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Lower urinary tract dysfunction in uncommon neurological diseases: A report of the neurourology promotion committee of the International Continence Society

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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 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, and the relevant disease-specific research on the impact of the neurologic condition on the lower urinary tract. Among the degenerative and traumatic brain disorders, we have included frontotemporal dementia, amyotrophic lateral sclerosis, Huntington's Disease, progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy, and traumatic brain injury. Among the autoimmune disorders, we reviewed transverse myelitis, neuromyelitis optica spectrum disorders, Myelin oligodendrocyte glycoprotein antibody-associated disease, glial fibrillary acidic protein astrocytopathy, and meningitis-retention syndrome (a form of aseptic meningitis that presents with urinary retention). Hereditary spastic paraplegia, VACTERL association, and several peripheral neuropathies (Guillain Barre syndrome, chronic inflammatory demyelinating polyneuropathy, autoimmune autonomic gangliopathy, Wolfram syndrome spectrum disorder (a progressive peripheral neuropathy disorder with early onset diabetes, optic atrophy and megacystis in the early stage), Charcot Marie Tooth disease, and amyloid neuropathy are included. Practice points specific to the disorders are included where appropriate.

1. Introduction

The extensive regulation of the lower urinary tract (LUT) at all levels of the neuraxis [1,2] makes neurological disease a substantial part of functional urology practice. The large number of neurological diseases with potential urological impact may appear daunting, but an understanding of fundamental LUT regulation provides general themes which facilitate anticipation of potential relevant effects of most 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 the perception of sensations (which is a higher order function)

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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 centers (sometimes called nuclei) while their processes extend in the white matter or peripheral nerves Some key structures for the LUT are:

1. Motor
    (a) The parasympathetic nucleus, which controls the detrusor muscle, is located in the intermediolateral horn of the spinal cord gray matter.
    (b) Onuf's nucleus in the anterior horn of the sacral spinal cord. Damage here leads to sphincter weakness, hence stress urinary incontinence and fecal incontinence.
    (c) 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.
2. Sensory
    (a) The bladder has proprioceptive nerves responsible for the ordinary filling sensations which travel via the pelvic and hypogastric nerves to the sacral cord and then through the dorsal columns of the spinal cord. This overlaps with the nerves that provide rectal and lower body sensation.
    (b) The bladder also has noxious/pain sensory nerve fibers in the pelvic and hypogastric nerves which are triggered by stimuli such as overdistension or inflammation. These go to the thoracolumbar part of the spinal cord.
    (c) The sensory nerves of the urethra travel via the pudendal nerve, delivering information important for voiding [4], and generating the sensation of urine flow.
    (d) Sensory signals relay at the periaqueductal gray (PAG), which is a key midbrain center vital in numerous sensory and reflex functions, including determining what sensory information progresses to become a consciously perceived sensation.
3. For reflexes affecting the LUT, by far the most important location is the pontine micturition center (PMC) in the brainstem. It functions to keep the spinal nuclei of the lower spinal cord in the appropriate configuration for 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.
4. Higher order functions are complex and not easily mapped onto specific parts of the brain [5]. Functions such as conscious perception of sensation, planning and social appropriateness are underpinned by multiple cerebral centers 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. It is important to remember that neurologic dysfunction can also impact sexual and bowel function. Damage to either the cell body or its process leads to loss of function, so a lesion can affect functions of the centers located there, but also fibers 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 an acontractile bladder, respectively. People with a partial or complete Onuf's nucleus lesion could develop 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 acontractility, since reflexes require sensory input. Partial loss of sensory 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 centers may be impaired in early stages of some conditions, like multiple system atrophy, or rarely with infarction or hemorrhage. 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 detrusor sphincter dyssynergia (DSD), difficult initiating a micturition reflex or detrusor underactivity.
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 recognized 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, detrusor underactivity, involuntary voiding [6] or enuresis can occur, if cortical impairment affects its role in ensuring situational appropriateness of behavior.

