Urological Care for Patients with Progressive Neurological Conditions

John T. Stoffel
Elizabeth V. Dray
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Part I
Fundamentals of Neuro-urology

Chapter 1
Introduction

John T. Stoffel and Elizabeth V. Dray

Introduction

Urologic care for patients with progressive neurologic conditions is both similar and different than care for other neurogenic bladder patients. Although the goals of safe urine storage and evacuation remain consistent among all neurogenic bladder patients, there are considerably more variables to consider when treating patients with progressive neurologic conditions. First, progressive disease may cause ongoing changes in bladder physiology. For example, overactive bladder symptoms may transition into an underactive bladder or new incontinence may develop as higher brain function is lost. Second, continuing cognitive changes may mean that self-care options that were previously effective may become unsuitable for patients over time. This coincides with a loss of independence as patients are unable to remember to take medications or follow a timed schedule. Third, changes to muscle strength and dexterity may force adjustments in bladder management strategies. The most obvious change includes switching from voiding or intermittent catheterization to an indwelling catheter, but other factors such as inability to ambulate, talk, or breathe weigh heavily on urologic treatment strategies. Given these changes over time, it is clear that care for progressive neurologic patients is many times more reactive and less scheduled compared to other neurogenic bladder neurogenic bladder patients.

If properly addressed, most neurogenic bladder patients, including those with a progressive condition, can expect reasonable urinary-specific quality of life and protection against morbidity such as urinary tract infections and renal failure.

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However, many practitioners have limited understanding on how to best treat patients with neurogenic bladder problems related to a progressive neurologic condition. Some conditions such as multiple sclerosis are more common and the urologic needs are a better understood among the urologic community, but other conditions such as cerebral palsy or Huntington's Chorea are rarely encountered by urologists. In fact, there is little guidance supported by data on how to best establish urologic care for most progressive neurologic conditions. Barriers to consistent urologic care in this population include lack of knowledge regarding disease pathophysiology, lack of knowledge on how to best evaluate these patients, and a lack of knowledge regarding risk/benefit stratification for available treatments (Fig. 1.1).

Lack of knowledge regarding disease state is the first barrier to overcome. By definition, *a neurogenic bladder is a condition in which urinary symptoms are related to an underlying neurologic condition*. It is our feeling that great attention should be focused on understanding the relationship between neurologic condition and neurogenic bladder symptoms. Looking at Fig. 1.2, it is easy to see how care for patient with a progressive brain involvement such as Huntington's chorea can be very different than a patient with a process that affects neuromuscular junctions such as Eaton Lambert just based on the different involved regions of the nervous system. Interpreting symptoms in this light leads to a more holistic approach that appreciates the different needs of patient groups.

The other barriers to good urologic care are less easy to overcome. Urologic testing strategies regarding neurogenic bladder patients, in general, are likewise not always clear. It is understood that urodynamics are helpful in understanding neurogenic bladder physiology, but there are no standardized, disease-specific urodynamic protocols that address the unique pathophysiology or limitations of patients with progressive conditions. Similarly, there are no guidelines for imaging, quality of life assessment, or home health care for these patients. Lack of knowledge of regarding risk stratification for treatments can also limit options for these patients. Since many of the patients fall outside standard procedural and preoperative assessment protocols, it frequently falls on the urologists to determine if an intervention is worth the risk to the patient. Consequently, this lack of knowledge regarding risk/

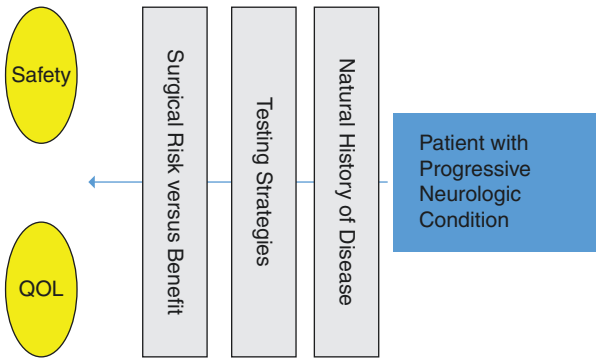

Fig. 1.1 Barriers to urologic care for the patient with a progressive neurologic condition

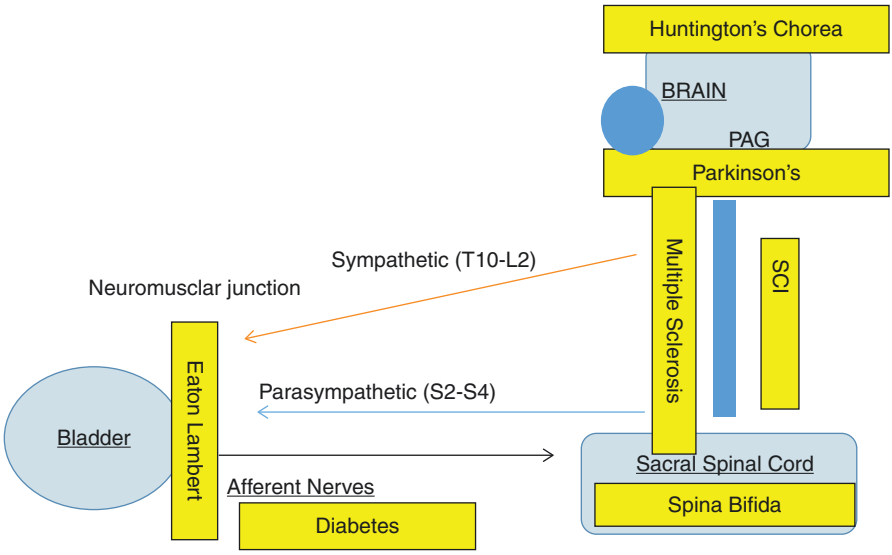

Fig. 1.2 Some neurologic conditions causing neurogenic bladder

benefit can unfortunately lead to under treatment in some of the patients and over treatment in others.

The purpose of this textbook, *Urologic Care for the Patient with a Progressive Neurologic Condition*, is to address these knowledge gaps and provide readily available information for the reader to use in the care of these patients. Our goals are to create a resource where providers can quickly access a summary of a specific disease pathophysiology, see the timeline of symptom progression, and understand unique characteristics about the disease which can impact urologic care. In short, the book should be a practical reference for the learner to quickly review and ensure appropriate urologic care is provided for this patient.

In Part 1, Chaps. 2, 3, 4, 5, 6, 7, and 8, we emphasize areas of knowledge that can be applied to any patients with progressive neurologic conditions, such as basic bladder physiology, neuro-anatomy, fundamentals of a neurologic exam, urodynamic testing, imaging modalities and limitations, quality of life assessments, and generalized neurogenic bladder care strategies. Special note is made in these chapters on how to apply these tests to patients with progressive neurologic conditions, if applicable.

In Part 2, Chaps. 9, 10, 11, 12, 13, 14, 15, 16, 17, and 18, we focus on providing a high level summary regarding the urologic care for patients with Parkinson's disease, Alzheimer's/dementia, ALS, cerebral palsy, Huntington's chorea, multiple sclerosis, Friedrich's ataxia, Guillain Barre, Eaton Lambert, and diabetes. Each progressive disease is reviewed for disease pathophysiology (mechanism of action) and the organs that are affected. Key tests for diagnosing the disease are discussed and timeline of disease progression is reviewed. Special attention is focused on

common urologic symptoms that are disease-specific, and if applicable, unique surgical risks for each disease state are highlighted.

In Part 3, Chaps. 19 and 20, we discuss how individual differences in disease states can be used to develop a home health care plan and prevent additional urologic morbidity.

It is our sincere hope that this textbook will raise awareness around the urologic care of this sometimes-marginalized population. It is important to remember that safe bladder and a stable urinary quality of life can be achieved for these people. Ultimately, we hope that this textbook can add to the health and happiness for patients with progressive neurologic diseases.

Chapter 2
Basic Bladder Physiology and Anatomy

Venkat M. Ramakrishnan and Jairam R. Eswara

Introduction

The urinary bladder is a critical organ at a key juncture in the urological outflow tract. Though it primarily serves as a storage reservoir for urine, the bladder's mechanical, contractile, and neurological properties allow humans and animals alike to adapt to a variety of scenarios, such as urinating at opportune or socially acceptable times, or holding urine during times of immense sympathetic stress such as the classic "fight-or-flight" response. Such examples clearly paint the bladder as an organ of convenience. These are scenarios that many take for granted, but those with bladder dysfunction (via bladder cancer, injury, neuropathy, or otherwise) are acutely aware of the sequelae that affect other organ structures (of particular interest to urologists are the upper urological tracts and kidneys) and overall quality of life. Many patients with a significant bladder-related component of their disease(s) often contend with a life of urinary frequency, loss of control, leakage, unpredictability, and – in several cases – significant social and psychological impairment [1]. To best understand the body of bladder dysfunction in the setting of degenerative neurologic conditions and treatment strategies presented in this book, we provide a brief overview of bladder structure, function, and physiology.

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Basic Urinary Bladder and Detrusor Function

The urinary bladder is a hollow subperitoneal organ positioned beneath the abdominal viscera and housed deep within the pelvis. It is situated superior to the prostate gland (the *space of Retzius* lies anteriorly and is often accessed during prostatectomy) and directly anterior to the rectum in males (bordered posteriorly by a space known as the *rectovesical excavation*, the base of which is comprised of *Denonvillier's fascia*). In females, the bladder lies directly anterior to the vagina (the conceptual space known as the *vesicouterine pouch of Meiring* separates the two). Given that the bladder originates from the urogenital sinus and was, at one point, continuous with the allantois, it remains loosely associated with the anterior abdominal wall via the obliterated *urachus* and related *median umbilical ligament*.

The body of the bladder itself is comprised of smooth muscle (the *detrusor muscle*) as well as up to 50% collagen (particularly types I, III, and IV) and 2–3% elastin [2]. The detrusor is primarily responsible for changes to *compliance* (defined as the change in volume per unit of pressure) and capacity. This is evidenced by the fact that bladder injury yields a dramatic increase in the amount of reparative collagen deposition (namely type III collagen) and a concurrent decrease in compliance. Moreover, increased age decreases the muscle-to-collagen ratio and the collagen, which cross-links over time, also decreases the overall bladder compliance. Anatomically, the low compliance bladder wall appears thickened on cross-sectional imaging (Fig. 2.1), partly as a result of these extracellular matrix changes.

The internal structure of the bladder and proximal urethra also contain notable features. Posteromedially, the ureters enter the bladder at their corresponding *ureteric orifices*, forming two corners of a triangle known as the *bladder trigone* that is positioned to guide urine down the bladder neck and into the proximal prostatic urethra. The ureteric orifices possess one-way mucosal flaps that prevent the reflux of urine back into the ureters *(vesicoureteral reflux)*; this anti-reflux mechanism can be defeated in instance of high intravesical pressure or defects to the native anatomy. In males, the smooth *internal urethral sphincter* (derived from the detrusor muscle) encircles the bladder neck just above the prostate gland. The striated *external ure-*

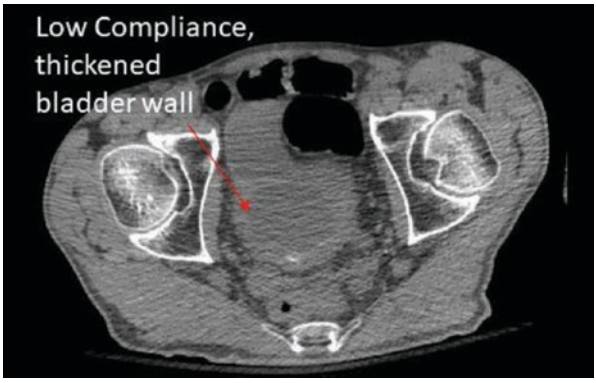

Fig. 2.1 CT image of a thickened, low-compliance bladder representing alterations in extracellular matrix

thral sphincter is positioned just inferior to the gland and medially to the *bulbo-urethral (Cowper's) glands*, and is contiguous with the urogenital diaphragm. In females, the sphincter complexes are positioned adjacent to one another. Compared to males, the female striated sphincter runs more longitudinally. The sphincter urethra wraps around the urethra, similar to males. The distal sphincter complex function is augmented by a urethrovaginal muscle and compressor urethrae muscle group which helps promote continence in the absence of urethral length (Fig. 2.2).

Arterial blood supply to the bladder comes from the branches of the iliac vessels, and specifically the internal iliacs, which give off the superior vesical and umbilical arteries as well as the inferior vesical artery with its prostatic branches. Venous drainage occurs via corresponding veins that feed into the internal iliac veins, with the exception of a prostatic venous plexus that envelops the inferior aspect of the bladder as well as the entire prostate. Posterior, lymph drainage of the bladder courses directly to the external iliac nodes and, from there, to the common iliac nodes. Anterior drainage is housed in the prevesical plexus that also joins the external iliac nodes.

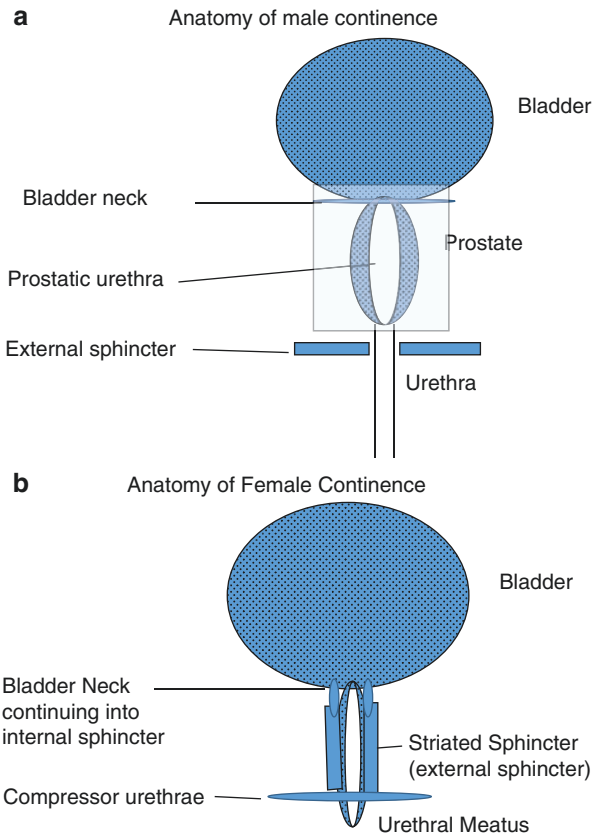

Fig. 2.2 Schematics depicting male (**a**) and female (**b**) continence

Urinary Bladder Neurological Control and Innervation

Neurological control of urinary bladder function is incredibly intricate (Fig. 2.3). Globally, there are three input sources that drive micturition. The bladder contains afferent fibers (myelinated A and unmyelinated C fibers) with mechanoreceptors that interpret pressure/stretch (A), irritation (C) in the bladder wall [3]. This conveys characteristics such as awareness, fullness, urgency, pain, and temperature. Also mentioned earlier was that the bladder is an organ of convenience. Cognitive interpretation of various situations and the "decision" to urinate is carried out by higher cortical centers. Lastly, emotional behaviors and stress responses are controlled by the limbic system. These three sources – bladder afferents, the cerebral cortex, and the limbic system – all provide information to the medial frontal cortex of the forebrain within the periaqueductal gray matter. From here, stimuli are sent to the pons, which houses the brain's micturition (medial pons) and continence centers (lateral pons). These are oppositional roles – that is, one function supports the contraction of the detrusor and subsequent expulsion or urine (i.e., *micturition*), while the other relaxes the detrusor and simultaneously stimulates the striated external urethral sphincter, thereby promoting the voluntary storage of urine (i.e., *continence*). The nerves that ultimately execute these functions originate from the spinal cord.

Anatomically, the innervation of the urinary bladder is an equally complex affair [2]. Multimodal control is obtained via sympathetic, parasympathetic, somatic efferent, and afferent nerve fibers. Interestingly, the framework for this level of control is laid during embryonic development, as the detrusor is of combined mesodermal and neural crest origin. At the lumbar spinal cord levels L1 and L2, *sympathetic preganglionic fibers* originating in the intermediate gray matter exit via the ventral root of the spinal cord, coursing through white rami communicantes and into the sympathetic trunk. At L1 and L2, these fibers can leave the sympathetic trunk and run along the aorta anteriorly and laterally via the intermesenteric (aortic) plexus

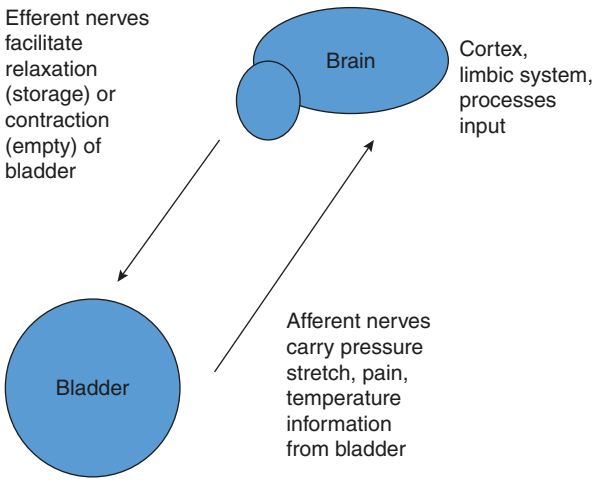

Fig. 2.3 Overview concept of bladder and CNS signaling

and the inferior mesenteric ganglion. Fibers can also exit the sympathetic trunk and join the sacral splanchnic nerves and inferior hypogastric (pelvic) plexus. All of these fibers and tracts ultimately coalesce with a complex web of *postganglionic fibers* to innervate the bladder wall, ureters, prostate gland, and the external genitalia. *Parasympathetic preganglionic fibers* exit the spinal cord at the levels of S2–4, briefly entering the sacral plexus before joining the pelvic splanchnic nerves prior to innervating the bladder wall. Afferent fibers (mechanoreceptors – that is, "stretch" or distensibility receptors) sense bladder fullness and travel back via the sacral and inferior hypogastric plexuses to the sacral spinal cord [3]. Of note, these fibers are also in close relation to (and in the case of the parasympathetic supply, the same as) those that innervate the descending and sigmoid colon as well as the rectum.

Neurological control of voiding is critically dependent on the activity of various neurotransmitters, all of which are released based on direction from the pons [4, 5]. Also vital to this process is coordinated communication between the bladder and the urethral sphincters. To start, one is stimulated to urinate when the bladder fills to a capacity of approximately 200–500 cc of urine, though maximal capacities can be significantly higher. The act of filling stretches the aforementioned mechanoreceptors and conveys to the pons a need to induce urination [2]. The pontine micturition center then signals for detrusor contraction, mediated by acetylcholine (ACh) via M_2, M_3, and M_5 muscarinic cholinergic receptors on detrusor myocytes via a G-protein–calcium channel mechanism. M_2 receptors are the most numerous (with up to 75% prevalence) as opposed to M_3 and M_5 (approximately 25%) [6]. When the detrusor is stimulated to contract, concurrent relaxation of the internal urethral sphincter primes the bladder to release urine when convenient. The pontine micturition center inhibits the spinal guarding reflexes which act to inhibit involuntary bladder emptying and relaxes the external urethral sphincter via *Onuf's nucleus* such that urethral pressure decreases. Combined with the concurrent increase in bladder pressure, urine flows down the pressure gradient and out the body. The act of voluntarily releasing urine via this process is what defines *urinary continence*.

Cessation of voiding is highlighted by detrusor relaxation, which is achieved via activation of the pontine continence center and the downstream sympathetic action of norepinephrine on β-2 and β-3 adrenergic receptors. This elicits a G-protein–potassium efflux-dependent mechanism that relaxes the detrusor and prevents contraction (this is also one of the mechanisms capitalized on by pharmaceutical β-3 agonists, which are often used to treat bladder overactivity [7]). Concurrent involuntary contraction of the smooth internal urethral sphincter is achieved sympathetically, with norepinephrine acting on α-1 adrenergic receptors that are G-protein–calcium channel-mediated. The external urethral sphincter can also be voluntarily stimulated to contract (thereby promoting continence) under the auspices of somatic parasympathetic control, via the pudendal nerve, with ACh binding to nicotinic inotropic receptors. Figure 2.4 summarizes the bladder receptor physiology.

With the basic overview of the interplay between the nervous system, detrusor, and urethral sphincter complete, several additional points must be made. First, sympathetic control of voiding can *override* parasympathetic inputs. The norepinephrine required to relax the detrusor can also act on α-2 adrenergic receptors in

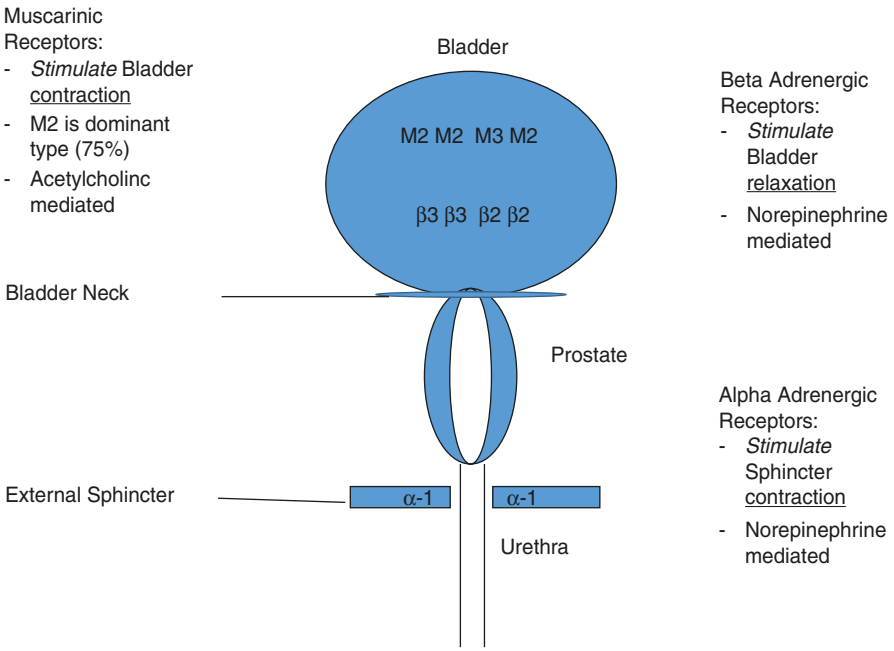

Fig. 2.4 Contraction and relaxation is mediated by receptors in bladder

the pelvic ganglia to block the transmission of parasympathetic signaling. Second, with the aforementioned framework, it is easy to understand why disruption of this *highly coordinated control system* – via multiple sclerosis lesions, for instance – often results in *detrusor-sphincter dyssynergia* (DSD), a condition in which the detrusor contracts against a closed urethral sphincter. Third, this intricate system is also active during sexual activity. Sympathetic overdrive during ejaculation forces the internal urethral sphincter to contact and creates a natural one-way valve that promotes the antegrade flow of semen out the penis [8]. Fourth, it is important to recognize that blood flow to the muscle and mucosa are directly affected by intramural tension [9]. Continued distension can lead to ischemia as the supplying vessels are stretched and resistance is increased. In diseases of severe distension – most notably in those with spinal cord injury or other neurological conditions – bladder sensation is diminished or completely absent. This results in a sequence of overdistension, ischemia, consequent injury and/or death of once-healthy mucosa and muscle, preferential remodeling of the affected areas with collagen over muscle, and ultimately the permanent alteration of bladder compliance.

