 0.6/100,000 | Adulthood | Usually not | Normal for most patients; varies with neurological disabilities | Genetic role not clear | Cerebrum, meninges, spinal cord and optic nerve |
|  | *Meningitis-retention syndrome* | Unknown | Any age | No | Normal | Genetic role not clear | Presumably meninge and spinal cord |
| **Spinal cord disorders** | *Hereditary Spastic Paraplegia (HSP)* | 2-5/100,000 | Childhood to early adulthood | Yes | Normal for most patients | SPAST(formerly SPG4), most common gene, found in up to 25-50% | Spinal cord |
|  | *VATER Syndrome/ VACTERL association* | 2-10/100,000 | Congenital | No | Reduced lifespan due to complications of the disease | TRAP1 has been identified as the first autosomal-recessive disease causing gene for the full clinical picture of the VATER/VACTERL association. | Cauda equina/sacral/peripheral lesion |
| **Peripheral neuropathies** | *Guillain Barre Syndrome (GBS)* | 1.2-2.3/100,000 | All ages | No | Normal for most patients | NA | Peripheral neuropathy |
|  | *Chronic inflammatory demyelinating polyneuropathy (CIDP)* | 1-9/100,000 | All ages | Yes | Normal for most patients | NA | Peripheral neuropathy |
|  | *Autoimmune autonomic ganglionopathy (AAG)* | Unknown | Adulthood | Unknown | Unknown | Unknown | Autonomic ganglion |
|  | *Wolfram Syndrome* | 0.18/100,000 | Childhood | Yes | Reduced - 65% mortality by age 35 years | Recessive autosomal disorder caused by mutations in the Wolframin1 (WFS1) gene; a less common variant (WFS2) is caused by mutation in the CISD2 gene which encodes protein ERIS (endoplasmic reticulum intermembrane small protein) | Limited data available suggest neurologic findings are progressive and result from general brain atrophy most prominently of the cerebellum, medulla, and pons; optic nerves and the posterior part of hypothalamus |
|  | *Charcot Marie Tooth disease* | 40/100,000 | First two decades of life | Yes | Normal for most patients | Hereditary with >1000 genetic mutations in 80 genes implicated | Motor and Sensory Neuropathy |
|  | *Amyloid neuropathy*  | 1/100,000 | Adulthood | Yes | Normal for most patients; severely reduced if cardiac involvement | Heterogenous group of acquired and inherited disorders. TTR gene (autosomal dominant, variable penetration) in hereditary cases | Peripheral and autonomic neuropathy, myopathy |

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