If the physician understands the likely distribution of neurologic deficit the potential consequences can be derived for the LUT. The physician should be aware of potential simultaneous urologic or gynecologic conditions that may affect voiding (and not assume that the neurologic disease is the only potential etiology), the impact of pharmacologic interventions associated with these neurologic conditions, and the patients functional and cognitive status. 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 on therapy and follow up (surveillance) requirements. This understanding must be combined with a careful history and physical exam [7], and in most cases urodynamic studies. A careful assessment of sacral sensation (dull touch (which travels via the posterior column) and sharp touch/pain (which travel via the spinothalamic tract)), sacral reflexes and anal tone is important, and very relevant when assessing for a potentially undiagnosed neurologic disease [8]. The objective of this report is to summarize selected uncommon neurological diseases (listed in Tables 1–4) and review the available literature relevant to the associated LUT dysfunction. For some diseases, important practice points are highlighted in Table 5. Diseases and conditions were nominated by the International Continence Society neuro-urology promotion committee members, and then categorized into groups. For our first report,

Table 1
Characteristics of selected degenerative and traumatic disorders of the brain.

Disease/Disorder	Estimated Frequency in the population	Usual Onset	Progressive?	Average lifespan of patient	Gene (if known)	Neurological site of lesion (if known)
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 specialized 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

we selected degenerative brain disorders, autoimmune disease of the brain and spinal cord, and peripheral neuropathies as the focus. Each topic was researched by a committee member using medical database searches of key words related to that disease and lower urinary tract dysfunction, with no date limits.

2. Degenerative and traumatic disorders of the brain

2.1. Frontotemporal dementia (FTD)

Dementia is an overarching term that includes memory loss/disorientation, problems with communication, reasoning, and mood

Table 2
Characteristics of selected autoimmune and inflammatory disorders of the central nervous system.

Disease/Disorder	Estimated Frequency in the population	Usual Onset	Progressive?	Average lifespan of patient	Gene (if known)	Neurological site of lesion (if known)
Transverse myelitis (TM) in general	1–4/100,0000	Adolescents, 30-39year	No	Normal	NA	Spinal cord
Neuromyelitis optica spectrum disorder (NMOSD) with transverse myelitis	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 antibody disease (MOGAD) +/- transverse 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	Acute disseminated encephalomyelitis, spinal cord and/or 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

Table 3
Characteristics of selected spinal cord disorders.

Disease/Disorder	Estimated Frequency in the population	Usual Onset	Progressive?	Average lifespan of patient	Gene (if known)	Neurological site of lesion (if known)
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

changes. 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 one of three distinct forms: primary progressive aphasia, behavioral variant and movement disorder predominant.

It is estimated that 1.3% of the population can be affected with dementia in general, and the prevalence is set to rise with advancing age with 7.1% above 65 years [24]. It is estimated that between 53 and 90% of people with any type of dementia can be affected with urinary symptoms [25]. 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 [26]. It has been suggested that impaired mobility has a stronger correlation with incontinence than cognitive decline in patients with dementia.

Among people with FTD, neurogenic lower urinary tract dysfunction (NLUTD) can be both psychogenic and neurogenic (due to neurogenic detrusor overactivity from a lack of inhibition of the spinobulbospinal micturition reflex) [27]. The proportion of FTD patients with incontinence is between 19%–26% in two case series [28,29]. 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 NLUTD (one with a large PVR, and one with detrusor overactivity) [27]. FTD and Alzheimer's disease have lower rates of incontinence (25%–40%) compared to Lewy body and vascular dementia (80%–90%) [27]. The treatment of dementia often involves cholinesterase inhibitors, which increase acetylcholine levels. This may result in new urinary incontinence [30]. A systematic review on the use of cholinesterase inhibitors and OAB anticholinergic medications identified four studies (with limited methodological quality), and none demonstrated that this combination resulted in significantly worsen cognitive function [11,12].