Thus far, we have outlined a complex system of higher cortical control for voiding and storing urine. Concurrently, there also exist primitive autonomic reflexes within the spinal cord and extra-neurological urothelial factors that affect these processes. Regarding the latter, factors such as obesity and metabolic disease (in particular, diabetes and associated neuropathies), fibrosis, ischemia, inflammation, and even various foods all play a role in establishing long-term lower urinary tract dysfunction. Many of these factors are well integrated with one another.

Tools for Evaluating Function of Bladder Anatomy

Bladder Diaries

There exist a whole host of methods for assessing bladder (and specifically, detrusor) function, the simplest of which is to have patients complete a bladder diary. Factors such as time of day, fluids and food (type and quantity), frequency and volume of urination, and in-depth analysis of accidents (such as leakage, urge to urinate, and surrounding activities (for e.g., sneezing, exercising, running, etc.)) are all systematically measured over a period of time. This provides clinicians and patients with useful information regarding possible intrinsic and extrinsic factors that contribute to a patient's symptoms. Recent studies have demonstrated that 3 days' worth of data collection are sufficient enough to assess lower urinary tract symptoms in adults [10, 11] and 2 days in children [11], though shorter durations are expectedly associated with a higher false-negative rate. The diary remains a good evaluation to determine how bladder physiology is impacting daily functioning.

Bladder Scanning and PVR

An additional tool for evaluating bladder physiology is to have the patient attempt to void and measuring a *post-void residual* (PVR) with a bladder-scanning ultrasound can provide immediate numerical data and, depending on the scanner, correlative imaging. PVRs of less than 10% of the voided volume are considered insignificant. It is important to recognize that false-positives for urinary retention can result in patients with excessive adiposity, gynecological disease [12], severe cardiovascular disease [12], and oncologic burden, for instance. In conjunction with measuring PVR, evaluation of the patient's electrolytes (particularly, the renal function) and renal ultrasound can provide evidence of possible upper tract involvement.

Urodynamics

Urodynamics (UDS) is a critical tool for bladder and voiding evaluation and is part of the armamentarium of every urologist. Urodynamic testing is covered in more detail in chapter 8. Broadly, UDS is comprised of a group of metrics that interrogate bladder physiology, define abnormalities of the lower urinary tract, and elucidates issues with the transport, storage, and evacuation of urine in the context of the patient's urological symptoms. The first metric, *cystometry*, can be further subdivided into filling and voiding cystometry and is the key test that evaluates detrusor function. Filling cystometry establishes a pressure–volume curve for bladder filling and can easily assess bladder sensation, capacity, compliance, and detrusor activity. This helps the practitioner determine if the bladder physiology is normal or has been

potentially impacted by a neurologic condition. Voiding cystometry does the same, but for bladder emptying. Critical to both of these tests is an awareness of *intravesical pressure* (P_{ves}) as well as the *abdominal pressure* (P_{abd}) surrounding the bladder, which can be estimated via probes inserted into the rectum, vagina, extraperitoneal space, or ostomy. From these pressures, the *true detrusor pressure* ($P_{det} = P_{ves} - P_{abd}$) can be determined. The resultant graph is primarily comprised of two key phases – the filling/storage phase and the voiding phase. In short, urodynamics can summarize how the bladder anatomy described above functions in real time.

Uroflowmetry is also part of the suite of UDS metrics and simply measures the flow rate of urine (in mL/seconds) over a defined time period (seconds). The emphasis is made on identifying the maximum flow rate, the time to maximal flow, the voided volume, and the total flow time from start to finish. As mentioned earlier, voiding is critically dependent on the carefully orchestrated interplay between the bladder and urethral sphincters. Uroflowmetry provides data that is a direct combined reflection of the effectiveness of detrusor contraction, degree of urethral sphincter relaxation, and patency of the urethra via *urethral pressure measurement* [13].

Two final subsets of UDS worth emphasizing are *Video-UDS* and *electromyography*. Video-UDS combines the analytics of UDS with real-time fluoroscopic imagery of the lower urinary tract and is particularly useful for differentiating bladder neck obstruction from dysfunctional voiding. The modality can also be used to visualize vesicoureteral reflux, evaluate neurogenic bladder disease, and has the added benefit of potentially identifying malignancies/anatomic abnormalities along the urinary tract including the bladder mucosa by visualizing filling defects or outpouching during the cystogram. Electromyography, on the other hand, relies on electrodes placed in or near pelvic floor muscles of interest. This facilitates the quantitative analysis of muscle depolarization and expedites the evaluation of underlying neurological abnormalities affecting urethral sphincter and pelvic floor muscle function.

Concluding Remarks

The urinary bladder plays a critical role in the storage and expulsion of metabolic waste products. The detrusor is, quite literally, central to the action, though its function and tone depend on how a complex web of neural inputs interact with end organ receptors in the bladder and adjacent sphincters. Neurologic diseases can impact signaling to the bladder and cause changes in storage and emptying to ultimately result in the wide spectrum of symptoms and signs associated with a neurogenic bladder.

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Chapter 3
Neuroanatomy: Overview of Functional Signaling Pathways

Blayne Welk and Jalesh N. Panicker

Introduction

The lower urinary tract (LUT) has two essential functions: storage and voiding of urine. During the storage mode, urine is allowed to passively fill the bladder: the kidneys must be able to drain freely into the bladder, the bladder must have a normal capacity, the walls of the bladder must be compliant and able to accommodate the increasing volume of urine, a normal sensory signal must be relayed to the central nervous system (CNS) for conscious perception of fullness, and the urinary sphincter must be competent and be able to prevent leakage. During the voiding phase, urine is allowed to fully exit the bladder: a conscious decision is made to urinate at a socially acceptable time, the urinary sphincters and other pelvic floor muscles relax, and there is a coordinated contraction of the bladder which is then able to fully empty through an unobstructed urethra. The neurologic control of storage and voiding of urine is dictated by several key structures and pathways in the central and peripheral nervous system that control and coordinate the bladder's detrusor muscle (urinary reservoir) and the urethral sphincter (urinary outlet).

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General Neuroanatomy Review

The CNS consists of the brain and spinal cord. The peripheral nervous system (PNS) consists of the afferents (sensory fibers that travel *toward* the CNS to relay sensations from the body or environment), and efferents (motor fibers that travel *away* from the CNS and signal organs or muscles in the body). Sensory afferents from the bladder sense fullness and enter the CNS through A-delta fibers via the dorsal root ganglia of the spinal cord. C-fibers are another afferent; however, they remain dormant in the healthy bladder. In pathological situations, such as following spinal cord injury or exposure to noxious stimuli, these become active and also respond to bladder filling, leading to abnormal bladder sensations or pain. Motor efferents exit the CNS via the ventral roots of the spinal cord.

Within the PNS, there is a somatic nervous system (which allows voluntary control of structures such as the urinary sphincter), and the autonomic nervous system (which provides unconscious control over visceral and endocrine function). The only somatic control of the LUT is through the pudendal nerve, which is derived from the cell bodies in an area of the ventral gray matter of the sacral spinal cord (S1–S3 segments) that is called Onuf's nucleus.

The autonomic nervous system has both parasympathetic (cranio-sacral) and sympathetic divisions (thoraco-lumbar) based on their anatomic relationship to the CNS (Fig. 3.1). The parasympathetic nervous system pathways relevant to urination arise from a different region of the gray matter of the sacral spinal cord and innervate the LUT through the pelvic nerves; the parasympathetic preganglionic motor efferents are long, and their ganglion are located near the bladder in the pelvic plexus. The sympathetic nervous system pathways relevant to urination arise from the T10-L2 spinal cord segments and innervate the LUT through the hypogastric nerve; the sympathetic preganglionic motor efferents have varying lengths. The pudendal, pelvic, and hypogastric nerves have both efferent and afferent fibers, which regulate motor and sensory functions of the LUT. There are several voiding

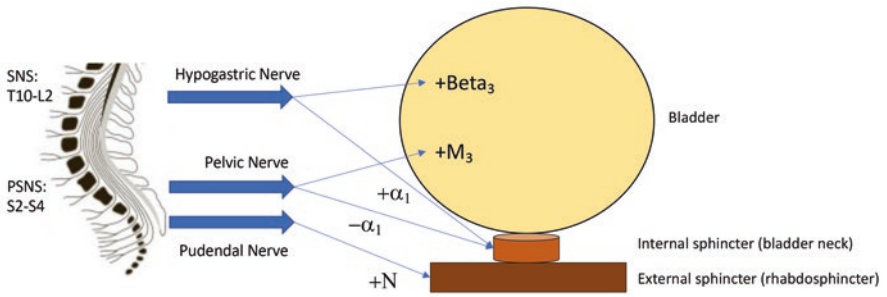

Fig. 3.1 Schematic of the sympathetic and parasympathetic pathways leading to the bladder. The hypogastric nerve stimulates $beta_3$ receptors in the bladder (to relax the bladder), and $alpha_1$ receptors (to contract the sphincter) during storage of urine. The pelvic nerve stimulates $muscarinic_3$ receptors (to contract the bladder) and inhibits $alpha_1$ receptors (relaxing the sphincter) during voiding of urine. The pudendal nerve contracts the external sphincter by activating nicotinic receptors

and storage spinal reflexes mediated by interneurons in the T10-L2 and S2–S4 spinal cord segments.

The bladder itself is made of smooth muscle, extracellular matrix, and urothelium. The smooth muscle component is referred to as the detrusor. There are two urinary sphincters: the internal (or bladder neck) sphincter and the external (or rhabdosphincter) sphincter. Conceptually, these are often considered as separate structures; however, there is considerable overlap and intermingling between the smooth muscles of the internal sphincter and the striated muscles of the external sphincter [1, 2].

Central Control of the LUT in Health

Functional brain imaging has greatly improved our understanding of the role of different regions of the brain in urine storage and voiding [3, 4]. The pontine micturition center (PMC, previously referred to as Barrington's nucleus in animal studies) and the periaqueductal gray (PAG) are key centers in the brainstem and midbrain that are involved in urinary control. During the storage of urine, sensations of bladder fullness are conveyed from the LUT, and the first point of relay is the periaqueductal gray (PAG) in the midbrain. The insula, hypothalamus, thalamus, and dorsal anterior cingulate cortex are important regions involved in the conscious perception of bladder fullness. The medial prefrontal cortex is the "checkpoint" where the conscious decision to void occurs. Until this decision is made, the medial prefrontal cortex inhibits the PAG, which in turn inhibits the PMC. As the sensory afferents are increasingly activated during storage, this leads to increasing activation of the bladder's sympathetic efferent innervation of the bladder and the internal urethral sphincter to promote further storage of urine. The sympathetic efferents release the neurotransmitter norepinephrine which activates beta-3 receptors in the bladder, resulting in relaxation of the detrusor, and alpha-1 receptors in the internal urethral sphincter that results in contraction of the urinary outlet. At the same time, the sympathetic nervous system inhibits contraction of the bladder by inhibiting the parasympathetic ganglia. Pudendal nerve efferents are activated and through the neurotransmitter acetylcholine activates nicotinic receptors, thereby increasing the tone of the striated external urethral sphincter [5–7].

At an appropriate time and place to void, inhibition of the PAG from different brain regions including the medial prefrontal cortex and the hypothalamus ceases; this in turns removes the PAG-mediated inhibition of the PMC and facilitates voiding. Inhibition of pudendal nerve functions results in relaxation of the external urethral sphincter. Sympathetic-mediated activity is inhibited, and the parasympathetic innervation mediates detrusor contractions. The neurotransmitter acetylcholine activates muscarinic receptors in the bladder wall, and inhibits the internal urethral sphincter with the release of nitrous oxide, leading to further relaxation of the urinary outlet [5–7].

The guarding reflex is a spinal reflex relevant to many neurologic diseases [8]. As the bladder fills, there is an unconscious and involuntary contraction of the external urethral sphincter-mediated through the bladder sensory afferents (in the pelvic

nerve), sacral spinal cord, and pudendal nerve. When the sensory input from a full bladder penetrates consciousness, the reflex is further augmented by the somatic efferents in the pudendal nerve that further contract the external urethral sphincter and is associated with awareness of this action. As the guarding reflex is activated, pudendal sensory afferents inhibit parasympathetic innervation of the bladder through interneurons in S2–S4 of the sacral spinal cord, thus allowing further bladder filling. Input from the PMC is required to regulate the guarding reflex. For example, in complete suprasacral spinal cord injuries, there is often incomplete bladder emptying due to the failure of the PMC to switch off the guarding reflex during voiding. Other pathways can activate the guarding reflex, such as the ventrolateral medulla (nucleus retroambiguus), which activates the Onuf's nucleus following the anticipation of a cough or sneeze to prevent stress incontinence.

LUT Dysfunction Following Progressive Neurologic Disease

The neural control of LUT functions is affected following neurological disease, and from an understanding of neuroanatomy, it is possible to infer the pattern of LUT dysfunction. However, the constellation of storage and voiding symptoms that a patient may experience can be influenced by different variables such as severity of disease, coexisting non-neurogenic urological complications (such as stress incontinence, or benign prostatic enlargement) and functional status. Diseases that affect signaling or function of the cerebral cortex (such as dementia, or Huntington's chorea) are often associated with urgency and urgency incontinence due to inconsistent control of the PMC. Diseases that affect both the brain and spinal cord (such as multiple sclerosis) can lead to a variety of urinary symptoms such as urgency and urgency incontinence (due to damage to the pathways controlling the PMC), and urinary retention (due to damage to the nerves in the spinal cord that control bladder emptying), or detrusor sphincter dyssynergia resulting from a neurological disconnect between the PMC and the guarding reflex. Other diseases (such as Guillain-Barre syndrome, or diabetes) affect the peripheral nervous system, and therefore damage to the pelvic, hypogastric, and pudendal nerves can lead to urinary retention and an areflexic bladder. In most cases, as disease severity increases, the urologic symptoms also get worse.

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Chapter 4
Measuring Urologic Quality of Life in People with Progressive Neurologic Conditions

John T. Stoffel

Introduction

When caring for patients with progressive neurologic diseases, it is important to remember that almost all medical decisions are influenced by two factors: safety and quality of life. Patient safety issues center around avoiding morbidity and/or mortality. Urologic patient safety examples include preventing and treating urinary tract infections, managing bladder pressures to reduce risk of hydronephrosis, and treating urinary incontinence to avoid progression of sacral decubitus ulcers. Quality of life, however, is a more complicated variable to measure among neurogenic bladder patients with progressive neurologic conditions. Rate of disease progression, physical impairment, and cognitive decline will all impact how a person "measures" his or her quality of life. An example of differences in QOL perception is seen among multiple sclerosis patients at different stages of disease progression. In one study, relapsing/remitting patients reported more severe urinary symptoms than secondary progressive patients despite having very similar urodynamic findings and voiding diaries [1]. This chapter will review some common health-related quality of life measures (HRQOL) and patient-reported outcome measures (PROM) relevant to neurogenic bladder care among patients with progressive neurologic diseases. By better understanding the domains and target populations of these instruments, it is hoped that practitioners will begin to use questionnaires to assess quality of life more frequently for these patients.

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Questionnaires

Patient-reported outcomes (PRO) is a general term used to describe a patient's perspective on his/her quality of life and overall health. HRQOL and PROMS measurements utilize validated questionnaires to report on PROs, usually regarding a specific question [2]. A validated questionnaire should demonstrate consistent, reproducible ability to measure differences among a population. A good validated questionnaire will produce a bell curve of score distribution around a mean score, indicating a range of severity among a population. Questionnaires that trend toward only accurately measuring the edges of the bell curve are described as having a ceiling or floor effect [3, 4]. HRQOL and PROMS can cover general conditions across many populations [5] or focus on specific conditions such as bladder/bowel/pelvic floor disorders [6, 7]. Many HRQOL and PROMS are specific only for the population in which it was validated. Consequently, altering a validated questionnaire or applying to different population may result in inaccurate PRO measurements.

General HRQOL and PROMS

As noted above, general HRQOL/PROMS instruments measure perceptions around physical abilities, mental health, and general satisfaction with life functioning. It should be kept in mind, however, that many of these questionnaires make general assumptions about the population that may not be applicable to a patient with a progressive neurologic illness, particularly regarding ability to ambulate.

Quality of Life Scale (QOLS)

QOLS was one of the first widely applied general QOL measurement tools. Developed in the 1970s by Flanagan, *QOLS used 16 items to measure satisfaction in the domains of Physical and Material Well-being; Relations with other People; Social, Community, and Civic Activities; Personal Development and Fulfillment; and Recreation* and was initially applied to measure differences across a general population of adults living in the United States [8]. It tested well across age groups and cultural background. This tool has been since applied to study QOL in chronically ill populations. Although it is not widely used in the urologic literature, it has been used to study QOL in patients with long-term ureteral stents [9].

Satisfaction with Life Survey (SWLS)

The SWLS is one of the most widely used general HRQOL/PROMS instruments. Developed in 1985, *it is a five-item questionnaire that assesses satisfaction with well-being* and has been used in multiple populations, including children, and is translated into several different languages [10]. Recently, a group reviewed the SWLS use over the past 30 years and noted that there were meaningful comparisons between genders among survey responders but less meaningful comparisons across age groups and cultures [11].

Medical Outcomes Study Short Form (SF 36, SF 12)

The SF 36 is a 36-item questionnaire that was derived from the RAND corporation Medical Outcomes Study. Outcomes for this study included the physical, social, and role functioning of people during everyday living, people's perceptions of general health and well-being; and their satisfaction with medical treatment received [12]. Over the past 25 years, the SF 36 has been widely used to study chronically ill populations. The SF 12 is an abbreviated 12-question instrument stemming from the SF 36 and is many times used interchangeably with the SF 36. The SF 36 has eight scales [13, 14] including:

- Perception of general health
- Vitality
- Physical functioning
- Physical role functioning
- Mental health
- Bodily pain
- Emotional role functioning
- Social functioning

The SF 36 is a commonly used in neurogenic bladder research as reported in a 2014 systematic literature review of QOL measurements for neurogenic bladder and neurogenic bowel [7].

Urinary-Specific Questionnaires

Urinary-specific HRQOL and PROMS are used to assess impact of bladder symptoms and measure the outcome of interventions. Multiple instruments are available which assess severity and bother of conditions such as stress incontinence,

overactive bladder/urge incontinence, bladder outlet obstruction, and bladder pain. There is no universally accepted urinary-specific questionnaire and each instrument has its merits and limitations. Furthermore, many of the questionnaires are not validated for some progressive neurologic disease populations with significant urinary symptoms, such as Parkinson's disease [15]. Some of the urinary symptoms associated with less common progressive neurologic conditions have not been assessed formally with a urinary-specific questionnaire.

International Prostate Symptom Score

The IPSS and its close associate the American Urological Association Symptom Index (AUA-SI) is one of the most commonly used urinary-specific questionnaire. *The IPSS has seven questions which assess incomplete emptying, urinary frequency, intermittency of stream, urgency, weak stream, and nocturia and it has one additional question about the person's perceived quality of life* [16]. Originally validated for men with benign prostatic hyperplasia, it has been used to study diverse populations including urinary symptoms in women [17] and patients with progressive neurological conditions such as multiple sclerosis [18] and Parkinson's disease [19]. The IPSS has a limitation in that it does not measure perceptions on the severity of urinary incontinence. It also requires a patient to have an intact sensorium, thus reducing its applicability to some neurogenic bladder populations.

Michigan Incontinence Symptom Index (M-ISI)

The M-ISI is a 10-item validated questionnaire that assesses severity and bother of urinary incontinence. It has domains for stress incontinence, urge incontinence, and pad usage as well as a bother domain [20]. It differs from the IPSS in that the M-ISI focuses more on measuring the severity of urinary incontinence rather than obstructive or irritating urinary symptoms.

Incontinence Quality of Life (I-QOL)

The I-QOL is a validated 22-question instrument that measures health-related quality life of impact related to urinary incontinence. It has three domains: avoidance/limiting behaviors, psychosocial impact, and social embarrassment [21]. The instrument is widely used and has been translated into 15 languages [22]. In contrast

to many other urinary-specific questionnaires, the I-QOL is validated not only for assessing idiopathic overactive bladder, but also for neurogenic urinary incontinence in general [23] and multiple sclerosis patients with urinary symptoms, in particular [24].