2.2. Amyotrophic lateral sclerosis (ALS, also know as Motor neuron disease)

ALS is an idiopathic, progressive neurodegenerative disease of the motor neuron system that leads to death. ALS can be familial, with a Mendelian pattern of inheritance disease in 5%–10%, however the majority (90% of the cases) are sporadic. ALS 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 [31,32]. In most cases, there is a relative sparing of neurons innervating the extraocular muscles and

Table 4
Characteristics of selected peripheral neuropathies.

Disease/Disorder	Estimated Frequency in the population	Usual Onset	Progressive?	Average lifespan of patient	Gene (if known)	Neurological site of lesion (if known)
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	Heterogeneous group of acquired and inherited disorders. TTR gene (autosomal dominant, variable penetration) in hereditary cases	Peripheral and autonomic neuropathy, myopathy

sphincters [33]. Direct involvement of the autonomic system does not occur. Mobility (inability to visit the toilet) and life expectancy (usually short after diagnosis) play an important role in management decisions.

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 [34]. 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% [35]. In a recent cohort study with 30 patients, LUTS increased from 24% before to 76% after the ALS diagnosis and the prevalence of storage symptoms increased from 3% before, to 25% after the diagnosis of ALS [36]. 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 [37].

There are little urodynamic data available, however a study of 55 ALS patients 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 detrusor sphincter dyssynergia [38].

2.3. 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 [39,40]. 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 [41]. Their symptoms (urinary frequency, urgency, nocturia, and incontinence), appeared 6 years after the onset of HD [41]. 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 [42]. In a cohort study of 54 HD patients and 10 asymptomatic HD gene carriers [43], 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 [44].

Urodynamics were performed on 12 patients with HD and revealed detrusor overactivity in 2 pts (17%), DSD in 5 pts (42%), and detrusor underactivity in 2 pts (17%) [43].

2.4. 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 to diagnose 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.

Table 5
Relevant neuro-urological practice points for selected uncommon neurological diseases.

Disease	Practice points
Frontotemporal dementia	1. It is important to consider mobility, dexterity, the level of care assistance, and disease progression/life expectancy. In many cases, diapers, condom (external) catheters or indwelling suprapubic catheters may be appropriate management options. 2. The reversible causes of LUT dysfunction should be explored and treated where possible. [9] The treatment is generally conservative with emphasis on understanding the cognitive and functional aspects. 3. Bladder retraining and pelvic floor exercises may have a role in the setting of cognitive impairment or behavioral disturbances and dementia. [10] They may be most appropriate in patients with the ability to learn. Timed voiding or alarm devices might be helpful if caregivers are able to provide consistent support. 4. If necessary, the use of both a cholinesterase inhibitor and OAB anticholinergic medication may be appropriate with careful observation; the level of evidence on this topic is limited by methodological flaws, and studies have reported mixed results [11,12]
Progressive supranuclear palsy	1. Although a treatment strategy that is specific for PSP is not available, patient's older age and susceptibility to cognitive decline should be considered when selected medical treatment for OAB symptoms. [13,14] 2. Patients may have autonomic instability, and therefore alpha-blockers should be used with caution. Patients may be on midodrine (an alpha agonist) for hypotension and in this case use of an alpha blocker may not be appropriate. [15]
Corticobasal degeneration	1. Like PSP, it may be preferable to start with a beta3 adrenergic agonists or antimuscarinics that do not easily penetrate the blood–brain barrier. [14,16]
Multiple system atrophy	1. Patients may visit a urologist before the correct diagnosis is made; therefore, collaboration of neurologists and urologists is highly recommended. Video-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 urgency incontinence, beta3 antagonists or antimuscarinics can be used but the patient's PVR should be monitored for changes over time. 3. Elevated PVRs (>100 mL) can start in the second year of MSA [17]; therefore, the specialist continence nurse has an important role to teach intermittent self-catheterization (ISC) in this group of patients with symptomatic PVRs. 4. Transurethral resection of the prostate should be avoided because the retention is mostly caused by detrusor underactivity, and there is an increased risk of urinary incontinence due to impaired external urethral sphincter function [18–20]. 5. Patients may have autonomic instability and hypotension, and therefore alpha-blockers should be used with caution. Patients may be on midodrine (an alpha agonist) and in this case use of an alpha blocker may not be appropriate [15].
Hereditary Spastic Paraplegia	1. Given the potential for renal deterioration, patients should have neuro-urological 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 a few weeks apart from the skeletal muscle treatments; total botulinum toxin dose that the patient is receiving should be monitored [21].
Guillain-Barré syndrome	1. Post-void ultrasonography is recommended in patients with a higher Hugh's motor grade, higher age and defecation dysfunction. The management of urinary symptoms is mainly supportive [22].
Amyloid Neuropathy (AN)	1. Alpha blockers must be used with caution since they might trigger or exacerbate postural hypotension that often co-exists with amyloidosis. [23]

PSP causes significant NLUTD; [45–48] most commonly this includes urinary urgency and frequency 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. In a comparison of patients with PSP, MSA and Parkinson's disease, the magnitude of NLUTD of PSP was similar to MSA, and generally more severe than that of Parkinson's disease [46].

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 [49,50].

2.5. 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 similar to Parkinson's Disease [16]. 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 [16].

2.6. 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 NLUTD) disorders [51]. 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, with symptoms or signs such as urinary urgency/frequency, elevated PVR, and urinary

retention [47,52]. Up to 18% of MSA patients may present with NLUTD alone, and urinary retention may be a presenting feature [17].

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 [53]. On video-urodynamics, an open bladder neck early in filling with detrusor overactivity is sometimes observed in MSA [47].

2.7. Traumatic Brain Injury (TBI)

TBI results principally from vehicular accidents, falls, acts of violence and sports injuries. This mechanical force acting on the brain damages neuron tissue; this 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. Patients may have associated spinal cord injury, pelvic/bladder injury, or any combination of the above, which makes interpretation of the NLUTD more challenging. Frontotemporal lesions may lead to dysregulation of the learned bladder behaviors, and socially inappropriate voiding. It is important to note that urinary incontinence is a risk factor for falls, and in the elderly these falls could result in a TBI [54].

Although NLUTD 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 [55]. Symptoms may be influenced by the increased secretion of brain natriuretic peptide and resulting polyuria during the early injury period [56]. The incidence of 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 [57,58]. 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 [57]. 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 catheterization at the time of discharge from rehabilitation [57].

Urodynamic studies have demonstrated detrusor overactivity and impaired bladder contractile function 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. Synergistic urinary sphincters are the norm [55,58].

3. Autoimmune and inflammatory disorders of the central nervous system

3.1. 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 [59]. Although general weakness might vary between individuals, nearly all patients have NLUTD, which may outlast general motor and sensory deficit and recovery [60]. Symptoms related to NLUTD range from urinary urgency and incontinence to incomplete bladder emptying and urinary retention. Since TM is an immune-mediated process, treatment of the neurological symptoms usually consists of corticoids and or plasma exchange [61]. Only approximately 1/3 patients will have complete resolution of their urinary symptoms with time (usually among those with mild motor, sensory and LUT symptoms at presentation) [60,62,63].

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 [60,64]. TM extending over a significant length of the spinal cord is significantly predictive of NDO [65]. Since NLUTD 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 intermittent self-catheterization and or treatment for detrusor overactivity by means of anticholinergics and intradetrusor onabotulinumtoxinA injections, and beneficial effects of sacral neuromodulation have also been reported [66,67]. Patients should be carefully monitored, as upper tract deterioration can occur, and persistent urodynamic abnormalities despite motor improvement are common [60,62,63]. Two diseases that include a transverse myelitis component (Neuromyelitis Optica spectrum disorders and Myelin oligodendrocyte glycoprotein antibody-associated disease) are discussed below.