Neurogenic Bladder-Specific Questionnaires

Recently, more work has been done to better understand the unique urinary symptoms and practice patterns associated with neurogenic bladder patients. These neurogenic bladder-specific questionnaires more thoroughly address the changes in sensorium, use of catheters, and consequence of decision-making.

Neurogenic Bladder Symptom Score (NBSS)

Developed by Welk et al. the NBSS is a 24-item instrument that assesses urinary incontinence, storage and emptying, urinary-specific complications, and quality of life. It has been validated in patients with multiple sclerosis, spinal cord injury, and spina bifida [25] as well as cerebral palsy [26]. The NBSS was a key instrument in a Neurogenic Bladder Research Group (www.NBRG.org) multiple institutional QOL assessment of satisfaction with bladder management strategies among spinal cord injury patients. It was found to be sensitive in differentiating perceptions of quality of life between spinal cord injury patients using an indwelling catheter and performing intermittent catheterization [27, 28].

Qualiveen

The Qualiveen is a 30-item Likert scale instrument that was developed to measure every day urinary-specific QOL in spinal cord injury patients. It focuses on four key domains: bother with limitations, frequency of limitations, fears, and feelings [29]. An eight-item short questionnaire has been developed and has been used in multiple sclerosis patients [30]. The instrument is sensitive in detecting small changes within the domains. Each domain is measured with a 5-point Likert scale and research suggests that a change of 0.5 represented a clinically significant change in quality of life in that domain [31]. The Qualiveen is available in multiple languages.

Intermittent Catheterization Difficulty Questionnaire (ICDQ)/ Intermittent Catheterization Acceptance Test (I-CAT)

This questionnaire was developed to help measure a patient's difficulties when performing intermittent catheterization. *The ICDQ is a 13-item questionnaire with items that measure the ease of catheter insertion and withdrawal, the presence of pain during catheterization, limb and urethral sphincter spasms, and local urethral bleeding during catheterization* [32]. The questionnaire was validated through a 70-patient neurogenic bladder cohort consisting of spinal cord injuries, multiple sclerosis, cauda equina syndrome, Parkinson's, and spina bifida. Expanding on this validation study, the developers of the ICDQ have also *published Intermittent Catheterization Acceptance Test (I-CAT) survey. This developmental work currently has 14 items and seeks to measure the psychological acceptance of intermittent catheterization* [33].

Conclusions

Practitioners frequently need to assess a neurogenic bladder patient's quality of life, particularly when the neurologic condition is progressing. It is important to understand how health-related quality of life and patient-reported outcome measures can be employed to improve the care of these patients. General QOL questionnaires can help a practitioner determine how the illness impacts perceptions on daily functioning. Urinary-specific instruments can be used to focus treatment to specific areas of urinary bother and determine the effectiveness of the interventions. Neurogenic bladder-specific questionnaires allow practitioners to best appreciate the impact of bladder symptoms as they relate to the underlying disease. More work is needed to integrate QOL assessment into the daily care of the neurogenic bladder patient with a progressive disease.

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Chapter 5
Fundamentals of the Neurologic Exam and Other Considerations in the Setting of Progressive Neurological Disease

Yang Mao-Draayer, Catherine Dowling, and Mini Singh

Introduction

Some neurological diseases like multiple sclerosis (MS) and motor neuron disease tend to be progressive. The rates of progression can vary; for instance, motor neuron disease has a much faster rate of progression than MS. Physicians and care teams will certainly encounter a progressive neurologic disease in any urologic practice at some point in time. MS, for example, affects approximately 85 per 100,000 people and occurs in women two to four times more frequently than in men [1–3]. However, a progressive neurologic disease may vary even within a disease type: MS in particular has shown gender differences regarding the speed of disease progression, motor symptom severity, and cognitive function of people affected [4, 5]. Consequently, a key to understanding the progressive disease lies with the clinician accurately describing the neurologic picture through the physical exam.

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Gait/Motor Exam

A complete neurological examination includes the mental status exam which includes an assessment of cognition, language, and speech, evaluation of cranial nerves I to XII, tests of motor, sensory, and cerebellar systems, as well as the gait. Performing a complete neurological exam can be time-consuming and this short chapter attempts to cover the most informative portions of a neurologic exam allowing a non-neurologist to closely monitor for any disease progression. Several components of the neurological examination can be incorporated into a routine office visit. *A detailed history remains the most important aspect in following disease progression and is supplemented by the neurological examination*.

The neurological examination can be performed in no specific sequence and in fact begins with an observation of the gait while the patient first walks into the office. *A patient's gait provides significant information and is an important marker of disease progression*. Although it can be confounded by orthopedic problems and systemic illness, the gait test is more informative than individual motor testing, as it incorporates sensory, cerebellar, and motor components. For the gait test: observe the patient's posture, use of arms, length of step, turns, and abnormal movements. Lack of arm swing is common in Parkinson's disease (PD) and shuffling with increased steps on turning is also a feature of this disease.

Patients with progressive neurologic conditions can have a variety of physical findings as well as gait patterns (Table 5.1). The patient's ability to walk on heels is

Table 5.1 Gait patterns in neurological diseases

Gait	Patient complaints	Exam features	Causes
Spastic, hemiplegic gait [6]	Unilateral weakness, dragging a leg; early on foot drop is common	Muscle weakness in the lower extremity. Often the affected leg will be in extension with increased tone; circumduction of the leg in order to clear the floor.	Progressive MS, stroke (may see arm flexed and adducted as well), and traumatic brain injury.
Diplegic gait [6]	Bilateral leg weakness	Spastic gait with unopposed hip adductors causing "scissoring" where the legs cross the midline; paraparesis.	Progressive MS, CP.
Shuffling (Parkinsonian) gait [7, 8]	Slowness, stiffness, shuffling	Trunk often leans forward and the patient may take small, shuffling steps; trouble initiating steps (freezing of gait), especially when turning or walking through a door frame; The arm swing is usually reduced—initially on one side but as the disease progresses, can affect both sides. Patients with Parkinson's disease may have features of rigidity, resting tremor, bradykinesia (slow movement), and postural instability (poor balance).	Parkinson's disease, Parkinsonism: anti-dopaminergic medications, vascular disease (mini-strokes), corticobasal degeneration, progressive supranuclear palsy, and multiple system atrophy.

Table 5.1 (continued)

Gait	Patient complaints	Exam features	Causes
Ataxic (cerebellar) gait [9]	Unsteady	Wide-based; patients are unable to tandem (heel-toe) walk. Associated signs can include nystagmus, discoordination of limbs, and the patient's trunk may swerve while standing still.	MS, CP, sporadic and hereditary degenerative diseases, alcohol abuse, hemorrhage, leukodystrophies, and autoimmune disorders such as gluten allergy.
Sensory ataxic gait [6]	Unsteady especially at night	Patients slam their feet on the ground in order to sense foot placement; exacerbated with eyes closed/ night as they cannot see their leg/foot position; decreased proprioception and position sense.	Injuries to peripheral nerves (diabetes) or dorsal columns (B12 deficiency), MS.
Neuropathic (steppage) gait [6]	Foot drop	Patients lift the leg up in order to prevent the foot from scraping the floor, which could result in a forward fall. The affected foot tends to slap the floor with a characteristic smacking sound; peripheral cause is associated with decreased tone and reflexes, no hip flexor weakness.	Unilateral injury at the L5 nerve root, sciatic nerve, or peroneal nerve. This gait is also seen with ALS (bilateral steppage), muscular dystrophy, and poorly controlled diabetes mellitus.
Myopathic (trendelenberg, waddling) gait [10]	Proximal hip abducting weakness	Weakness of the proximal hip muscles causes the pelvis to drop on the contralateral side of the stance leg triggering the patient to shift the weight of his torso over the affected hip to compensate. Bilateral lesions lead to "waddling," as the weight is shifted back and forth to compensate for weak hip abductors.	Myopathies such as muscular dystrophy, unilateral lesions caused from injury to superior gluteal nerve or avulsion of the abductor muscle tendon.
Choreiform gait [11]	Excessive movement	Hyperkinetic involuntary, irregular movements superimposed on an otherwise normal gait; face and upper extremities are usually involved.	Lesions of the basal ganglia such as with Huntington's chorea; Parkinson's subjects may sometimes have dyskinesias resembling chorea resulting from peak levels of carbidopa/ levodopa.

a sensitive test for subtle foot drop (dorsiflexors) which is often an early sign of MS progression. Later signs of progression in MS may include a spastic hemiplegic or diplegic gait due to muscle weakness in the lower extremities. Often, the affected leg will be in extension with increased tone and circumducted in order to clear the foot off the ground.

Manual motor tests can confirm unilateral dorsiflexor and hip flexor weakness. With further progression, hemiparesis including upper extremity weakness can also

be seen. Walking on toes can test the strength of ankle plantar flexors. Tandem gait tests midline cerebellar function as well as gait and coordination. Additional information can be obtained with the Romberg test. It is performed by asking a patient to close their eyes with their feet together; any instability suggests the involvement of one or more of the spinal dorsal columns, vestibular system, or midline cerebellum.

Reflexes/Mental Status

Deep tendon reflexes can help differentiate between upper and lower motor neuron lesions. Performing this test correctly requires some skills. If possible, have the patient sit with legs dangling freely over the edge of the exam table. To avoid striking an improper area, the tendon should first be palpated and the lightest tap that will elicit the response should be given. The most common sites for reflex testing include the biceps, triceps, brachioradialis, patellar, and Achilles tendons. Table 5.2 summarizes a commonly used reflex grading system.

The examiner will first look for asymmetry of reflexes comparing right and left. Hyporeflexia is seen in muscle, peripheral nerve, and nerve root disorders; hyperreflexia is seen in upper motor neuron lesions such as MS, spinal cord injuries, and stroke. Babinski's sign is the most important pathological reflex. It is elicited by stroking the lateral aspect of the plantar surface of the foot from back to front with a semi-sharp object. A normal response is plantar flexion of great toe; Babinski's sign consists of dorsiflexion of the great toe with or without fanning of the other toes. Asymmetrical lateralized increased reflexes in conjunction with weakness, spasticity, and Babinski's sign are indicative of an upper motor lesion involving the contralateral descending cortical spinal tract, again commonly seen in MS [12].

The *mental status examination*, including cognition as well as language, and speech, can be assessed while obtaining the history. *Cognition is an essential component of the neurological examination* especially in a patient with MS. For example, 35–65 % of patients with MS will experience cognitive dysfunction at some point in the condition. Cognitive dysfunction results in slowed processing speed, decreased working memory, and issues with attention [13]. It may be found early in some disease courses, preceding motor symptoms [14] or occurs with increased frequency and severity in progressive MS [15]. At baseline, patients have deficits in tasks of abstract reasoning, verbal memory, and linguistic processes, and after 10 years, additional deficits in tasks of attention, and short-term spatial memory are

Table 5.2 Reflexes: graded on a 1–4 scale

0 – Absent reflexes
1 – Decreased reflexes
2 – Normal reflex strength
3 – Hyperreflexia, "Brisk" or increased speed of reaction
4 – Clonus, series of rhythmic contractures (seen most commonly in ankle)

frequently seen [16]. Importantly, cognitive defects complicate the management of a disease and negatively impact significantly on rehabilitation potential, as is seen in MS [17]. Cognitive problems also contribute to reduced employment and social interactions which may have significant impact on the quality of life [18]. It is important to rule out depression as part of the evaluation since it affects both memory and attention. Fatigue is another contributor to cognitive impairment and needs to be considered [19].

Brief cognitive screening exams can be performed by a non-neurologist and include both the Mini-Mental State Exam (MMSE) and the Montreal Cognitive Assessment (MoCA). A MoCA consists of a one-page 30-point scale which concentrates on short-term memory recall, visuo-spatial skills, language, constructions, and executive functions. It is useful for early detection of mild cognitive impairment, early stages of Alzheimer disease, vascular dementia, and dementia associated with Parkinson disease as well as MS. It is essential to evaluate for cognitive impairment in patients with secondary progressive multiple sclerosis with detailed neuropsychiatric testing. Of the usual batteries available, the Minimal Assessment of Cognitive Function in MS (MACFIMS) battery may be particularly useful [19].

Sensory/Cranial Nerve Exam

A complete sensory exam including pinprick, vibration, light touch, temperature, and position sensation could be the most time-consuming neurological test to administer. This test is also less objective compared to others such as reflexes as it involves the patient's perception and reporting. Usually, an intelligent and cooperative patient can describe and define the area of sensory deficits, which would enable the physician to do a focused exam. Sensory level testing is important to determine if there is a spinal cord lesion; one could either run a finger or a cold tuning fork up the back until sensation changes. When a peripheral neuropathy is suspected, one could run a cold tuning fork distally from foot to ankle and shin proximally to see if sensation is decreased at certain level and comparing to both sides.

The cranial nerve exam combines motor, reflex, and sensory components to test the 12 cranial nerves (Table 5.3).

Table 5.3 Cranial nerve (CN) exam

Smell (CN I)
Visual fields by confrontation (CN II)
Eye movements (CN III, IV, and VI)
Pupillary reflex in response to light (CN II, III)
Touch forehead, cheek and chins (CN V)
Shut eyelid tight and grin (CN VII)
Hearing (CN VIII)
Taste and gag reflex (CN IX and X)
Shrug shoulder (CN XI)
Stick tongue out (CN XII)

Evaluation of Comorbidities - MS Examples

Just as a variety of "non-disease-related" factors can confound the clinical exam; a variety of potentially addressable comorbidities can resemble clinical progression in MS [20]. We will use MS as an example to emphasizes the importance of the patient's history in understanding disease progression. Comorbid conditions affecting perceived disease progression in MS patients run the gamut from normal aging and sleep disorders to psychiatric illness and chronic diseases. Psychiatric diagnoses are more common in patients with MS. When compared to matched controls, MS patients have a higher incidence and prevalence of anxiety, depression, bipolar disorder, and schizophrenia [21]. Depression alone has recently been associated with relapse severity [22], a relationship exacerbated by a concurrent substance use disorder [23]. Primary sleeping disorders and those secondary to other comorbidities are common among general MS patients [24, 25]. Furthermore, the relationship between mood symptoms and sleep disturbance was recently described by Bamer et al. in 2010 [26]. These authors found that the primary driver of variance in sleep problems among MS patients was depression [26]. Obesity and poor diet are associated with disease progression and relapse. Vascular comorbidities such as diabetes mellitus, hypertension, hypercholesterolemia, and peripheral vascular disease have all been associated with disability progression in MS patients [27]. Moreover, improved glycemic control through medical management of diabetes has been shown to improve MS relapse rates [28]. All these factors may impact clinical exam findings, again emphasizing the importance of patient history prior to exam.

Conclusions

As our understanding of this disease process is advancing, we have seen promising advances in our understanding of comorbidities, disease progression measures, imaging measures for progression along with promising new treatments. History and exam are still the most valuable information to detect disease progression, though none by itself is sufficient.

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Chapter 6
Urodynamic Studies

Christopher Chermansky and Katherine Shapiro

Introduction

Urodynamics (UDS) is an interactive diagnostic study of the lower urinary tract which examines the interaction of the bladder and urethra. The goal of UDS is to reproduce the patient's symptoms, when present, and determine the cause of the symptoms. The purpose of UDS is to obtain and confirm the diagnosis, thereby allowing the urologist to suggest effective therapy and predict clinical course. Urodynamics is important in the management of patients with neurogenic bladders from progressive neurological diseases such as multiple sclerosis (MS) and Parkinson's disease (PD). It is not uncommon for urinary symptoms to be the first presenting signs of an undiagnosed neurologic condition. Urodynamics encompasses multiple tests, and these tests will be discussed in more detail below.

As per the American Urological Association UDS guidelines, video urodynamics (VUDS) using simultaneous fluoroscopy with contrast-based UDS is appropriate in the assessment of neurogenic bladder patients [1]. The European Association of Urology (EAU) has put forth guidelines that state VUDS is the gold standard for invasive UDS in neuro-urological patients [2]. Mandatory baseline UDS is recommended during initial urological evaluation, and UDS should be repeated at regular intervals in high-risk patients. Also, UDS should be repeated during changes in clinical status, such as after initiation of new therapy, the development of new bladder symptoms, or worsening renal function thought due to changes in bladder function.

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Purpose and Choice of UDS Tests

As defined by Wein, neurogenic lower urinary tract dysfunction is classified as either failure to store, failure to empty, or a combination of both [3]. Failure to store or empty is due to dysfunction of either the bladder or the bladder outlet. Because serious tract damage can result in the absence of symptoms in patients with neurological conditions, UDS remains the only method that objectively evaluates lower urinary tract function. A thorough history and physical exam must be performed in conjunction with UDS in patients with neurogenic bladders. Information such as manual dexterity, body habitus, home environment, and family support dictates treatment as importantly as UDS.

To prepare for UDS evaluation, the urologist must decide on the questions to be answered by the urodynamic study and design the study to answer these questions [1]. Proper performance of UDS involves careful attention to technical details, and this should result in accurate interpretation of bladder function. The Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (SUFU) convened a Best Practice Panel on urodynamic antibiotic prophylaxis, and they recommended peri-procedure antibiotics in patient with known neurogenic lower urinary tract dysfunction [4]. Table 6.1 lists and defines the various urodynamic tests used in the evaluation of neurogenic bladder patients.

Filling Cystometry

Filling cystometry is performed first by emptying the bladder with a straight catheter. Then a bladder urodynamic catheter in placed, and the bladder is filled with either sterile water or contrast (VUDS). For those patients who void, simultaneous abdominal pressure recording is performed by placing a second urodynamic catheter in either the rectum or vagina for women. Important parameters to record during filling cystometry in neurogenic bladder patients include bladder filling sensations, the presence of neurogenic detrusor overactivity (NDO), bladder compliance, and maximum cystometric capacity (MCC) [5]. The filling rate in ml/min should ideally not exceed body weight in kg [6]. Higher filling rates can result in early NDO, thereby resulting in a reduced and false MCC.

Table 6.1 Urodynamic tests utilized for patients with progressive neurological conditions

Urodynamic test	Definition
Filling cystometry	Invasively evaluates bladder filling
Pressure-flow studies	Invasively evaluates bladder emptying
Urethral sphincter electromyography	Assesses urethral sphincter activity
Cystography – VUDS	Images the bladder during filling and emptying with the use of fluoroscopy

The measurement of bladder compliance during filling cystometry is important in the evaluation of neurogenic bladder patients [7]. Bladder compliance is calculated by dividing the change in bladder volume over the change in detrusor pressure during that change in bladder volume, and it is expressed in ml/cm H_2O. Normal bladder compliance is generally ≥40 ml/cm H_2O. When bladder filling pressures rise with increasing bladder volumes, bladder compliance is decreased or impaired. Poor bladder compliance contributes to increased bladder storage pressure, thereby increasing the risk of upper urinary tract deterioration [8]. Bladder management strategies should strive to normalize bladder compliance, and filling cystometry should be repeated after treatment is administered to confirm improved compliance as an adequate treatment response. Bladder compliance is one of the most reliable and reproducible urodynamic measurements.

Detrusor leak point pressure (DLPP) is seen during filling cystometry in some patients with progressive neurologic conditions. DLPP measures the resistance of the urethral outlet (sphincter) to detrusor pressure as an expulsive force in the absence of a detrusor contraction or abdominal strain [9]. As the bladder is filled, DLPP is defined when urine leakage occurs in the absence of a detrusor contraction. DLPP is a measure of bladder storage function. McGuire showed that a DLPP of ≥40 cm H_2O during bladder storage in myelodysplastic children led to upper urinary tract damage with resultant hydroureteronephrosis and vesicoureteral reflux [10]. Because rapid urodynamic filling rates can result in bladder compliance values that are falsely decreased, it is imperative to use a slow filling rate during urodynamics in these patients. As with decreased bladder compliance, filling cystometry must be repeated after treatment is administered to ensure that DLPP has improved or resolved.

The abdominal leak point pressure (ALPP) is the lowest abdominal pressure (during Valsalva or Cough) that causes urine leakage in the absence of a detrusor contraction [7]. Unlike DLPP, ALPP is a measure of urethral function, and it is commonly used to characterize stress urinary incontinence [11]. ALPP <60 cm H_2O suggests intrinsic sphincter deficiency. The measurement of ALPP is useful in neurogenic bladder patients who have symptoms of stress urinary incontinence (SUI).

Table 6.2 lists normal measurements seen during filling cystometry.

Table 6.2 Normal filling cystometry measurements (Ref. [7])

Urodynamic measurements	Normal
Volume at first sensation of filling	100–250 cc
Volume at first desire to void	200–350 cc
Volume at strong desire to void	350–550 cc
Presence of detrusor overactivity	None
Detrusor leak point pressure (DLPP)	None
Compliance	>40 cm H_2O
Maximum cystometric capacity	400–600 cc

Electromyography of the Urethral Sphincter

Electromyography (EMG) measures the external urethral sphincter activity during both bladder filling and emptying [7]. Patch or needle electrodes are placed over the skin of the external anal sphincter as in most instances, anal sphincter EMG is the same as urethral sphincter EMG. Although concentric needle EMG is thought to be superior to surface patch EMG in signal recording, needle EMG is generally uncomfortable to the patient, and the needle can be easily dislodged [12]. EMG testing diagnoses detrusor sphincter dyssynergia (DSD), which is characterized by simultaneous urethral sphincter contraction during a detrusor contraction [13]. DSD only occurs in individuals with neurologic conditions. DSD is a concerning urodynamic diagnosis since it results in elevated bladder storage pressures and subsequent renal deterioration. Patients with DSD require close upper urinary tract follow-up to monitor for hydroureteronephrosis.