3.2. Neuromyelitis Optica spectrum disorders (NMOSD)

NMOSD are inflammatory diseases of the central nervous system that preferentially affect the optic nerves and the spinal cord (causing TM). They frequently follow a relapsing course, with disabling episodes of Optic Neuritis and Longitudinally Extensive Transverse Myelitis (LETM) [68]. 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 [68–70]. 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 [68].

The prevalence of NMOSD varies throughout the world, and in most regions, NMOSD is less prevalent than MS [71]. NLUTD is present in 78%–83% of the patients and has a significant negative impact on quality of life [72,73]. 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 [73]. 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 [72]. 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.

3.3. 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 glycoprotein on myelin sheaths, causing oligodendrocyte damage and primary demyelination [74]. Clinical manifestations include acute disseminated encephalomyelitis (ADEM), mostly in young children, and an opticospinal presentation in adults (including TM). Although MOGAD has clinical and radiological similarities with NMOSD and MS, these conditions have distinct demographics and are immunologically and pathologically different [69,70]. 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 [70]. MOGAD is considered milder and less relapsing than NMOSD, but clinical outcomes and predictors of relapses remain unknown [69,70,75,76]. MOGAD can present at any age, with a slight female preponderance and no apparent ethnic bias [75]. 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%) [75]. 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 [76,77].

Urodynamic findings in patients with a history of TM predominantly showed detrusor overactivity and/or DSD, consistent with a supraconal lesion [77].

3.4. Glial fibrillary acidic protein (GFAP) astrocytopathy

GFAP (an intracellular astrocytic intermediate filament) astrocytopathy is an autoimmune inflammatory CNS disease first defined in 2016 [78]. Most patients have a meningoencephalomyelitis and can rarely manifest with isolated myelitis. Preceding flu-like symptoms are present in 40%–66% [79]. 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 [80]. Coexisting autoimmune diseases such as diabetes mellitus, autoimmune thyroid disease and rheumatoid arthritis are present in approximately 20% of the patients [81]. 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 [80].

Lower urinary tract symptoms have not been characterized in patients with GFAP but studies mention a rate of 21%–28% of autonomic dysfunction (most commonly unspecified "urinary dysfunction"), which can persist after disease remission [82].

3.5. Meningitis-retention syndrome (MRS)

MRS is an inflammatory neurological condition [83–86]. 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 found [87]) and b) acute urinary retention. Aseptic meningitis is a common condition, which is caused by many viruses but may also be 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 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 [85]. 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 [88]. 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.

4. Spinal cord disorders

4.1. 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 [89]. 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 [90–93]. 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% [90]. Other reports have noted a significant PVR in more than 50% of patients [93]. There was a high frequency of coexisting detrusor overactivity with detrusor underactivity [91,92]. Up to 2/3 patients may have DSD [91,93]. 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 [91]. Conversely, a series of 33 HSP people found that 8% had hydronephrosis, 20% had stone disease, and 17% had chronic renal failure [93]. Some of these differences in urinary disease presentation is likely a result of either case series recruited from neuro-urological practices (with a higher rate of LUTS) as opposed to neurological practices. It is possible that the spinothalamic pathways are partially impacted, or that pelvic floor spasticity results in secondary bladder changes over time.

4.2. 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 [94]. Vertebral abnormalities are one of the most common defects, occurring in about 65%–95% of patients [95]; this can include missing vertebrae, vertebral malformations (fusions, clefts and hemivertebrae), sacral agenesis, spina bifida and tethered spinal cord. These abnormalities may cause NLUTD mainly secondary to a cauda equina/sacral lesion. A proportion of these patients may have spina bifida occulta, and MRI of the spine is appropriate depending on the initial spinal xrays [96]. 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 due to high pressure from reduced bladder compliance [97]. Patients with 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 [98].

5. Peripheral neuropathies

5.1. Guillain-Barré 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 [99].

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 [100]. 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 [101].

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 [22]. 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) [100].

5.2. 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 [102]. The management is supportive [103].

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 [103]. 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 [104].

Urodynamic data were available for 4 patients and it showed abnormal bladder sensation in two, “bladder acontractility” in one and neurogenic changes of the external sphincter in one [103].

5.3. 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 [105]. 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. Therefore 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 [106].

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. Importantly, urinary symptoms improved in most patients following immunotherapy [107] .

5.4. Wolfram syndrome spectrum disorder (WSSD)

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 neurological abnormalities (cerebellar ataxia, peripheral neuropathy, dementia, psychiatric illness, and urinary tract atony) [108,109]. 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 [108]. 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 [109].

NLUTD affects up to 90% of the patients with WSSD and may lead to end-stage renal disease [109,110]. 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 [109–111]. 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 [110,111]. Studies have shown that brain volume is decreased in patients with WSSD and decreased pons volume is associated with worse NLUTD [111]. Bowel dysfunction is also common in WSSD and deserves proper attention [109]. 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 [109,111].

5.5. 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 [112]. 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 [112].

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 [113,114].

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 [115].

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

5.6. Amyloid Neuropathy (AN)

Amyloidosis refers to a heterogeneous 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) [116]. 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) [117]. 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 [117]. The absence of any unique pathognomonic feature makes the diagnosis elusive (the "great mimicker"); a high index of suspicion is necessary and diagnosis is confirmed by tissue biopsy [116].

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 [23,116]. In patients with hereditary ATTR, a systematic review noted urinary symptoms in 83% patients [118]. Onset was noted in the 4th decade (mean age 30 years in males and 34 years in females) with age-associated progression [119]. LUTS include voiding difficulty, frequency, urgency, urinary incontinence and propensity for urinary tract infection [23,118]. 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) [118].

On urodynamics, detrusor underactivity is a consistent finding and is noted in 78% of patients with familial amyloidotic polyneuropathy [23,119]. Other findings are impaired sensation, poor compliance, urethral incompetence, failure of sphincteric relaxation and DSD [23,119,120]. Timed voiding, use of alpha-adrenergic blockers (in men) and intermittent self-catheterization are key components of management.

6. Conclusions

We selected neurological diseases that may not all be immediately familiar to specialists 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. We plan to provide additional review papers summarizing the neurourological management of other uncommon diseases that we could not include in this review.

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 LUT management and any potential interventions should be done in the context of the patient's neurological disease, functional capabilities, prognosis, and their wishes.

CRediT authorship contribution statement

Blayne Welk: Project conception, Writing of individual sections, Writing – original draft, Revised the manuscript and approved the final version. **Ryuji Sakakibara:** Project conception, Writing of individual sections, Writing – original draft, Revised the manuscript and approved the final version. **Sanjay Sinha:** Project conception, Writing of individual sections, Revised the manuscript and approved the final version. **Collette Haslam:** Project conception, Writing of individual sections, Revised the manuscript and approved the final version. **Desiree Vrijens:** Project conception, Writing of individual sections, Revised the manuscript and approved the final version. **Cristiano Gomes:** Project conception, Writing of individual sections, Revised the manuscript and approved the final version. **Stefan De Wachter:** Project conception, Writing of individual sections, Revised the manuscript and approved the final version. **Charalampos Konstantinidis:** Project conception, Writing of individual sections, Revised the manuscript and approved the final version. **Giulio Del Popolo:** Project conception, Writing of individual sections, Revised the manuscript and approved the final version. **Pawan Vasudeva:** Project conception, Writing of individual sections, Revised the manuscript and approved the final version. **Marcus J. Drake:** Project conception, Writing of individual sections, Revised the manuscript and approved the final version. **Rizwan Hamid:** Project conception, Writing of individual sections, Revised the manuscript and approved the final version.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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