Pressure-Flow Testing

Pressure-flow testing is performed with the simultaneous measurement of vesical and abdominal pressures at the time of uroflow [9]. The purpose of pressure-flow testing is to assess detrusor contractility and to determine if urethral obstruction is present. The addition of fluoroscopy can define the site of obstruction as the narrowest segment of the urethra at maximum flow. Bladder outlet obstruction (BOO) is defined by low flow in the presence of elevated detrusor voiding pressure, often with enhanced contraction velocity and prolonged voiding duration. Impaired bladder contractility is defined by low flow in the presence of a low magnitude detrusor voiding pressure, usually with reduced contraction velocity and prolonged voiding duration. Ensuring normal voiding (for those neurogenic bladder patients who void) is important in assessing adequate treatment response. Bladder function is optimized in those with normal voiding pressures. It is important to remember that patients with progressive neurological conditions can be men with either BOO from benign prostatic hyperplasia (BPH) or urethral stricture disease and women with BOO from acquired voiding dysfunction, advanced stage pelvic organ prolapse (POP), or suburethral sling obstruction. Thus, pressure-flow studies are important in patients with a history or physical exam suggestive of these other voiding dysfunctions.

Urodynamic Findings in MS

Urodynamic evaluation is essential in the evaluation of MS patients, and the typical UDS findings include NDO in over 60% of patients and DU in 20% of patients [14, 15]. Detrusor external sphincter dysnergia (DESD) is another common and

concerning urodynamic finding in patients with MS. The location of the MS plaques play a critical role in the type of resultant bladder dysfunction. Studies have shown that patients with cervical cord lesions or pontine lesions are more likely to suffer from emptying symptoms, including DU, whereas those with cerebral cortex lesions are more prone to storage symptoms such as DO [16].

Urodynamic Findings in PD

The most common bladder dysfunction found in PD patients is NDO [17]. The etiology of NDO is thought to be related to a dysregulation of the PMC in the basal ganglia that affects the voluntary control of the micturition reflex [18]. DU is also seen in PD. In one series, DU was noted in 16% of PD patients [19]. In contrast, Liu et al. performed urodynamics in 58 PD patients and found DU in 53% of those tested [20]. Although the pathophysiology underlying DU in PD is currently not well understood, Liu correlated DU to the patient's overall motor function. Both pseudodyssynergia of the external urethral sphincter (EUS) during NDO and bradykinesia of the EUS during the onset of voluntary micturition can occur in PD patients [21]. Both of these EUS abnormalities can lead to impaired detrusor bladder contractility and DU.

Urodynamic Findings in Diabetes Mellitus (DM)

It is known that up to 50% of men and women with DM will develop diabetic bladder dysfunction [22]. The types of bladder dysfunction in patients with DM range from sensory-urgency to impaired bladder emptying with eventual DU [23]. The sensory impairment seen in diabetic cystopathy is thought to be due to bladder afferent damage with impaired signaling between the bladder stretch receptors and the central nervous system (CNS).

Table 6.3 summarizes common neurologic findings in various neurological conditions.

Table 6.3 Urodynamic findings in common progressive neurological conditions (Ref. [3])

Neurologic condition	Urodynamic findings
Multiple sclerosis	NDO, DESD (30–50%)
Parkinson's disease	NDO, bradykinesia of striated sphincter
Diabetes mellitus	Bladder with sensory and motor impairment
Cerebral palsy	NDO, DESD (25%), and voluntary sphincter impairment

Limitations of UDS Testing

Repeat VUDS testing can be burdensome for patients. It is an invasive test that can result in pain and UTI. Yet, patients with progressive neurological conditions who have vesicoureteral reflux could be at risk for pyelonephritis without appropriate antibiotic prophylaxis. As previously stated, peri-procedure antibiotics are recommended in patients with known neurogenic lower urinary tract dysfunction [4].

Conclusion

Because most many progressive neurological diseases can be unstable and because patients may develop other diseases (BPH, SUI, POP) common in aging adults, regular, yearly follow-up is necessary. Bladders that are hostile (decreased bladder compliance) require closer follow-up. The EAU Guidelines on Neuro-urology recommend yearly UDS testing and renal ultrasonography every 6 months in these individuals to be sure that effective treatment has resulted in safe bladder storage pressures [2]. Timely diagnosis and treatment in these individuals is essential in preventing upper and lower urinary tract deterioration, thereby optimizing life expectance and quality of life.

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Chapter 7
Neuro-urologic Imaging: A Practical Guide

John T. Stoffel

Introduction

Radiologic imaging is an important component in the care of neurogenic bladder patients. Although there are few standardized recommendations regarding modality or schedule, regular imaging can help detect upper tract changes, define irregular anatomy, or determine functionality of an organ group. It can offer specific detail that is of great interest to practitioners caring for neurogenic bladder patients such as identifying hydronephrosis, progressive vesicoureteral reflux, ureteral obstruction, soft tissue infections, and fistulas. In this chapter, we will discuss how fluoroscopy, ultrasound, computer tomography, and MRI imaging can aid in care for neurogenic bladder patients with progressive neurologic conditions.

Fluoroscopy

Fluoroscopy is not commonly used during most urodynamic studies (6.2% of studies nationally) [1]. However, neurogenic bladder patients remain a special group in which fluoroscopy during urodynamics can be tremendously beneficial. This is recognized in the 2012 American Urological Association guidelines on urodynamic practices [2]. In the guidelines, it is specifically stated that fluoroscopy during urodynamics can add:

– More precise localization of obstruction in bladder and urethra

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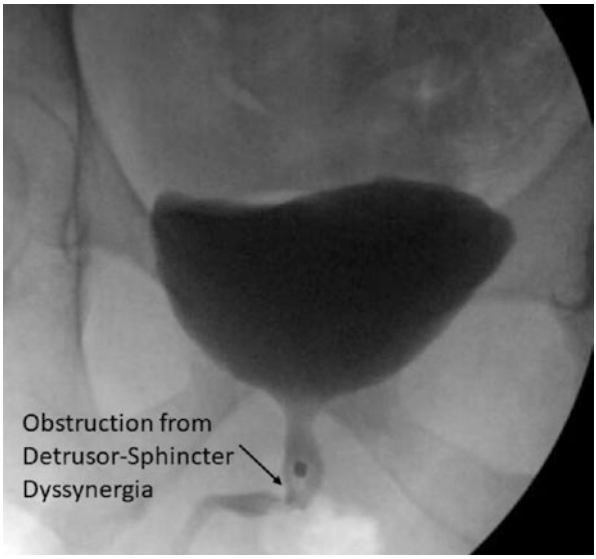

Fig. 7.1 Detrusor sphincter dyssynergia (DSD) on voiding cystourethrogram. DSD is clearly a source of obstruction on this film

– Gives anatomic understanding during pressure-flow studies

– Improves diagnosis of vesicoureteral reflux, bladder diverticulum, and bladder neck abnormalities

Fluoroscopy during urodynamics can be particularly helpful in determining if bladder pressures can be accurately measured via cystometrogram or if there are anatomic pathologies such as diverticulum or ureteral reflux that can confound true detrusor pressure measurements. Patients with low bladder compliance may be at particular risk for confounding anatomy. It has been reported in one series that neurogenic patients with a bladder compliance of less than 20 cm H_2O on urodynamic studies had four times greater odds of having a bladder diverticulum or vesicoureteral reflux seen on concomitant fluoroscopy compared to non-neurogenic patients [3]. Knowledge of existing bladder diverticulum and reflux may also reduce inadvertent placement of the urodynamic catheter into a diverticulum or ureter. Although there are no formal recommendations regarding which neurogenic bladder studies require fluoroscopy, one urodynamic series examining bladder safety in multiple sclerosis patients recommended that fluoroscopy be used so that accurate pressures would be measured [4].

Fluoroscopy during urodynamics can also be an adjunctive tool to identify underlying bladder physiology. For example, a woman with progressive multiple sclerosis, quadriplegia, and cognitive impairment may not be able to give a history as to when she has urinary continence or be positioned properly to assess incontinence during Valsalva. In this scenario, fluoroscopy during urodynamics can readily differentiate stress from urge incontinence when paired with the CMG. A study which examined the use of fluoroscopy in 285 patients found that most common

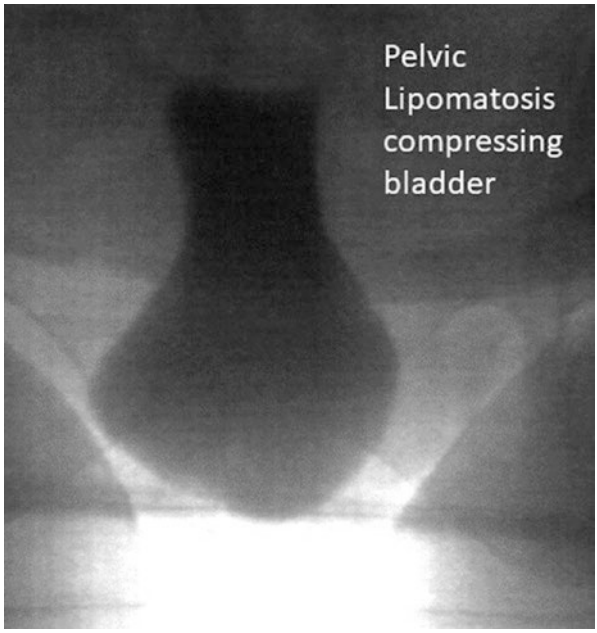

Fig. 7.2 Pelvic lipomatosis on voiding cystourethrogram during urodynamics. Mass is compressing bladder during storage

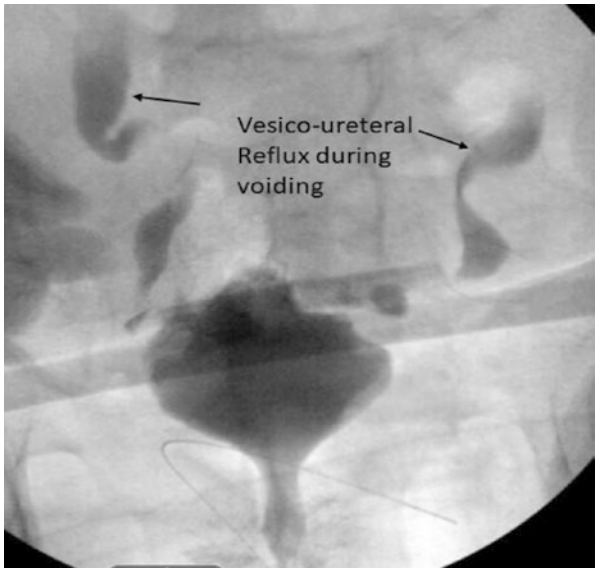

Fig. 7.3 Vesicoureteral reflux on voiding cystourethrogram. Note secondary obstruction of proximal ureters

Table 7.1 Radiation safety: key points

Keep X-ray tube current as low as possible by keeping tube potential as high as possible
Keep image intensifier as close to patient as possible
Keep X-ray tube at a maximum distance from the patient
Position the x-ray tube under the patient

indications to use fluoroscopy were to differentiate stress from urge incontinence, assess anatomy, and to assess bladder safety [5].

However, the benefit of using fluoroscopy during urodynamics should be weighed against the potential risk of radiation exposure. A study of 203 urodynamic studies of all patients, including those with neurogenic bladder, noted that the fluoroscopy time was not insignificant at 100.2 sec and overall radiation exposure was 560.9 radcm^2. Risk factors for additional fluoroscopy time included larger capacity and vesicoureteral reflux [6]. When using fluoroscopy, it is important to remember the US Nuclear regulatory Commission Guidelines that recommend practitioners follow the ALARA (As Low As Reasonably Achievable) principle [7]. Table 7.1 summarizes radiation safety key points.

Ultrasound

Since neurogenic bladder patients can be at risk for renal morbidity, ultrasound imaging is frequently used as a screening modality to identify hydronephrosis. The European Association of Urology published guidelines in 2016, which suggested that neurogenic bladder patients at high risk for renal complications should be evaluated with ultrasound every 6 months [8]. Ultrasound is usually performed as gray scale sonography (B Mode) to assess for collecting system dilation. This will yield information regarding renal unit size, shape, and degree of hydronephrosis, if present. Additionally, hyperechoic structures like stones will appear bright on ultrasound and hypoechoic structures will appear dark. Typically, a healthy kidney will measure between 9 cm and 12 cm longitudinally and have greater than 1.5 cm of cortical thickness [9]. Cortical thickness on ultrasound generally tracks with of renal function and rate of cortical thickness change over time may be predictive of time to dialysis [10].

Hydronephrosis classically presents on ultrasound as a dilated collecting system. Chronic hydronephrosis may include additional features such as intrarenal collecting system dilation and loss of cortical thickness. These findings may be helpful in differentiating acute from chronic hydronephrosis. Figure 7.4 shows an example of chronic hydronephrosis.

However, ultrasound of the kidneys can be confounded by several variables, Body habitus can significantly limit visualization of the retroperitoneal space. This can be particularly important when attempting to image neurogenic bladder patients who are obese or who have joint contractures. Detection of hydronephrosis via ultrasound can also be challenging if the patient has parapelvic cysts overlying the collecting system.

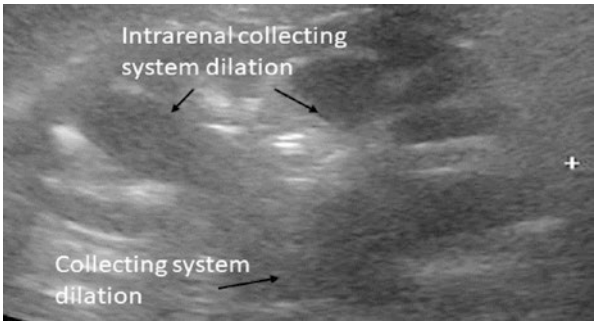

Fig. 7.4 Chronic hydronephrosis with dilated intrarenal collecting system

Severity of hydronephrosis has not been standardized to a common scale. This can make it challenging to compare the severity of hydronephrosis when studies are performed at different points in time or by different ultrasound technicians. The Society of Fetal Urology (SFU) has described a subjective hydronephrosis grading scale, ranging between 0 and 4, in an attempt to standardize ultrasound comparisons. Similarly, a urinary tract dilation (UTD) scale and anterior–posterior diameter measurements are also used to follow antenatal hydronephrosis in fetal medicine. Further study, however, suggested that inter-rater agreement between individuals comparing severity of hydronephrosis ranged between slight and moderate [11]. The UTD scale, when compared to the SFU scale shows similar limitations [12]. Neither hydronephrosis scales have been validated in adult neurogenic bladder populations.

Ultrasound can also be used to follow the size of known urinary calculi in neurogenic bladder patients. It can be an unreliable screening tool, however, and cannot always accurately detect the number, size, and location of stones when compared with other imaging modality [13]. When detected, many nephrolithiasis demonstrate characteristic acoustic posterior shadowing on ultrasound. Figure 7.5 demonstrates ultrasound imaging with stone in kidney.

Most patients with progressive neurological conditions are not screened for urinary calculi in the absence of symptoms or cause. Currently, the risk for developing urinary calculi among neurogenic bladder patients is not known. Data from a longitudinal study following spinal cord injury patients from Holland noted renal calculi in 6% of patients during routine ultrasound exams [14]. However, stone incidence among patients with progressive neurologic diseases is not known, although a retrospective study of 118 MS patients with stones suggests that MS patients form similar stone types (calcium phosphate and struvite) as spinal cord injury patients, which are detectable on ultrasound [15].

Ultrasound imaging carries a minimal risk of injury to the patient because it does not use ionizing radiation. In theory, ultrasound waves can cause cavitation "bubbles" which can then lead to thermal injury. However, contemporary ultrasound sound imaging machines do not generate enough power output to cause injury when used properly.

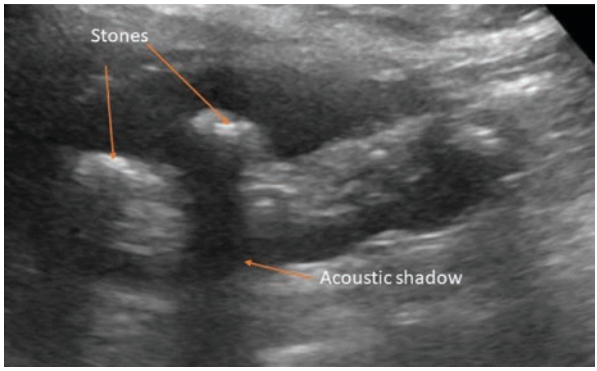

Fig. 7.5 Renal ultrasound showing posterior acoustic posterior shadowing from renal stones

Computed Tomography (CT)

Similar to fluoroscopy, CT uses ionizing radiation during imaging. Contemporary CT scanners move patients through a gantry and continually rotate the radiation source and detectors. This allows for complex images to be created [16]. CT scans are frequently used to assess upper tract safety for neurogenic bladder patients. When a 5% Medicare cohort of Spinal cord injury patients were retrospectively studied, it was noted that, of those who had upper tract imaging, the majority (39%) were followed with CT scans [17]. CT can offer a more comprehensive assessment of the urinary tract, compared to ultrasound, and is less limited by patient body habitus or operator experience. For example, hydronephrosis caused by obstructing urinary calculi in the ureters or bladder can more easily be identified with a CT of the abdomen pelvis compared to an ultrasound alone (Fig. 7.6).

CT scan can also offer a functional assessment of renal perfusion and drainage when the study is performed with intravenous contrast. However, radiation dosage is higher when using a CT urography protocol and radiation exposure to the patient can be 1.5 greater compared to conventional CT [18]. Many times, contrast studies are not necessary when previous studies are available and renal cortical thickness can be compared to determine the impact of hydronephrosis on renal function over time.

CT imaging can be particularly helpful in caring for neurogenic bladder patients who have had previous reconstructive urologic surgery. CT techniques such as multichannel high resolution detectors allow more high quality images to be obtained in less time and with little artifact. These high-quality images can then be used to focus on a specific area in more detail or combined to create three-dimensional reconstructions of specific organ systems. They can be particularly helpful when surgeons are attempting to define ureteral pathology (Fig. 7.7):

Stenzl et al. have demonstrated the utility of 3D CT reconstructions to identify potential ureteral or urethral anastomotic complications in their orthotopic bladder substitution series [19]. Cirvellaro et al. similarly have reported on using both 3D CT and urodynamics to better understand how the anatomic location of an orthotopic bladder substitution could impact storage physiology [20].

Since CT urogram imaging caries risk, both related to radiation exposure and contrast-induced nephropathy, practitioners should carefully consider imaging

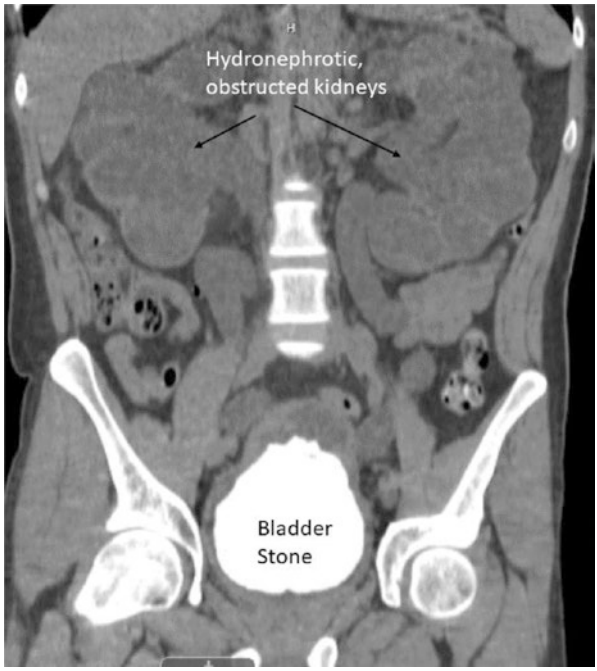

Fig. 7.6 CT study showing bilateral hydronephrosis caused by a massive bladder stone in a neurogenic bladder

Fig. 7.7 Three-dimensional CT reconstruction showing location and length of ureteral stricture

goals before selecting this as an imaging modality. Although CT-related malignancy is difficult to determine across populations, one study estimated that almost 30,000 cancers in 2007 could be attributed to radiation from CT scans [21]. Consequently, CT imaging is discouraged for routine renal surveillance in the asymptomatic neuro-urologic population.

MRI (Magnetic Resonance Imaging)

MRI imaging uses radiofrequency (RF) pulses from externally applied magnetic field to cause characteristic responses in hydrogen atoms within a target area. T1 weighted images use short intervals between RF pulses and T2 weighted images use longer intervals between RF pulses [16] (Table 7.2).

These differences between T1 and T2 images make MRI useful in many aspects of neuro-urology. Similar to ultrasound and CT, MRI also be used to assess severity of hydronephrosis in neurogenic bladder patients and grade scales have been proposed to compare severity [22]. MRI also can be particularly helpful in identifying and staging the soft tissue infections, pressure ulcers and abscesses that can occur in a debilitated population [23]. Figure 7.8 shows early detection of a sacral decubitus ulcer.

In our practice, MRI is the imaging modality of choice to study urogenital fistulas and osteomyelitis (Fig. 7.9).

In addition to better visualization of soft tissue inflammation, MRI technology is also starting being used to better understand the neuroanatomy that is associated with neurogenic voiding dysfunction. Functional MRI (fMRI) tests combine nuclear medicine infusions with MRI imaging so that physiologic activity can be superimposed over anatomic images. fMRI studies have been used to study the neurologic control of the urinary tract during storage and emptying. For example, one recent study suggested that degenerative brainstem changes in the region on the pontine continence center are prominent in Parkinson's patients [24]. Additionally, MRI can be combined with nuclear medicine studies to achieve a functional map of the target organ. Khavari et al. have used this fMRI technology to study the impact of lesion location and size in multiple sclerosis patients with voiding dysfunction. Although the predictive aspect of this study is limited by a small sample size (27 pts), the authors were able to postulate some relationships between the size of the lesion and the impact on urinary symptoms [25]. fMRI has also been used to better define neurologic control of pelvic floor muscle during voiding [26].

However, MRI studies generally take longer to perform and can cause claustrophobia in some patients due to the confined space. Patients with renal insufficiency are also at risk for a contrast-induced nephropathy if gadolinium is

Table 7.2 MRI imaging

T1
Images highlight tissues containing fat
Fat is bright
Muscle is gray
Fluid is black
T2
Images highlight tissues with fat and water
Fat is black
Muscle is gray
Fluid is bright

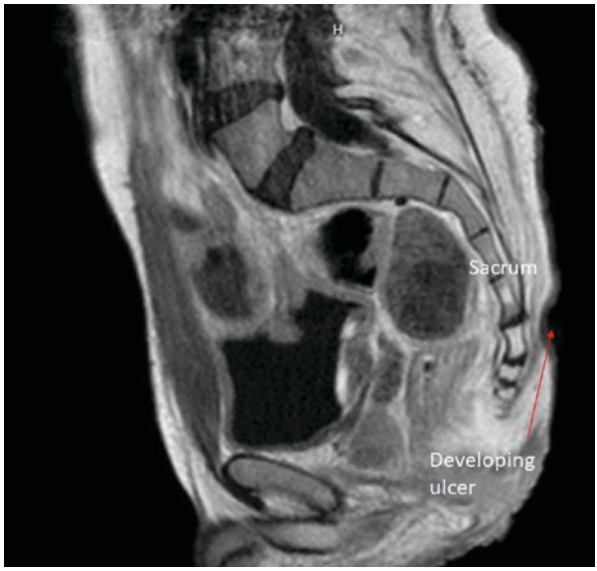

Fig. 7.8 MRI of neurogenic bladder patient showing developing sacral decubitus ulcer

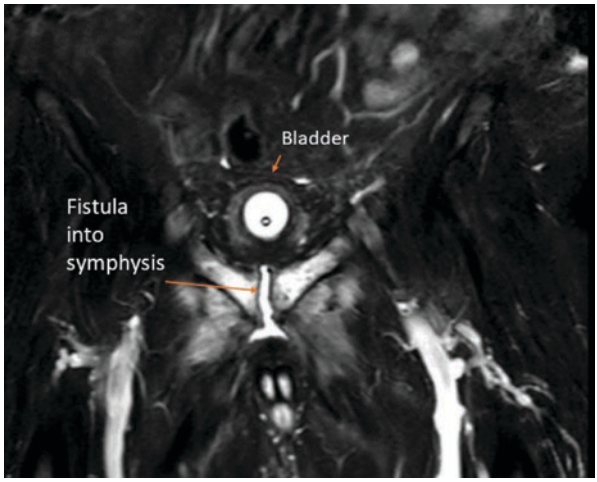

Fig. 7.9 MRI showing fistula from bladder into pubic symphysis

used. Most importantly, MRI is contraindicated for patients with metal implants. Non-ferrous implants, such as titanium materials, are generally allowed. Urinary implants, such as the Boston Scientific™ artificial urinary sphincter AMS 800 and AMS 700 penile prosthesis, are generally considered MRI safe [27]. Similarly, many long-lasting ureteral stents use nonferrous coils and are also considered MRI safe. Neuromodulation systems for the treatment of overactive bladder are currently not approved for MRI testing, but these systems are being reviewed and may be reclassified in the future. Table 7.3 summarizes the contra-indications for MRI.

Table 7.3 Contraindications for MRI studies in neurogenic bladder patients

Urinary/Gyn
Metal urinary penile clamps
1-piece penile prosthesis
Permanent contraceptive devices, diaphragm, or pessary
Cardiac
Aneurysm clip(s)
Coronary and peripheral artery stents
Aortic stent graft
Prosthetic heart valves and annuloplasty rings
Cardiac occluder devices
Cardiac pacemaker
Implanted cardioverter-defibrillator (ICD)
Retained transvenous pacemaker and defibrillator leads
Vascular
Vena cava filters and embolization coils
Hemodynamic monitoring and temporary pacing devices
Hemodynamic support devices
Vascular access port and/or catheter
Neuro
Neurostimulation system
Shunt (spinal or intraventricular)
ENT
Cochlear, otologic, or other ear implant
"Triggerfish" intra-ocular pressure monitoring contacts
Hearing aid
Metal fragment in eye
Ortho
Joint replacement (e.g., hip, knee, etc.)
Endocrine
Electronic implant or device, for example, insulin pump or other infusion pump
Other
Tissue expander (e.g., breast)
Body piercing jewelry
Any metallic fragment or foreign body related to previous injury (e.g., bullet)

Modified from Dill [28]

Conclusion

Patients with a degenerative neurologic condition will likely need imaging as part of his/her neurogenic bladder care plan. Although there are no formal recommendations as to which study type to use or how often to study the patients, fluoroscopy, ultrasound, CT, and MRI, each has unique properties that all add

important information that contribute to patient care. Practitioners caring for these patients should understand the risks and benefits of for each imaging modality.

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Chapter 8
Common Bladder Management Treatments for Patients with Neurogenic Bladder

Jeremy B. Myers

Introduction

The neurologic control of bladder function is very complex; however, when reduced to simple terms, neurogenic lower urinary tract dysfunction (NLUTD) causes problems with two aspects of bladder function, *Storage* and *Voiding*. The *Storage* phase of bladder function is dependent upon active relaxation of the bladder wall leading to very low-pressure storage even as volume increases. The ability to store is often impacted by neurogenic bladder (NGB) and commonly results in incontinence from bladder spasticity. In addition, loss of normal innervation of the bladder can cause progressive fibrosis in the bladder wall and worsened compliance. This stiffening of the bladder wall leads to bladder contraction and a failure to store adequate volumes within the bladder. Poor bladder compliance, in some cases, can cause very high pressures within the bladder leading to reflux of urine, hydronephrosis, and renal insufficiency or renal failure. High bladder pressures are also highly associated with urinary tract infection, urosepsis, and urinary calculi [1].

The *Voiding* phase of bladder function is also often impacted by NGB. Commonly, voiding dysfunction manifests itself as impaired or absent bladder emptying. This impairment might be a minor annoyance to patients who have to strain or wait for some time for their bladder to empty or it can be much more of a problem and patients may not be able to empty at all. This is very common in disorders such as multiple sclerosis (MS), spinal cord injury (SCI), and Parkinson's. When patients cannot empty effectively they most often have to rely on some type of assisted emptying. Assisted emptying of the bladder can involve physical maneuvers such as Valsalva or Crede voiding, use of catheters, or surgery.

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Medical Management

Current medical management of NLUTD is concentrated upon control of *Storage* symptoms [1]. Multiple classes of medicines act to decrease bladder spasticity, as well as improve compliance in the bladder wall. Anticholinergic drugs, also referred to as antimuscarinics, are a mainstay of therapy for the management of *Storage* symptoms. Some other drugs can complement the effects of antimuscarinics upon the bladder dynamics, and a new class of drug (β3-adrenergic agonist) has gathered some evidence of efficacy for NLUTD storage symptoms.

The only drug currently used for *Voiding* dysfunction, at least within the United States, is bethanechol, which is a muscarinic agonist and has been used historically to augment bladder contraction. Unfortunately, the drug is not very efficacious and is associated with abdominal distention and pain [2]. Bethanechol is not commonly employed in neurogenic bladder management by most clinicians today.

Anticholinergic Drugs

Anticholinergic drugs act to decrease bladder overactivity and improve compliance in the bladder wall. The exact action of these drugs is not perfectly understood, but a simplistic explanation is that the drugs block the muscarinic receptors in the detrusor muscle and their ability to contract when acetylcholine is released at the motor endplate [3]. This mechanism has been suggested to be more complex and may involve inhibition of acetylcholine release from the afferent nerves through feedback from muscarinic receptors blocked in the urothelium or elsewhere in the bladder.

There are many anticholinergic drugs available (Table 8.1). Common side effects of anticholinergic drugs include dry mouth, constipation, and loss of mental acuity. These effects are related to metabolites created by first pass metabolism in the liver. Transdermal administration or extended release medications minimize these therapy limiting side effects. The majority of studies have investigated anticholinergics in patients with overactive bladder rather than NLUTD from NGB.

Recent literature has evaluated the use of two different anticholinergic medicines (oxybutynin and trospium) at the same time [4]. Investigators found that urinary incontinence episodes and bladder capacity had dramatic improvement with monotherapy with trospium and that combined therapy had no additional benefit. They also found that full continence was not common and that even incontinent patients' urodynamics commonly showed persistence of bladder spasticity with high pressures causing detrusor overactivity incontinence.

Another recent study, called the SONIC trial, reported the effects of solifenacin, as well as oxybutynin on urodynamic parameters and patient-reported outcomes [5]. Both solifenacin 10 mg and oxybutynin 15 mg substantially improved maximum cystometric capacity, as well as multiple other measures of bladder function compared to the placebo arms. The effects of the drugs appeared to be almost identical on primary and secondary outcomes. Oxybutinin had worse dry mouth associ-

Table 8.1 Drugs used for medical management of neurogenic bladder lower urinary tract dysfunction.

Drug class/mechanism	Drugs	Dosing	Comments
Anticholinergics: Block acetylcholine receptors at the detrusor muscle motor endplate	Fesoteridine	ER 4,8 mg	Extensive evidence in treatment of NLUTD, ER formulations minimize common side effects, such as dry mouth, constipation, blurry vision, and loss of mental acuity
	Oxybutynin	IR 5 mg, ER 5,10,15 mg, TD gel 100 mg, patch 3.9 mg	
	Solifenacin	5, 10 mg	
	Tolteridine	IR 1,2 mg, ER 2,4 mg	
	Trospium	IR 20 mg, ER 60 mg	
β3-adrenergic receptor agonist: Relaxation of bladder during filling phase	Mirabegron	ER 25,50 mg	Limited evidence for use in combination with anticholinergics or as monotherapy
Alpha adrenergic blocker: Multiple effects in the bladder, acts additively with combination of anticholinergics	Tamsulosin	0.4 mg	Limited evidence in combination with anticholinergic medicines
Tricyclic antidepressants: Anticholinergic like effects	Amitriptyline	10, 25 mg	Limited evidence in combination with anticholinergic medicines

IR immediate release, *ER* extended release, *TD* transdermal, *NLUTD* neurogenic lower urinary tract dysfunction.

ated with therapy; however, the study did not use sustained release medications, which has been shown to decrease this effect.

Transdermal delivery of oxybutynin has been studied in SCI patients with NLUTD [6]. This study was an open label titration study with endpoints including number of daily catheterizations and urodynamic parameters. All of the endpoints were positively impacted by use of the drug and patients tolerated up to three times the normal dose of the drug with only 8% experiencing dry mouth. Additionally, adverse events were not dose related; albeit the study had only 24 participants. The most common side effect of transdermal delivery was local skin reaction in 8%.

β3-Adrenergic Receptor Agonist

Mirabegron is a β3-adrenergic agonist, which acts to relax the bladder during filling and has similar efficacy to anticholinergics in treatment of idiopathic overactive bladder [7]. In a recent study, patients with MS or SCI were randomized to placebo or 50 mg of mirabegron. The treatment arm had improvements in urodynamic and patient reported outcomes compared to placebo groups with a very low adverse event rate of only 3%. This low adverse event rate is very attractive

compared to the relatively high rate of adverse events with anticholinergic drug treatments. Another smaller study did not show similar improvements in objective urodynamic parameters, but did show significant decreases in patient symptom burden [8].

Combination Therapy

The combination of anticholinergics and β3-adrenergic agonists for treatment of idiopathic overactive bladder has been investigated in two recent trials (the SYMPHONY and SYNERGY trials) [9, 10]. Both trials demonstrated improved response of patients treated with mirabegron in combination with solifenacin at different doses when compared to monotherapy with solifenacin alone. The results were unclear about whether there was any benefit to combination therapy compared to monotherapy with mirabegron alone. There are limited data on the use of combination therapy with anticholinergics and β3-adrenergic agonists in patients with NLTUD.

Anticholinergics can also be combined with other medicines known to also affect bladder pressures. In one study, patients treated with anticholinergics alone with continued evidence of poor compliance had tamsulosin and imipramine added [11]. Tamsulosin is an alpha-adrenergic antagonist that is typically used in patients with benign prostatic hyperplasia, in order to decrease bladder outlet resistance. Alpha-adrenergic receptors, however, may have more widespread effects in the bladder, especially in the changes to the bladder urothelium and muscle associated with neurologic injury or disease. Imipramine is a tricyclic antidepressant, which has known effects on bladder pressure and activity. In this study, patients who were on anticholinergics had the addition of both drugs (triple therapy). These patients had urodynamics before (on anticholinergics alone) and after initiation of triple drug therapy. The patients' urodynamic assessments demonstrated decreased pressure at maximum capacity as well as dramatic improvements in bladder compliance. Use of combination therapy with these drugs may only be relevant for a few patients today, given the widespread availability of onabotulinum toxin (BTX); however, using these drugs to augment the effect of anticholinergics may be helpful for patients who cannot get BTX or develop immunity to the therapy.

Key Points: Medical Therapy

- There is no effective medical therapy to augment voiding phase dysfunction.
- Anticholinergics block receptors for acetylcholine at the motor endplate and are the mainstay of treatment for NLUTD.
- β3-adrenergic agonists (mirabegron) is a new class of medicine that has some developing evidence for treatment of NLUTD.
- Combination therapy with older medicines or possibly β3-adrenergic agonists may augment the positive effects of anticholinergics on the bladder.

Indwelling Catheters

Indwelling catheter consists of either a Foley catheter, which is placed via the urethra or a suprapubic cystostomy. A suprapubic cystostomy, commonly referred to as a suprapubic tube (SPT), is the same catheter that is used in the urethra, but travels through the lower abdomen into the cephalad portion or "dome" of the bladder and drains the bladder like a siphon. Indwelling catheters are in the bladder all of the time and are typically changed once per month. Indwelling catheters can be a very simple arrangement for patients with NLUTD; however, they are associated with the greatest complications of any bladder management strategy.

Although not intuitive, indwelling catheters have the greatest risk for kidney obstruction and renal failure. One would naturally think that having a catheter at all the time would achieve very dependable drainage of the kidneys. In fact, indwelling catheters in individuals with SCI have a greater risk of proteinuria, renal insufficiency, renal failure, hydronephrosis, and urinary calculi [12]. One explanation for this apparent paradox is the reaction of the bladder to the constant irritant of the catheter. Patients with indwelling catheters are at higher risk for UTI and urosepsis [13, 14] and one sequelae of chronic cystitis is increased fibrosis within the bladder wall. This fibrosis may act to mechanically obstruct the drainage from the ureter acting similar to a ureteral stricture.

In addition to higher UTI rates and worse kidney drainage, catheters also are associated with higher rates of other SCI-related complications. In fact, in the Model Systems of SCI care, which consists of 26 hospital across the US pooling data in the National SCI database, patients with indwelling catheters had higher rates of all-cause hospitalization, longer hospitalizations, and a higher rate of decubitus ulcers [13].

Another concern related to NGB and indwelling catheters is increased cancer risk. In general, patients with NGB have increased risk of developing bladder cancer. This risk is low, but higher than the general population [15]. Cancer risk has been addressed after agumentation cystoplasty and there is little evidence augmentation cystoplasty increases any risk of bladder cancer over baseline increased risk in neurogenic bladder [16, 17]. Indeed, current guidelines do not recommend screening patients for bladder cancer after augmentation cystoplasty. Due to the chronic inflammation associated with indwelling catheters, many clinicians perform yearly cystoscopy after a decade of use. However, guidelines and systematic reviews have not found strong evidence for this practice [18–20]. Unfortunately, bladder cancer when it develops in patients with NGB is often aggressive and it is unclear if yearly surveillance would even be effective at detecting bladder cancer early and preventing death from bladder cancer [17]. Because of the aggressive nature of bladder cancer in NGB patients, we consider early cystectomy even in some case of low-grade bladder cancer where patients would not have an indication for cystectomy (Fig. 8.1); however, this is controversial and many treat bladder cancer in the NGB population, stage for stage, the same as non-NGB patients.

A common misconception among patients and the medical community is that SPTs have a decreased risk of infection compared to Foley catheters. This has not been demonstrated, and generally, the reasons for use of a SPT over a Foley catheter are to avoid urethral complications [21]. Since many patients with NGB do not have

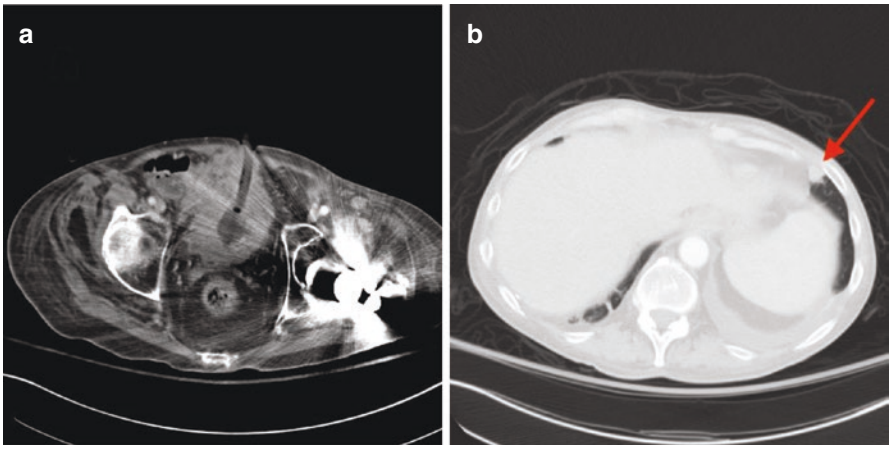

Fig. 8.1 (**a**) Large bladder tumor arising from suprapubic tube (**b**) metastatic pulmonary nodule at the time of presentation with bladder tumor. (With permission from Dr. Jeremy B. Myers)

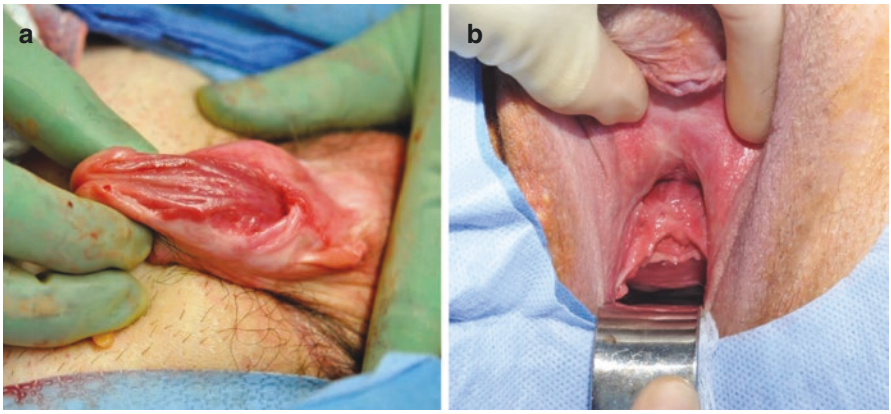

Fig. 8.2 (**a**) Ventral erosion of the penile urethra from pressure necrosis, (**b**) wide patulous erosion of the entire female urethra arising from a Foley catheter. (With permission from Dr. Jeremy B. Myers)

sensation in the bladder and urethra, they are prone to pressure-related complications from the indwelling catheter pulling against structures within the urethra. In men, this manifests itself as urethral erosion from the meatus to the penoscrotal junction by ventral pressure of a full urine bag dragging on the catheter (Fig. 8.2). Internally, in men, the catheter balloon causes pressure necrosis and pulls through the bladder neck into a cavity within the prostate or bulbar urethra. This can lead to incontinence and poor bladder drainage with hydronephrosis, UTIs, and even renal failure. In addition, once this problem is recognized and an alternative bladder drainage method is initiated, the urethral sphincters are no longer competent and patients will often have total incontinence from the urethra. In women, patients will have erosion of the bladder neck and sphincter, which usually manifests itself with catheters being pulled out inadvertently through the urethra with the balloon inflated. The first instinct for

care providers is to increase the size of the catheter or balloon of the catheter. This maneuver will work for a while, but eventually compounds the problem with worse pressure necrosis of the urinary sphincters. In addition, women can develop pubic symphysis fistulae and osteomyelitis from pressure necrosis of the bladder neck.

An SPT can be inserted in a small surgery or percutaneously and complications are rare. For the most part, insertion of an SPT will avoid these lower urinary tract complications and for this reason, most urologists recommend an SPT when patients plan on using indwelling catheters in the long term.

Key Points: Indwelling Catheters

- Indwelling catheters have the highest morbidity of any catheter-associated emptying.
- SPT may avoid urethral complications, which can cause serious morbidity from chronic indwelling Foley catheters.
- Despite increased morbidity, patient often favor indwelling catheters due to convenience and improved continence.

Onabotulinum Toxin Injection

The use of onabotulinum toxin (BTX) for treatment of NLUTD was approved by the Federal Drug Administration in 2011. There is strong level 1 evidence for BTX use in NGB for treatment of storage symptoms. The drug is administered by injecting the posterior wall of the bladder during a cystoscopy procedure (Fig. 8.3). Mostly, this is a short procedure done with local anesthesia in the clinic

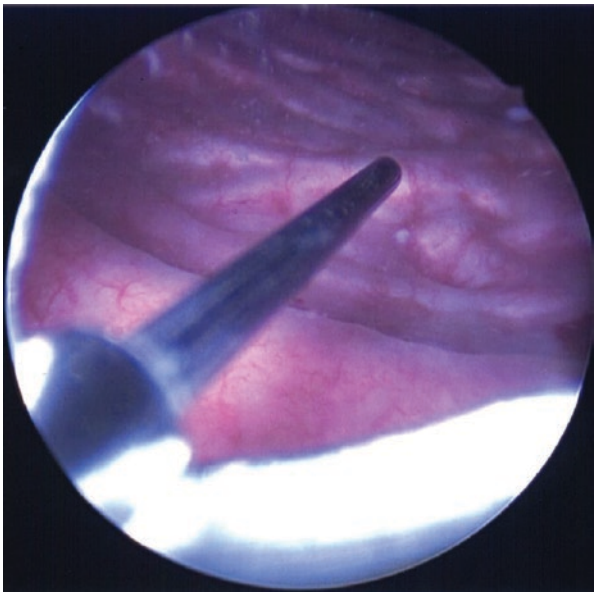

Fig. 8.3 Intravesical injection of botulinum toxin into the bladder wall with the aid of cystoscopy. The procedure takes about 5 min and most often is tolerated in the office with local anesthesia. (With permission from Dr. Jeremy B. Myers)

setting. Complications of the procedure include bleeding, patient discomfort, and urinary tract infection; rarely is the drug associated with systemic weakness [22]. Botulinum toxin, fortunately, works for a longer duration in smooth muscle, compared to skeletal muscle, and on average, it is injected about every 6 months into the bladder wall.

Two large studies, with essentially identical designs, randomized patients with either multiple sclerosis (MS) or spinal cord injury (SCI) to receive injection of placebo, 200 units, or 300 units of BTX [23, 24]. Outcomes of these studies were the change in number of incontinence episodes per week, urodynamic-based parameters (maximum cystometric capacity, maximum detrusor pressure during the first involuntary bladder contraction), and change in patient-reported quality of life. The results of these studies were dramatically positive in favor of injection of BTX over placebo. Patients had a decrease of 67–74% in number of urinary incontinence episodes (translating to about 20–25 less episodes per week), increased the maximum cystometric capacity by 150–160 ml, and decreased the pressures associated with involuntary bladder contractions. Patient-reported outcome measures included the Incontinence Quality of Life Questionnaire, which was also improved in the BTX groups compared to placebo [23, 24]. The studies also showed that there was no additional benefit to the use of 300 units over the results obtained with 200 units of BTX injection.

An additional meta-analysis was recently performed on individuals with SCI being injected with bladder BTX A [25]. Overall, the pre-BTX rate of incontinence, in the 734 pooled patients, was 23%, which was reduced to 1.3% after the use of BTX. In addition, the number of catheterizations per day and urodynamic assessed bladder pressures were also reduced with BTX injection.

Additionally, patients who respond to the initial botulinum toxin injection typically continue to respond and do not often develop resistance to the effect of injection [26]. In an extension of one of randomized studies mentioned above, there was a very low dropout rate over the 4 years of the study extension for adverse events (3%) or lack of efficacy (2%) [27]. It needs to be kept in mind that these are patients who responded to the therapy and requested retreatment and continuation of the study. Thus, they represent a population with inherent selection bias for positive response to BTX. When a patient has extensive fibrosis and bladder contraction, BTX injection is unlikely to be effective.

Key Points: Onabotulinum Toxin Injection

- There is good level 1 evidence that BTX injection can resolve incontinence, improve QoL and dramatically improve urodynamic parameters of bladder storage.
- BTX injection can mostly be given in the office, rarely has systemic side effects and most often can be used as long-term therapy.

Surgical Management

Bladder Augmentation

In bladder augmentation surgery, the bladder is opened and a patch of bowel is sewn onto the edges of the bladder expanding its volume and defunctionalizing the ability of the bladder to create coordinated spasticity. This surgery is also referred to as an enterocystoplasty because of the use of bowel to expand the bladder. Multiple bowel segments can be used in this surgery including small bowel, cecum and ascending colon, as well as sigmoid colon. In the past, stomach had also been used for enterocystoplasty; however, this was associated with hematuria and bladder-related complications.

Bladder augmentation has been demonstrated to have profound impact on bladder dynamics. When patients were assessed at an average follow up of 8 years, they were found to have substantial changes in urodynamics compared to their pre-augmentation urodynamics [28]. In one study, the mean bladder capacity increased from 200 cc to 615 cc, and the maximum detrusor pressure decreased from 81 to 20 cm H_2O. In this study, of the 26 patients only two continued anticholinergics and all but one patient had resolution or near resolution of incontinence. Bladder augmentation is also associated with the lowest patient-reported bladder symptoms and highest satisfaction when compared to those performing intermittent catheterization without augmentation or those who did CIC and had BTX injections [29]. This may be due to the profound change that occurs in the ability to store urine at low pressures.

The surgery can also be used to create an alternative channel to catheterize. This may be suitable for some patients that have urethral problems preventing catheterization, such as urethral strictures, false passages, and pain with passing the catheter. In addition, a catheterizable channel can help when patients lack adequate fine motor function or the strength and body habitus to position oneself in order to catheterize the urethra [30]. Usually, the catheterizable channel is also created from bowel segments, such as the appendix (called a Mitrofanoff), narrowed small bowel (Monti-Yang), or plicated terminal ileum (Fig. 8.4). These channels can come to the skin of the abdominal wall or to the base of the umbilicus where they form a small stoma that can be catheterized in a similar fashion to performing intermittent catheterization of the urethra.

Unfortunately, augmentation cystoplasty is a complex procedure that has significant peri-operative morbidity [30] and a high long-term revision rate. Both single center series and population-based analyses show that 34–46% of patients will need additional urologic interventions in the future, such as stone surgeries [28, 31, 32]. When patients are highly motivated to continue intermittent catheterization and have too much bladder fibrosis to respond to BTX injection or are not able to perform intermittent catheterization due to some of the reasons mentioned above,

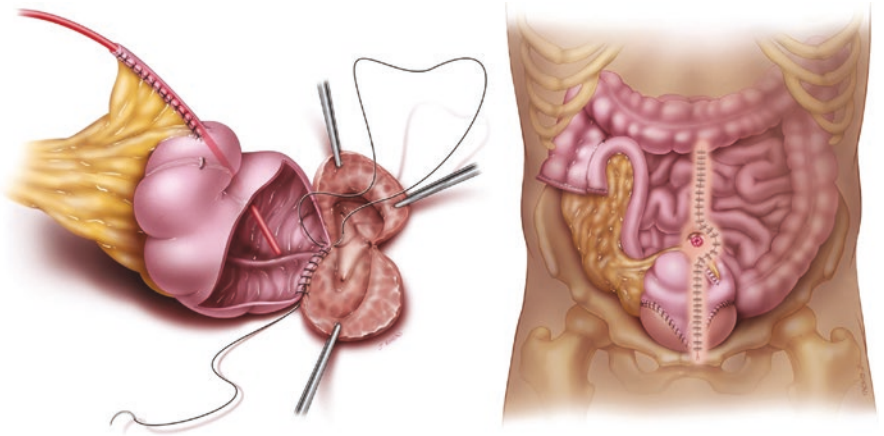

Fig. 8.4 Bladder augmentation with cecum, ascending colon, and creation of a catheterizable channel from plicated terminal ileum that makes a small stoma in the umbilicus to facilitate catheterization. (With permission from Dr. Jeremy B. Myers)

bladder augmentation with or without a catheterizable channel can preserve excellent bladder-related QoL. Patients just need to have a clear understanding of the potential for short- and long-term morbidity associated with the procedure.

Urinary Diversion

Conduit Urinary Diversion

Urinary diversion surgery involves the complete bypass of the bladder. Usually, urinary diversion consists of constructing a noncontinent urinary stoma out of bowel. The bowel segment connects internally to the ureters, which are disconnected from the bladder. The bowel segment is isolated from the fecal stream and the isolated segment is used as a "conduit" for urine from the kidneys and ureters to outside of the body. Most often, ileum is used to create the conduit, and the urinary conduit is referred to as an "ileal conduit." Many patients and practitioners also refer to urinary conduits as "stomas" or as a "urostomy." Both colonic and small bowel segments can be used to construct a urinary conduit. The reason that a portion of bowel must be utilized for this purpose rather than bringing the ureters directly to the skin is that cutaneous uretersotomies rarely stay patient in the long-term and are very prone to stenosis. Also, ureters tend to make a flat stoma, and for the urinary appliance or stoma bag, to fit over the stoma without leakage, the bowel has to have a nipple-like construction which projects from the abdominal wall 2–3 cm.

The most appropriate patients for urinary conduit construction are those who cannot or do not want to catheterize and do not tolerate an indwelling catheter. Often patients with tetraplegia or limited hand function will be treated with an indwelling catheter and chronic UTIs, urosepsis, or clogging of the catheter will necessitate

creation of a urinary conduit. From a patient perspective, there may not be much difference between an indwelling catheter and a "stoma," as both involve external bags for collection of urine. It is most often the complications from indwelling catheters that drive the decision for an incontinent urinary diversion.

Continent Catheterizable Pouch

Another type of urinary diversion, which can be used in NGB patients, is referred to as a continent catheterizable pouch. This surgery involves creation of a spherical bladder, made completely out of bowel. Rather than connecting to the urethra in the pelvis, this bladder is emptied with an intermittent catheter via a small stoma in the umbilicus or abdominal wall. Very often, this new bladder or "pouch" is made from the cecum and ascending colon. The channel that allows catheterization is made up of 8–10 cm of the tapered terminal ileum. This portion of the ileum is narrowed to about the same diameter of a pencil and the ileocecal valve is reinforced to prevent incontinence between catheterizations. This particular construction is referred to as a right colon pouch and arguably, the most common of these is the "Indiana Pouch" named after the institution where it was first described in the 1980s [33, 34]. The volumes of a right colon pouch are usually sufficient that patients catheterize four times daily to empty the pouch. Urinary diversion with a right colon pouch is an alternative to augmentation cystoplasty if the bladder has to be removed, such as in bladder cancer, fistula, and severe infection, or chronic debilitating pain. In these circumstances, preserving the remaining bladder, urethra, and native vesico-ureteral connections would not be possible, which are the main advantages of bladder augmentation cystoplasty rather than urinary diversion with a right colon pouch.

Neobladder

After removal of the bladder due to bladder cancer, a new spherical bladder constructed of bowel can be affixed to the urethral stump in the pelvis and patients void normally via the urethra. This arrangement is referred to as an orthotopic neobladder. However, in patients with neurologic disease this arrangement is rarely a solution, because function of the neobladder depends upon voluntary relaxation of the urinary sphincters and Valsalva voiding. Due to the neurologic dysfunction, patients who need urinary diversion, most often would not be able to coordinate sphincter relaxation and achieve spontaneous voiding. The neobladder can be emptied via intermittent catheterization via the urethra, but if intermittent catheterization is planned postoperatively, patients would likely just have an augmentation cystoplasty. Augmentation cystoplasty, compared to a neobladder, has the advantages of mitigating any risk of ureteral stenosis due to preservation of the natural connection at the vesico-ureteral anastomosis, and also allowing for less bowel to be used as the bladder will add a lot of surface area and volume to the spherically reconfigured bladder. For these reasons, few surgeons would treat patients with NGB with orthotopic neobladder.

Very similar to bladder augmentation, urinary diversion carries a very high perioperative and long-term morbidity. The reported mortality rates with the surgery vary, but range between 4 and 11% [35, 36]. Long-term complication rates are also high and include problems such as, UTI, urinary calculi, ureteral stenosis, metabolic and vitamin derangements, bowel obstruction, and hernias [37, 38]. In addition, surgical revision for urinary diversion complications is often needed. For instance, up to 22% of men need revision surgery at 16 months of follow-up after urinary diversion for complications of prostate cancer radiation [35] and up to 69% of patients need some revision surgery after right colon pouch [36]. Despite these complications, these surgeries can preserve QoL and are essential in treating serious complications of neurogenic bladder.

Key Points: Surgery

- The decision to undergo surgery is complex and the short and long-term morbidity must be weighed carefully against the patient's goals and preservation of renal function.
- Augmentation cystoplasty is associated with excellent patient reported QoL when the goal is to preserve the ability to perform intermittent catheterization.
- Urinary diversion may be needed in cases of bladder cancer, severe bladder dysfunction, or when patients do not have adequate hand function to perform intermittent catheterization.

Summary

Common treatments for neurogenic bladder span the spectrum from simple medical therapy to surgery to bypass or reconstruct the bladder. These treatments represent a time continuum and are not discrete choices. Some of the treatments work for a while and then more invasive treatments are needed as the bladder changes over time or patients experience neurologic disease progression. Follow-up and regular monitoring with a urologist or clinician familiar with the NGB and all of the treatment options available is essential in order to avoid or minimize complications and preserve patients' QoL.

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Part II
Neurourology in Specific Disease Processes

Chapter 9
Parkinson's Disease and Multiple System Atrophy

Anne P. Cameron

Description of Disease

Idiopathic Parkinson's disease (PD) is an extrapyramidal progressive neurodegenerative disease. It is the second most common degenerative neurological disease in humans after Alzheimer's disease, occurring in 100–180 people per 100,000 with an incidence of 4–20/100,000 annually [1]. It is caused by degeneration of cells in the substantia nigra of the midbrain that produce dopamine and intraneuronal Lewy body formation at this site [2]. PD is characterized by motor symptoms such as gait difficulties, postural instability, cogwheel rigidity, and resting tremor. The disease also has non-motor symptoms such as dysphagia, constipation (>50%), orthostatic hypotension (20–58%), depression, cognitive decline/dementia, and sexual dysfunction (43–81%), but lower urinary tract symptoms (LUTS) are among the most common nonmotor symptoms and affect 27–85% of patients [1, 3, 4]. Having LUTS is associated with poorer quality of life [5] and an increase in the risk of falls [6] and admission to skilled nursing facility. These Lewy bodies and dopamine neuronal degeneration are not confined to the brain and have also been observed in the peripheral nerves of the gut even before onset of symptoms [2].

The cause of bladder dysfunction in PD is via dopaminergic mechanisms that have inhibitory and excitatory effects on the voiding mechanism via D1 and D2 receptors. A D1-GABAergic direct pathway typically inhibits the micturition reflex. Also, an indirect pathway exists that also results in bladder inhibition. Cell loss in the substantia nigra results in loss of this D1-mediated inhibition and results in neurogenic detrusor overactivity. There is also a decrease in integration of sensory input from the bladder leading to poor coordination of voiding, but not true

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detrusor sphincter dyssinergia (DSD), given that the pontine micturition center is uninvolved [1].

Multiple system atrophy (MSA) is also a progressive neurodegenerative disorder that is caused by glial cytoplasmic inclusions that diffusely involve several neural systems [7]. Patients have symptoms of Parkinsonism along with cerebella ataxia and autonomic failure and because of this overlap up to 50% of MSA patients are initially misdiagnosed as PD. Differentiating between the two diseases is not purely academic since the urologic management is different. MSA involves the suprapontine area and is responsible for detrusor overactivity as well as atrophy of the parasympathetic nerves can cause poor bladder emptying. Onuf's nucleus is involved only in MSA (not PD) and this degeneration causes a weak outlet from an open bladder neck and a high rate of urinary incontinence from 60% to 100% [1].

Urologic Symptoms/Treatments

Urological symptoms in PD are confined to the lower urinary tract and also include erectile dysfunction. These symptoms typically occur 4–6 years after the onset of motor disturbances [8], but are not clearly related to the disease stage and not all bladder dysfunction worsens with time. It has also been postulated that patient aging rather than the disease progression is mostly responsible for any LUTS worsening [9]. It is difficult to determine the impact of PD itself on LUTS since no clear comparisons with age-matched controls have been performed, save a few studies [1].

The most common urinary symptom in PD is nocturia occurring in 60% [10], which is likely due to the bladder dysfunction since PD patients have similar prevalence of nocturnal polyuria as the general population, with urinary urgency occurring in up to 54%. Other very common LUTS include urinary frequency in up to 36% and urinary incontinence occurring in 25% regardless of gender [10]. Voiding symptoms such as poor urinary stream occurs in 70% of men and hesitancy in 44%, but these are not much higher than in a healthy age-matched male cohort likely due to benign prostatic hyperplasia (BPH) which is extremely common [11]. Women were far less bothered by these symptoms with 28% reporting straining to void.

MSA has quite a different urological presentation. LUTS and erectile dysfunction (ED) often precede other non-motor or motor symptoms hence these patients may be evaluated by a urologist first when neurological symptoms are subtle. Urinary urgency is more common (67%) as is urinary frequency (up to 45%), but what distinguishes MSA from PD are the high rates of urinary incontinence occurring in up to 60–100% and incomplete bladder emptying accompanied by obstructive symptoms [12] (Table 9.1).

Table 9.1 Distinguishing between PD and MSA

Distinguishing feature	Parkinson's disease	Multiple system atrophy
Prevalence	17.4–93.1/100,000 in ages 50–59 and 70–79 in USA	3/100,000 in >50 y/o
LUTS onset	4–6 years *after* motor symptoms	Often before motor symptoms
LUTS symptoms	Urgency, frequency, UUI, hesitancy	Voiding difficulty, urinary retention, urgency
Neurophysiology	Dopamine depleted in substantia nigra	Cytoplasmic inclusions in glial cells in many regions
Nonurologic symptoms	Gait difficulty, cogwheel rigidity, resting pill-rolling tremor, postural instability = parkinsonism	Can be Parkinsonism-predominant or cerebellar predominant with cerebellar ataxia
Dopaminergic drug therapy	Effective	Not effective
Transurethral resection of prostate for retention	Retention is likely due to BPH; TURP is effective	Retention is due to bladder dysfunction; TURP causes severe incontinence

Key Testing for Diagnosis

Diagnosis of PD or MSA is made neurologically but urological providers need to be aware of the common misdiagnosis of MSA as PD since there is significant symptom overlap and treatments are very different.

The foundation of the urological assessment is a good history focusing on the timing and severity of symptoms making sure not to neglect to ask about urinary incontinence and associated sexual or bowel symptoms. Also, knowledge about any prior urologic or gynecologic interventions is important. A standard urological physical exam assessing for prolapse in women and BPH in men is mandatory given their implication in both storage and voiding symptoms. No upper tract urologic imaging is routinely needed since upper tract deterioration is not associated with PD or MSA, but a post void residual is vital.

One of the clearest urological differences between PD and MSA is the postvoid residual. In PD mean post void residual is 78.0 ml; however, in MSA, it is 144.8 ml ($p = 0.001$, 13) with elevated residual considered by some to be a valid reason to explore the possibility of MSA as a diagnosis, given the rarity of elevated residual in PD.

Urodynamics are not routinely required in PD or MSA since poor bladder compliance is uncommon and treatment is based on symptoms; however, if surgical intervention is contemplated, it would seem prudent in these patients since, for example, in a woman with stress urinary incontinence (SUI) which is not a typical symptom for PD, one would want to confirm the SUI diagnosis before proceeding

Table 9.2 Urodynamic features of PD and MSA

Urodynamic finding	Parkinson's disease	Multiple system atrophy
Sensation	Normal or increased	Delayed
Detrusor overactivity	At smaller volumes and high pressure	At large volume and low pressure
Detrusor sphincter dyssynergia	No- this is bradykinesia of sphincter	Common detrusor external sphincter dyssynergia
Voiding efficiency	Preserved	Impaired
PVR	Low	High
Bladder neck on cystogram	Closed (normal)	Open

with a sling procedure. Also before proceeding with bladder botulinum toxin it would seem prudent to assess bladder contractility during voiding for counselling purposes since 63.3% of PD and 85.3% of MSA patients were found to have this finding on urodynamics. Detrusor overactivity occurs in 66.7% of PD and 64.9% of MSA ($p = 0.70$) [14] detrusor overactivity with impaired bladder contractility during voiding occurred in 42.1% of PD and 56.0% of MSA ($p = 0.002$).

On urodynamics compliance among patients with PD is a mean of 52.3 ml/cmH_2O and for MS 45.9 ml/cmH_2O among MSA ($p = 0.19$), but the percentage of patients with compliance less than 20 ml/cmH_2O is 21.5% and 35.5%, respectively ($p = 0.001$) [14]. Other urodynamics studies comparing these diseases found similar findings [15].

In terms of disease progression, none of the urodynamic parameters have been found to worsen with disease progression except impaired detrusor contractility [16].

Defining characteristics of MSA on fluoroscopy that are not present with PD include a gaping or wide open bladder neck that appears similar to the bladder neck after transurethral resection of the prostate [11]. Given the rarity of retention in PD, there may be value in this test in any patient presenting with these two conditions (Table 9.2).

Key Goals of Urologic Management

The primary goal in urologic care, given the expected progression of disease, in these diseases is quality of life. Patients with PD/MSA and urgency are at increased risk of falls [17] and those with incontinence suffer from poorer quality of life so these symptoms are clear targets for urologic care. Albeit rare, urinary retention requiring self-catheterization or an indwelling catheter places patients at risk for urinary tract infection (UTI) and other burdens related to catheters; hence, if there is a reversible cause such as BPH, the urologist can play a significant role in alleviating suffering.

Conservative management with timed voiding and fluid management as a primary treatment for urgency/frequency and urgency incontinence cannot be overstated.

Patients who void in a timed fashion do not have to rush to empty their bladder, which decreases fall risk. Most patients with PD who experience falls do so other way to the toilet [17]. Other simple treatments can include bedside commodes or urinals for men since falls at night are prevalent. Other conservative strategies include incontinence pads or condom catheters especially when mobility worsens later in the disease course (Fig. 9.1).

The traditional mainstay of medical therapy for urgency and urgency incontinence are anticholinergic medication. Several brands exist and solifenacin has been

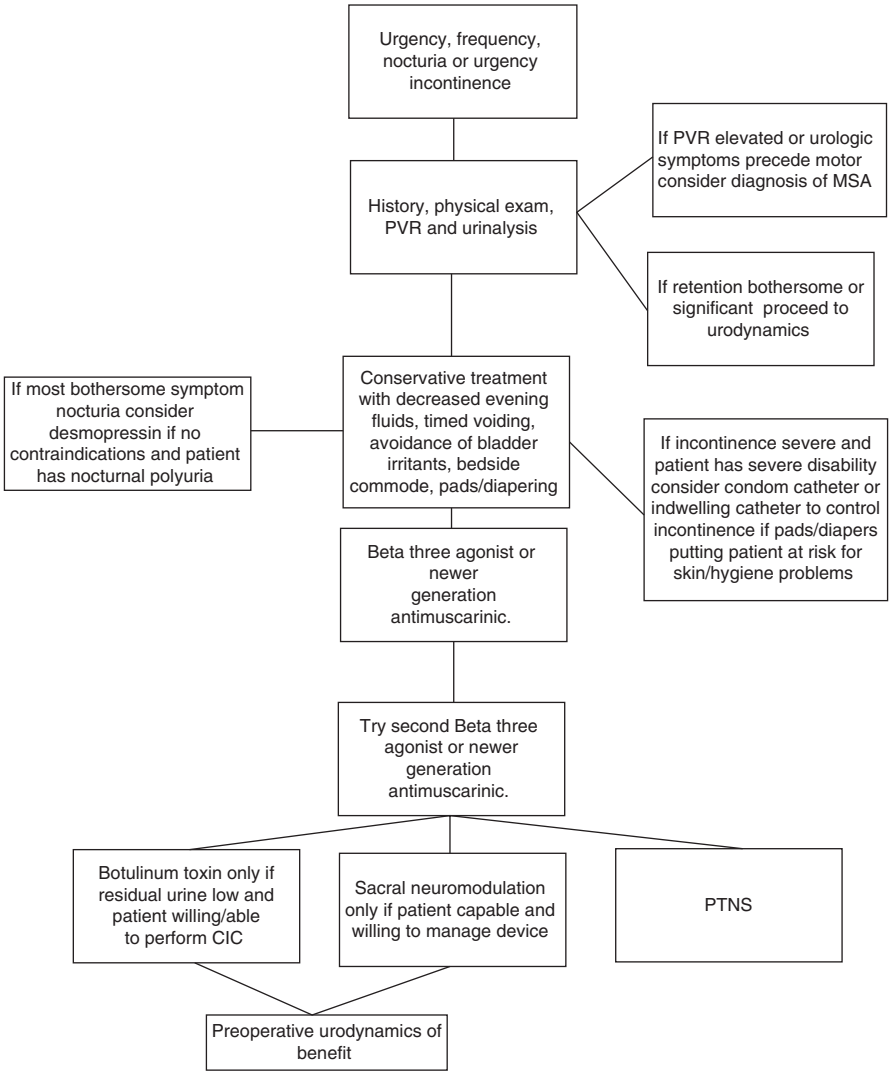

Fig. 9.1 Treatment algorithm for LUTS in PD

studied specifically in PD patients with a reduction in urgency incontinence and nocturia with self-limited side effects of constipation and xerostomia [18].

Side effects inherent to this class of medication are constipation, urinary retention, dry mouth and eyes, and cognitive impairment. Given that patients with PD and MSA are already at risk of cognitive impairment, caution must be utilized when prescribing these therapies. The beta3-agonist, mirabegron, has been retrospectively studied in 23 PD patients with nocturia, urgency, and urgency incontinence (UUI) with substantial resolution of these LUTS and without any of these side effects [19]. Also, since this class of medication dose not worsen voiding ability or increase residual urine, this may be a more ideal option in this population.

Desmopressin has been utilized for adults with nocturia due to nocturnal polyuria and could be of benefit in these patients, given the high rate of this complaint, but a voiding diary would be crucial to assess for polyuria exclusively at night and careful monitoring required given these drug's risk of hyponatremia [20].

PD patients have noted acute worsening of LUTS at onset of treatment with L-dopa, the mainstay of PD therapy; however, after chronic administration, many note a paradoxical improvement. This has been confirmed urodynamically and the provider should reassure patients to not abandon potentially helpful L-dopa therapy due to worsening LUTS since this exacerbation will subside with the chronic synaptic changes induced by the drug [21].

Operative Risk

Very few patients with PD or MSA require surgical intervention for their LUTS, but in the case of failed second-line therapy for urgency and urgency incontinence, the same third-line therapies for overactive bladder (OAB) are available for this population including percutaneous tibial nerve stimulation (PTNS), botulinum toxin injection of the bladder, and implantable sacral neuromodulation (Fig. 9.1).

Percutaneous Tibial Nerve Stimulation (PTNS) is a very minimally invasive office procedure with negligible local side effects. It has been studied in a small group of patients with PD and resulted in a reduction in frequency, urgency incontinence, and nocturia after the 12-week induction. Urodynamic parameters also improved with reduction in volume at DO (137–272 cc) and increased maximum cystometric capacity (MCC) [22]. Given the very low risk and morbidity from this treatment, urodynamics are not mandatory before initiating therapy.

Botulinum toxin bladder injections (BTX-A) are routinely utilized in neurogenic bladder patients with substantial efficacy particularly in those patients performing clean intermittent catheterization (CIC) where higher doses of 200U are utilized and there is no concern about retention as a side effect. Since PD patients typically void, there is particular concern about de novo urinary retention in this population even with the 100U dose. The effectiveness of 100U of BTX-A has been studied in PD with favorable outcomes and 80% of patients reported reduction in their LUTS. Residual urine, as expected, increased from a mean of 18 ml to 125 ml after

injection, but only 12.5% of patients required the initiation of CIC with higher pre-procedure post void residual (PVR) being significantly associated with retention and a lower chance of symptom resolution (49 ml vs. 16 ml) [23]. A dose of 200U has also been used successfully [24]; however, current recommendations advise starting at the lower 100U dose in voiding patients and the dosage can always be increased with subsequent injections if required [23]. It would certainly seem prudent to ensure that any patient receiving this therapy be advised of the increased risk of retention compared to OAB patients and be prepared to perform CIC should the need arise.

Implanted sacral neuromodulation devices are FDA-approved for OAB-related LUTS, but have been used off label in patients with neurogenic bladder. In a large retrospective series of voiding patients with and without neurological etiology of their symptoms, there was little difference in efficacy or complications between these two groups. This study included ten PD patients [25] and the therapy could be a reasonable option in patients who are capable of understanding and utilizing their device.

For men with retention requiring catheterization, a transurethral resection of the prostate can be considered when there is evidence of prostatic enlargement causing bladder outlet obstruction. Urodynamics are crucial in diagnosis since retention can be due to either atonic bladder, obstruction or both. In the past, transurethral resection of the prostate (TURP) was contraindicated in all PD patients due to the risk of incontinence; however, those studies included MSA patients who are virtually at 100% risk of incontinence due to their bladder neck dysfunction inherent to the disease [1]. Clearly ensuring a correct neurological diagnosis is key before proceeding. Less invasive and less morbid therapies such as Rezum™ or Urolift™ may be better suited for this population with a shorter life expectancy and greater prevalence of detrusor overactivity, but this has not yet been evaluated.

Deep brain stimulation (DBS) is used to treat motor symptoms of advanced PD; however, this therapy can also have positive effects on LUTS. In particular, DBS of the subthalamic nucleus improved urinary incontinence and frequency in a randomized clinical trial [26]. Hence, patients with a planned DBS or recently placed devices should avoid urological treatment changes until the impact of DBS is seen.

Conclusion

PD and MSA are progressive neurological conditions that very frequently are associated with LUTS that can be severe. The urologist may see the patient before a diagnosis is made and should be familiar with both diseases. Conservative therapy is a mainstay of treatment and oral agents can be of benefit. Occasionally, patients may require surgical intervention to relieve their symptoms and care must be taken to ensure a correct diagnosis. In particular, an elevated post void residual should question the diagnosis of PD in favor of MSA as does symptoms of erectile dysfunction and LUTS before motor symptoms.

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Chapter 10
Alzheimer's Disease and Dementia

Michael Harper and Anne M. Suskind

Description of Disease

Dementia is not a single disease. It is a term that describes a progressive loss of ability in more than one domain of cognition severe enough to result in a decline in an individual's capacity to perform everyday activities. The most common type of dementia is Alzheimer's disease (AD), affecting an estimated 5.7 million Americans [1]. Other common types of dementia are dementia with Lewy bodies, vascular dementia, and frontotemporal dementia. Dementia primarily affects older adults with a prevalence of 10% at age 65 and doubling every 5 years [2, 3]. By the age of 85, it is estimated that 25–50% of individuals will have dementia [4, 5].

Disease Pathophysiology

By definition, dementia is an acquired disorder, the clinical onset of which typically begins after the age of 60. The neuropathologic features that distinguish AD are the deposition of beta amyloid protein in the extracellular regions of the brain and the intracellular neurofibrillary tangles within neurons that are made up of hyperphosphorylated tau protein [6]. Beta amyloid plaques are associated with synaptic

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dysfunction, while the neurofibrillary tangles are linked to axonal loss and ultimately cell death [7]. These changes begin years, if not decades, before symptoms emerge and debate remains as to whether the pathologic changes seen in AD are the cause or result of the disease. Similar to AD, putative proteins have been identified for Lewy body dementia (alpha-synuclein inclusion bodies) and frontotemporal dementia (tau and ubiquitin proteins) [8, 9]. Vascular dementia is caused by any condition that leads to disruption of blood flow to the brain and vascular damage. The most common subtypes of vascular dementia are the result of atherosclerotic, cardioembolic, or small vessel disease.

Organs Affected

In the early stages of dementia, the primary symptom is most often a loss of memory, typically short-term memory, while memories from the remote past are preserved until later stages. Other common symptoms include aphasia (e.g., word finding difficulty), visuospatial dysfunction (e.g., impaired facial recognition and navigation), loss of executive function (e.g., poor judgment and planning), and apraxia or the inability to carry out learned motor tasks despite the presence of an intact motor system (e.g., inability to use a brush to comb one's hair).

A variety of psychological and behavioral symptoms are associated with most dementias and can manifest over the course of the illness. Common symptoms include sleep disturbance, wandering, perseveration, depression, hallucinations and delusions, apathy, irritability, disinhibition, and physical aggressiveness.

Key Testing for Diagnosis

The diagnosis of dementia is based primarily on the clinical presentation, focusing on the history and physical exam. Because of the nature of the illness, the clinician may not be able to rely on the information provided by the patient and therefore gathering information from collateral sources is often necessary. The history should focus on eliciting symptoms of cognitive decline, the onset and progression of the earliest deficits, and the impact on the patient's ability to perform routine daily functions, specifically probing basic and instrumental activities of daily living. The use of a standardized cognitive testing instrument can provide valuable information about the domains of cognition involved and the degree of cognitive impairment. Commonly used instruments include the Mini-Cog [10] and the Montreal Cognitive Assessment (MoCA) [11]. Performance on cognitive testing can be affected by years of education, and when available, cognitive tests should be administered in a patients' native language.

Laboratory and imaging studies are directed at identifying potentially reversible causes of dementia which are in fact rare. The American Academy of Neurology

recommends the following laboratory tests in the routine evaluation of dementia: complete blood count, glucose, serum electrolytes, blood urea nitrogen, creatinine, thyroid stimulating hormone, vitamin B12 level, and liver function tests [12]. Testing for syphilis and HIV is only recommended, if the patient is at high risk for one or both diseases. Neuroimaging looking for evidence of a previous stroke, tumor, hydrocephalus, and subdural hematoma is recommended for all patients being evaluated for cognitive decline. In most cases, a CT scan of the brain is adequate to rule out conspicuous pathology. Functional imaging studies such as functional magnetic resonance imaging (fMRI) and fluorodeoxyglucose positron emission tomography (FDG-PET) have some utility in distinguishing types of dementia but should not be considered a part of routine evaluation.

Timeline of Progression

Most dementia types begin insidiously and progress slowly; however, there can be wide variability among patients with the same disease. In less common cases, dementia can develop suddenly and progress rapidly with death occurring within months of diagnosis. Patients with AD have a median life expectancy of 4–8 years, but this can vary significantly from as little as 3 years to as long as 20 years [1]. The progression of dementia can be described based on the degree of cognitive loss or based on functional decline. The Global Deterioration Scale (GDS) describes seven stages of dementia using a framework of changes in cognition (see Table 10.1) [13].

Table 10.1 The global deterioration scale

Stages	Clinical characteristics
1: No cognitive decline	No subjective memory complaints
	No evidence of memory deficits with clinical interview
2: Very mild cognitive decline	Subjective memory complaints
	Names
	Placement of objects
	No evidence of memory deficits with clinical interview
	No objective deficits in employment or social situations
3: Mild cognitive decline	Earliest memory deficits can now be objectively identified through clinical interview. Deficits seen include the following:
	Concentration
	Limited memory retention
	Word finding
	Navigation
	Performance issues may arise in work and social situations
	Denial may be present

(continued)

Table 10.1 (continued)

Stages	Clinical characteristics
4: Moderate cognitive decline (mild dementia)	Clear-cut memory deficits are evident on clinical interview. Deficits seen include the following:
	Serial subtractions
	Reduced memory of recent events
	Managing finances
	Orientation and ability to recognize familiar people and faces and travel to familiar places are preserved
	Denial may be more prominent and withdrawal from challenging situations may occur
5: Moderately severe cognitive decline (moderate dementia)	Some assistance with routine activities is needed
	Individuals may no longer be able to:
	Recall their address, phone number, names of close relatives or friends
	Count backward from 40 by 4s or 20 by 2s
	Correctly identify time or place
	Recollection of spouse's and children's names is preserved as is the ability to eat and toilet
6: Severe cognitive decline (moderate dementia)	Deficits may include the following:
	Forgetting name of spouse
	Lack of awareness of recent events and life experiences
	Inability to count backward from 10
	Behavioral and emotional symptoms and personality changes may include the following:
	Delusions and hallucinations
	Anxiety and agitation
	Repetitive behaviors (e.g., phone calls, hand tapping)
	Sleep–wake cycle disturbances
	Assistance is needed with most if not all ADLs[a] and IADLs[b]
	Urinary incontinence episodes are common
7: Very severe cognitive decline (severe dementia)	Dependence for ADLs and IADLs is the rule
	Urinary incontinence predominates
	Walking requires assistance and may be completely lost
	Speech is limited to a few words or perhaps only grunting
	Swallowing and skeletal muscle functions become impaired

Adapted from Reisberg et al. [13]
[a]ADLs basic activities of daily living (bathing, dressing, transfers, toileting, feeding).
[b]IADLs instrumental activities of daily living (telephone, shopping, food preparation, housekeeping, laundry, transportation, medication management, management of finances).

Operative Risk

Patients with dementia may occasionally have an indication to undergo invasive procedures and surgery. It is important to recognize that in the early stages of dementia, many patients will maintain their ability to participate in conversations of informed consent and make independent decisions about their treatment.

For those patients with dementia who proceed with surgery, studies have shown that they are at increased risk for a variety of adverse outcomes including delirium, longer lengths of stay, and greater mortality [14]. Delirium is particularly common with an incidence of 15% after elective noncardiac surgery and can be as high as 35–65% in high-risk operations such as hip fracture repair [15, 16]. While preexisting dementia is considered the strongest predisposing risk factor for postoperative delirium, its presence should be considered in the context of other risk factors including advanced age, limitations in physical function, abnormal serum chemistries, and the type of procedure. While the type and route anesthesia have not been shown to have an impact on the incidence of delirium, using the lowest dose of anesthetic agent possible may reduce the risk [17, 18]. A 2014 best practice statement by the American Geriatrics Society described several recommendations to prevent postoperative delirium that included multifaceted nonpharmacologic interventions (e.g., sensory enhancement, early mobility, cognitive reorientation, sleep enhancement), pain management, avoidance of benzodiazepines, antipsychotics and other high-risk medications (e.g., anticholinergic medications), and assessment and management of other medical contributors to delirium [19].

Urologic Symptoms/Treatments

Expected Urologic Symptoms

Urinary incontinence among older adults with dementia is common, multifactorial, and may have different origins compared to incontinence among younger healthier adults. One study of patients with established Alzheimer's dementia revealed that urinary incontinence was significantly associated not only with age but also with disinhibition, deficits in attention and orientation, and reduced verbal fluency. These findings suggest that factors other than traditional neural control of continence likely play a role in the development of incontinence in this population [20].

Functional incontinence is a major cause of urinary incontinence among older adults with dementia (Table 10.2). It occurs when the individual has trouble getting to the bathroom due to physical impairment, cognitive impairment, or decreased motivation. Individuals with physical impairment may have physical limitations getting to the bathroom in general or getting to the restroom quickly enough in order to prevent leakage. Individuals with cognitive impairment may not know how to get to the bathroom or even that they need to get to the bathroom, presenting an entirely different set of problems. In more advanced cases of dementia, individuals may be entirely indifferent to continence and may have disturbed consciousness around this, and other self-hygiene issues [21].

Overactive bladder is another major cause of urinary incontinence in older adults with dementia (Table 10.2), which may be present in isolation or in combination

Table 10.2 Urologic symptoms among older adults with dementia

Urologic symptoms	Description of urinary symptoms	Expected urodynamic finding
Functional incontinence	The individual has a difficult time getting to the bathroom due to physical impairment, cognitive impairment or decreased motivation [21]	NA
Overactive bladder	Urinary urgency and frequency may be associated with nocturia and or incontinence [23]	Detrusor overactivity
Underactive bladder	Slow urinary stream, hesitancy and straining to void, with or without a feeling of incomplete emptying and dribbling, often with storage symptoms [22]	Detrusor underactivity
Stress incontinence	The symptom of involuntary leakage on effort or exertion, or on sneezing or coughing [23]	Observed leakage from the urethra seen at the exact time of exertion [24]
Nocturnal polyuria	More than 33% of the total daily urine output occurs at night	NA
Drug-induced incontinence and retention	Drugs that affect either the central nervous system or lower urinary tract (i.e., antipsychotic medications, antidepressants, benzodiazepines, sedatives, anticholinergics)	Inability to urinate

with other forms of urinary incontinence such as functional incontinence. For example, if an individual has a strong urge to urinate and has physical limitations or a gait disturbance that makes it difficult to get to the restroom quickly, this may result in leakage that could have otherwise been avoided. Urodynamics, which may be challenging in this patient population, may show associated detrusor overactivity as an objective sign of overactive bladder symptoms.

Other potential urologic problems associated with dementia are outlined in Table 10.2. Underactive bladder, which is defined as a slow urinary stream, hesitancy and straining to void, with or without a feeling of incomplete emptying and dribbling, and often with storage symptoms [22], can occur in isolation or in combination with OAB. The latter case results in detrusor hyperactivity with impaired contractile (DHIC) function. Stress incontinence, the symptom of involuntary leakage on effort or exertion, or on sneezing or coughing [23], may also be present in older adults, particularly in older women, with dementia. Nocturnal polyuria, defined as more than 33% of the total daily urine output that occurs at night, is common in the older population and hence may also be present in older adults with dementia. Finally, drug-induced incontinence and retention are important potential causes of urinary symptoms in older adults with dementia, with particular emphasis on antipsychotic medications, antidepressants, benzodiazepines, sedatives, and anticholinergics [21].

Key Goals of Urologic Management

The goals of urologic management should take into account the degree of bother/distress for both the patient and the caregiver, which may be dissimilar at times, making management difficult and nuanced in some cases. In patients with more advanced dementia, the individual may not be particularly bothered by their urologic symptoms; however, the caregiver may be quite distressed, particularly in cases of urinary incontinence. Urinary incontinence among older adults with dementia is a leading cause of institutionalization and therefore, the burdensome effects on the caregiver should be taken seriously.

A literature review of ten studies looking at patients with urinary incontinence living in long-term care facilities revealed that while these individuals value having bladder function, they often believe that urinary incontinence is inevitable and intractable. This attitude is often met with low expectations and many individuals decline further evaluation and treatment. Some express satisfaction with the state of urinary incontinence, even though it is not consistent with their life preferences and those with more severe cognitive impairment often respond with anxiety when caregivers attempt to provide continence care [25].

Studies on caregivers emphasize the importance of treating their loved one with dignity, taking them seriously as equal human beings, and making sure that their relational needs are met (i.e., not treating them as an object or task). These findings highlight the importance of understanding a *dignifying caring relationship*, with meaningful interaction between the patient and the physician [26]. These attributes call for a different medical paradigm that incorporates the psychosocial aspects of providing continence care in this population that meet the needs of individuals with complex health conditions who are dependent on another person for assistance [27].

Treatment Options

Treatment of urinary symptoms in adults with dementia should begin with ruling out any underlying reversible/treatable causes. The "DIAPERS" pneumonic for urinary incontinence is a helpful place to start, whereby each letter represents a different potentially treatable cause: delirium, infection, atrophic vaginitis, psychological/behavioral causes, pharmaceuticals, endocrine causes, restricted mobility, and stool impaction.

Once the above factors have been ruled out and or addressed, there are several treatment strategies specific to older adults with urinary incontinence and dementia that can be considered. Toileting regiments/behavioral therapy may be of benefit in the form of prompted voiding, whereby the individual is asked on a regular schedule whether they need toileting assistance, combined with positive reinforcement for using the restroom. This is particularly helpful among individuals with decreased

motivation, cognitive disability, and gait disorders. Additionally, changes to environmental factors such as hallway handrails, canes, walkers, and wheelchairs, easy toilet access and visibility, improvements to bathroom facilities such as lighting, grab bars, toilet seat and height, commodes, and well-designed clothing that can easily be taken off (i.e., Velcro or elastic waistbands instead of buttons or zippers) can help maximize independence and toileting [21]. Discussion of and assistance with continence care products, such as pads and absorbent undergarments, is also important in this population.

For patients with OAB, anticholinergic medications should be used with caution. Alzheimer's dementia is characterized by a central cholinergic deficit. Anticholinergic medications can block cholinergic receptors in the central nervous system (M1-muscarinic receptors in the cerebral cortex and M4 receptors in the basal ganglia), potentially exacerbating declines in cognitive function. Additionally, these medications can interact with acetylcholinesterase inhibitors given to individuals with cognitive impairment to improve cognitive function, further worsening cognition [28]. Studies specifically addressing the efficacy of pharmacotherapy (either anticholinergic or beta3-agonist medications) in individuals with an existing dementia diagnosis are lacking [29].

Treatment Map

Figure 10.1 presents a treatment map for urinary incontinence among older adults with dementia. It emphasizes the importance of addressing both medical and psychosocial issues associated with this problem in this population and is informed by

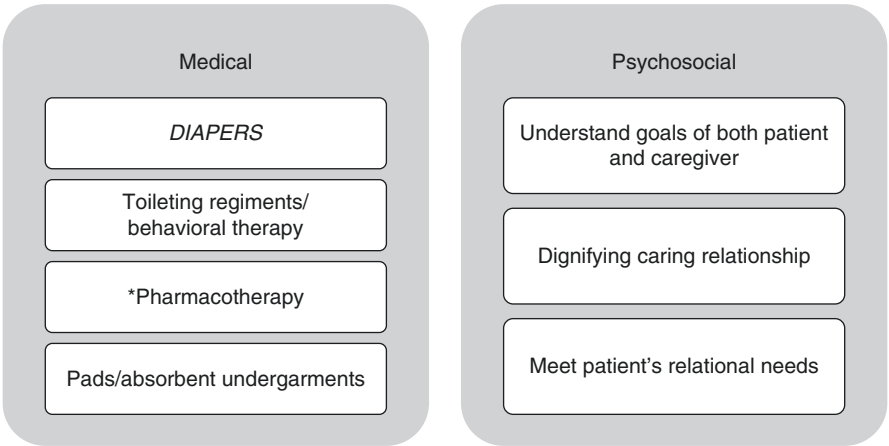

Fig. 10.1 Treatment Map for management of urinary incontinence among older adults with dementia.

Ostaszkeiwicz et al. [27]. Important to the model are the psychosocial aspects of care including: (1) understanding the goals of both the caregiver and the patient; (2) interacting via a dignifying caring relationship, whereby both the patient and the care provider interact and participate in a meaningful, personal and responsible way; and (3) meeting the patient's relational needs meaning that the caregiver treats the patient as more than an object or task [26].

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Chapter 11
Cerebral Palsy

Joseph J. Pariser and Sean P. Elliott

Introduction

In contrast to the other chapters in this text, cerebral palsy (CP) represents a nonhereditary, "nonprogressive" disease. It arises from brain injury in early development, such as fetal hypoxia, untreated jaundice, infection, or trauma in utero, during delivery, or shortly after birth. Roughly 3–4 children out of 1000 are affected [1]. While CP is "non-progressive," in that it is a fixed brain injury, urologic (and nonurologic) manifestations can change over a person's lifetime. For example, patients may become more spastic or develop increased incontinence after childhood, and hence, CP is included in this text.

Description of Disease

The most common form of CP is the "spastic" form, which is caused by cortical injury and characterized by muscle spasticity. Other less common types of CP include ataxic CP (injury to the cerebellum) and dyskinetic CP (injury to the basal ganglia). These latter types are less common and have fewer urologic sequelae. Therefore, this chapter will focus on spastic CP.

The severity of CP is related to the quantity and location(s) of brain involvement of the original insult. While muscle spasticity is nearly ubiquitous, intellectual disability is not. The estimated prevalence of intellectual disability in CP is 38–52% [2–7]. Intellectual disability is associated with severity of motor impairment and gray matter injuries [7].

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The degree of motor dysfunction can be described on a 1–5 scale (5 denotes most affected) using the Gross Motor Function Classification System (GMFCS), which is validated in children. For example, Level 1 is characterized by minor impairments such as limited balance and coordination, but individuals can climb stairs without assistance. Level 3 is characterized by the ability to climb stairs with assistance or self-propel a manual wheelchair. Level 5 is associated with severely limited self-mobility even with the use of assistive technology [8].

This chapter will focus on the urologic sequelae and keys to management in adults with CP as the management is unique compared to other conditions in this book that are associated with neurogenic bladder.

Disease Pathophysiology

The lower urinary tract pathophysiology of CP is complex. As a cortical level disorder, CP would be expected to result in an "upper motor neuron bladder," characterized by detrusor overactivity, urge incontinence, and eventually, reduced bladder compliance. However, *the picture is complicated by the intense motor spasticity that defines CP. This leads to overactivity of the somatic muscles of the pelvic floor, resulting in a tight external urethral (and anal) sphincter. The closed sphincter during voiding can result in an outlet obstruction that hastens the loss of bladder compliance, or paradoxically, can result in chronic urinary retention and a large capacity low pressure bladder.* We refer to this closed sphincter as "pseudo-dyssynergia" rather than "detrusor-sphincter-dyssynergia" because it is a result of constant high muscle tone (not just during voiding) and a cortical (rather than spinal cord) lesion.

Symptoms

While CP results from a nonprogressive cortical injury, some patients have progressive symptoms or manifestations of disease. Anecdotally, individuals with severe CP often present to the urologist in early adulthood (18–35 years). In contrast to the adult *spina bifida* population, most adults with CP have not had any urologic reconstruction as children. Those with mild-to-moderate CP may have voided volitionally as children and present as adults with lower urinary tract symptoms. Those with severe CP may have voided to a diaper all their life. There are relatively few reports about the lower urinary tract symptoms present in adults with CP. History taking is challenging because muscle spasticity results in communication difficulty. Thus, completing standardized questionnaires to assess lower urinary tract symptoms is often not practical. We previously reported that of 121 people with moderate-to-severe CP (GMFCS 3–5) in our transitional/adult congenital urology clinic, 60% voided volitionally and 40% were incontinent to

Table 11.1 Urologic symptoms

Void into diaper – 40%
High volume urinary incontinence
Urinary frequency/urgency
Slow stream
Constipation

a diaper [9]. Of those who void volitionally, urinary complaints can range from irritative symptoms (urgency or frequency) to obstructive symptoms (slow stream or retention). Of those who are incontinent to a diaper, many hold their urine for 8 to 12 and even 24 h and then "flood" (a large void that overwhelms the diaper and soaks their clothing and/or bed sheets). In addition to these symptoms, other common reasons for urologic referral are recurrent urinary tract infections or hydronephrosis.

Constipation is common and the etiology mirrors that of the bladder pathology – a spastic pelvic floor leads to constipation and incomplete emptying. *Briefly, management of constipation can include stool softeners or laxatives to thin the stools or a colostomy to divert stool above the level of sphincteric obstruction. Antegrade continence enemas should be avoided since the etiology of the problem is sphincter tone.*

Table 11.1 Summarizes common urologic symptoms.

Key Testing for Diagnosis

For patients presenting with new or worsening urologic complaints, we perform a thorough history and physical. We utilize a customized, standardized urologic intake for all patients with neurogenic bladder in our transitional/adult congenital urology clinic, which facilitates nursing staff intake of complex patients to streamline physician workflow (Fig. 11.1). This includes a functional assessment along with a history of catheterization, infections, stones, and bowel habits. It is important to comanage the bladder and bowel problems, whether medically or surgically. Finally, we incorporate an assessment of the patient's living situation and availability of in-home help in our management decisions, especially for those patients who will require assistance with intermittent catheterization.

All patients have renal function testing and renal ultrasound at initial evaluation and annually. For patients who are presenting with new complaints, we recommend urodynamics if not recently completed. This is critical, especially for patients with communication challenges, to identify issues with poor detrusor compliance or an overactive urethral sphincter/pelvic floor. We previously reviewed our urodynamic findings in 49 patients in our transitional/adult congenital urology clinic. Over half had bladder compliance <20 cc/cm H_2O. Detrusor overactivity was present in 30% and pseudodyssynergia in 12% [10]. Figure 11.2 represents a urodynamic tracing of a typical patient with CP who lives in chronic urinary retention. Table 11.2 describes common urodynamic findings in adults with CP.

UROLOGY ASSESSMENT
Name _____
MRN _____ Age _____ M _____ F ____
SB, level _____ Shunt _____
SCI, level _____ Shunt _____ ITB pump _____
CP, GMFCS _____ Shunt _____ ITB pump _____
Other Dx _____

UROLOGIC SURGICAL HISTORY
Augmentation_____
Continent cath channel _____
Indiana Pouch _____
Vesicostomy_____
Ileal conduit _____
Bladder neck closure _____
Urethral sling _____
Bladder neck sling _____
Urethral AUS _____
Bladder neck AUS _____
Bulking injections _____
Other: _____
_____
_____

UROLOGIC HISTORY:
Hydronephrosis: _____ Solitary Kidney:_____
VUR: _____

FUNCTION:
Communication_____ Sensation_____
WC type _____ Transfers _____

URINATION HISTORY
Void on own_____
Retention_____ # of Hours_____
Discomfort_____ Urgency_____ Frequency_____

CATHETERIZATION New_____Lubricant_____
Catheter_____
Cath schedule_____Difficultly____
Volumes_____Who performs/technique_____

OTHER URINE COLLECTION
Suprapubic_____ Foley_____
Pouch_____
Other collection information_____

LEAKAGE
Leak_____ From where do you leak_____
Pads/day_____ Dry over night_____

ANTICHOLINERGIC/BOTOX
Current:_____
Previously tried/last dose:_____

PCP_____**NS**_____**PM&R**_____

STONES
Hx bladder stone_____ Kidney stone_____
Blood/ pain/ symptoms:_____

UTI HISTORY
Last UTI_____ UTI/YR_____
S & S UTI_____
UTI prophylaxis_____

IRRIGATION
Irrigate_____ Schedule_____
So ln/ process_____

INSTILLATION
Bladder instillation_____ Schedule_____
Solution_____

BOWEL MANAGEMENT HISTORY
Chait ACE
ACE
ACE solution_____
Schedule_____
Timeuntil BM_____
Colostomy
Ileostomy
BMs/week_____ Bristol #_____
Bowel program_____
_____
Bowel accidents per/week_____
Time spent_____Assistance Needed_____
Fluid intake_____ Fiber/Diet_____
SKIN
Breakdown/wound_____

REPRODUCTIVE/SEXUAL HEALTH_____

SOCIAL HISTORY_____
FAMILY MEDICAL HISTORY_____

IMAGING HISTORY
RUS_____ KUB_____ ABDX-ray_____
Cystogram_____ CT_____

TEST HISTORY
CMG_____
CYSTOSCOPY_____
Cr_____ B12_____
TODAYs APPOINTMENT
Bladder Management Satisfaction_____
Bowel Management Satisfaction_____
Questions/concerns today_____
_____
_____
Prescriptions needed_____
Pharmacy_____
Vendor_____

Fig. 11.1 Sample transitional urology clinic intake form

Urologic Symptoms/Treatments

Most CP patients come to the urologist voiding per urethra; very few are on intermittent urethral catheterization (approximately 5% in our series) [9], and even fewer have an indwelling catheter. The goal should be to preserve volitional voiding whenever possible. Of the 121 patients in our series who were voiding per urethra at presentation, we were able to avoid intermittent or indwelling catheterization

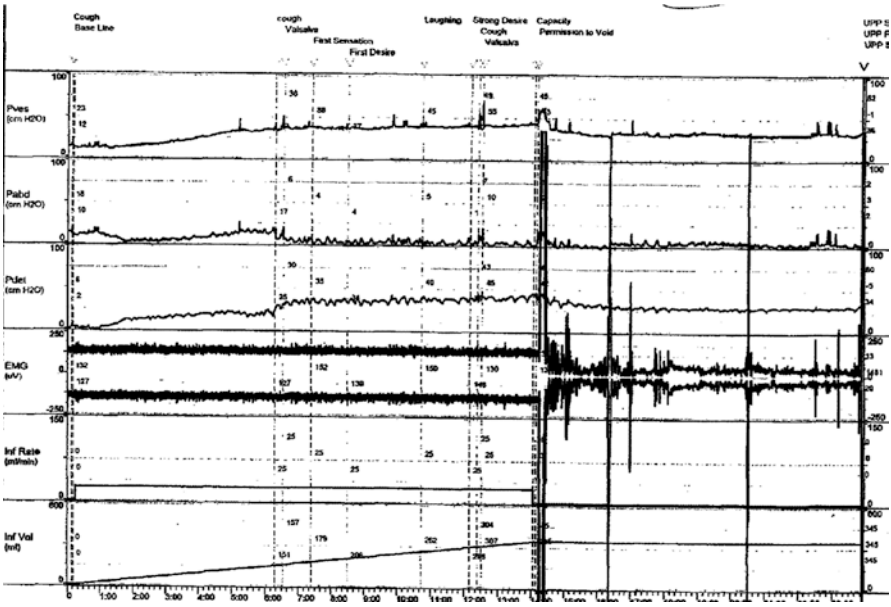

Fig. 11.2 Urodynamic tracing of patient with CP with chronic urinary retention. Note increasing Pdet pressure (loss of compliance) as the bladder fills and hyperactive EMG during attempted voiding phase

Table 11.2 Typical urodynamic findings in adults with CP

	Typical urodynamic findings	Atypical urodynamic findings
Bladder characteristics during storage phase	*If intermittent or indwelling catheter:*	
	Detrusor overactivity Poor compliance	Good compliance
	If in chronic retention:	
	Good compliance, large capacity	Detrusor overactivity Poor compliance
Electromyogram (EMG) activity	Hyperactive throughout all phases	Hyperactive only during voiding or quiescent
Voiding phase	Often unable to void spontaneously upon request	Bell-shaped curve

in 77% at 3 years. The reasons for initiating intermittent catheterization were hydronephrosis in 9 patients, persistent urinary retention in 10, and refractory lower urinary tract symptoms in 9.

We tolerate conservative management in patients with large capacity bladders in chronic urinary retention without intervention unless the patient suffers from problematic incontinence, bladder stones, recurrent urinary tract infections, or worsening hydronephrosis. Problematic incontinence may manifest as flooding, skin irritation, or decubitus ulcers.

When we do intervene, anticholinergics are used sparingly, typically in those who void spontaneously and do not have pseudodyssynergia. In those with urinary retention and flooding, intermittent catheterization per urethra is often poorly tolerated. *Unlike some other conditions associated with neurogenic bladder (e.g., spina bifida and spinal cord injury), patients usually have normal sensation of their urethra, which, along with a spastic pelvic floor, can make catheterization very painful*. Additionally, lower extremity spasticity makes positioning for urethral catheterization a challenge, especially in women. Instead, we favor cystoscopic injection of botulinum toxin (onabotulinumtoxinA 100u in 2–4 mL sterile saline) into the external urinary sphincter to facilitate spontaneous voiding.

Chemodenervation of the sphincter has been performed for DSD in the setting of spinal cord injury and MS. Most studies focus on patients with true DSD, with very few including any patients with CP. A review of chemodenervation for functional, neurogenic bladder outlet obstruction demonstrated improvement in some urodynamic measures but noted lack of long-term outcomes and need for repeat treatments. Of note, injections should be deeper than for a bulking agent, as it should inject the muscle and not the submucosal space [12]. Postinjection urodynamic studies can demonstrate less obstructed voided, but at times, the intensity of electromyographic (EMG) activity can remain relatively unchanged as most of the pelvic floor muscles remain spastic after chemodenervation of the external sphincter. Therefore, we generally rely on symptoms and other objective measures of adequate emptying (decreased hydronephrosis). Figure 11.3 demonstrates a

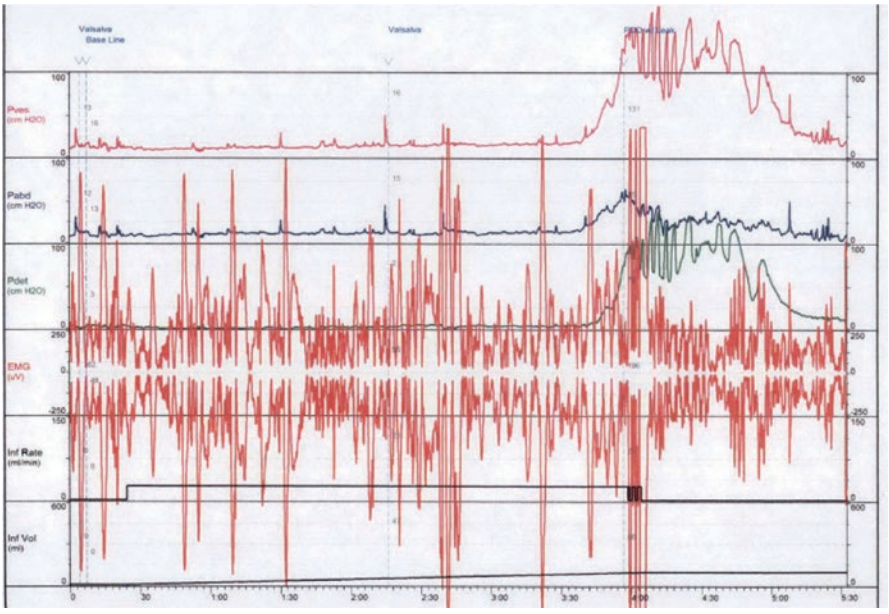

Fig. 11.3 Urodynamic tracing of patient with CP with chronic retention successfully managed with botulinum toxin to external urethral sphincter. EMG activity remains high, likely confounded by pelvic floor spasm

postinjection urodynamic tracing of an adult with CP managed successfully with botulinum toxin injection to the external urethral sphincter every 6 months. Note active EMG, likely indicating pelvic floor spasms. If doses up to 200U fail, we offer catheterizable channel (CC) creation to facilitate painless catheterization in the wheelchair without transferring. We avoid sphincterotomy due to the high failure rates reported in the spinal cord injury population [11].

If the urethra is abandoned, then suprapubic tube, CC and incontinent diversion become options. Suprapubic cystostomy is a simple, widely performed procedure, which allows for bladder emptying without incontinence. However, for a variety of reasons, patients may not desire an indwelling catheter. Therefore, we offer CC creation for patients who want to perform CIC and are unable to do so through their native urethra. We routinely review urodynamics when determining if augmentation is needed at the time of CC creation, focusing on the storage phase: bladder capacity, compliance and uninhibited contractions. Many of our patients with CP present for CC creation with a distended, chronically obstructed bladder due to pseudodyssynergia. These patients can have large bladders with good compliance preoperatively, but their bladder storage dynamics can change after decompression. We recently reported our experience performing CC creation without augmentation in patients with CP with seemingly favorable bladder characteristics preoperatively, most of whom (75%) were in chronic retention [13]. All patients in chronic retention required escalation of their neurogenic detrusor overactivity management (e.g., anticholinergics, botulinum toxin injection) postoperatively, and 67% had lower maximum cystometric capacity on follow-up urodynamics. While we have not augmented any of these patients, some are suboptimally managed on botulinum toxin injection and would have been well served by an augmentation. Therefore, we do not trust favorable preoperative urodynamics in patients with CP in chronic retention when considering whether to perform bladder augmentation at the time of CC creation. Options include preoperative decompression with CIC (which can be difficult given sphincter tone and lower extremity spasticity), suprapubic tube followed by repeat urodynamics, performing a prophylactic bladder augmentation at the time of CC creation, or proceeding with CC without augmentation as long as the patient is aware that an escalation of therapy may be required in the future.

In contrast to some other patients with neurogenic bladder, such as those affected by spina bifida, the bladder outlet does not need to be addressed in the majority of patients with CP. Their pelvic floor and urethral spasticity generally allows for continence as long as the bladder is a compliant reservoir and regular catheterization is maintained.

Choice of catheterizable channel (e.g., appendicovesicostomy, Monti, tapered ileum) and augment (e.g., colon vs. ileum) follow the same principles as in other patients with neurogenic bladder. Small bowel resection is generally less morbid than large bowel. While the appendix is more often used in children, more adult patients have had an appendectomy or have an appendix unsuitable for use (too short for adult-sized patient). While a combined ileal augmentation and channel is feasible, we often utilize an ileocecocystoplasty (right colon augment with tapered

Table 11.3 Key urologic interventions

Aggressive management of constipation
Conservative management of urinary retention in absence of safety issues
Onabolulinum Toxin treatment to external sphincter for obstructive voiding patterns on EMG
Avoid intermittent catheterization due to pelvic floor spasms
Continent catheterizable channels, possible augment for patients unable to perform CIC
Annual upper tract imaging

ileal channel). Benefits include a built-in continence mechanism of the ileocecal valve and the ability to perform the procedure with a laparoscopic hand-assist approach through a Pfannenstiel incision to limit morbidity [14].

Some consideration should be made regarding bowel management if urologic reconstruction is chosen. For example, adults with CP often live with insidious constipation secondary to pelvic floor spasticity. Thus, a careful bowel history including frequency, hardness (Bristol stool scale) and hygiene is needed. *For patients without an existing colostomy, careful consideration of a diverting colostomy at the time of urologic reconstruction allows for a single surgery and optimization of choice of bowel segments for urinary and fecal streams*. Simultaneous double diversion is associated with similar perioperative morbidity as urinary diversion alone after previous colostomy [15]. For patients with an existing colostomy desiring an incontinent urinary diversion, we work together with colorectal surgeons to limit the need for an anastomosis by converting an existing colostomy to a urostomy. In a multiinstitutional series of patients with an existing colostomy, we found a lower rate of perioperative complications in patients who did not require a bowel anastomosis using this approach compared to a conventional approach of bowel harvest proximal to an existing stoma [16]. Table 11.3 summarizes key urologic interventions in managing CP patients.

Unique Surgical Considerations

There are unique challenges for patients with CP who are undergoing surgery. First, the degree of spasticity may lead to positioning issues, whether performing cystoscopic, laparoscopic, open abdominal, or percutaneous renal procedures. Spasticity in the lower extremities can alter the ability to be placed in lithotomy. Affected upper extremities may necessitate placing the arms on the chest during the procedure – rather than tucking the arms or leaving them completely horizontal. Difficulty with intubation can also occur in the setting of severe contractures. Comorbidities, such as dehydration, malnutrition, epilepsy, reflux, and impaired pulmonary function, are common [17]. Communication challenges are also

common, which can lead to challenges preoperatively (e.g., accurate history) and postoperatively (e.g., pain control).

In terms of nutrition, patients with cerebral palsy are at higher risk for obesity than age-matched controls [18]. However, a significant number actually suffer from malnutrition and may be underweight. This may be related to the spasticity/high muscle tone constantly burning calories, which may be combined with inadequate caloric intake (especially in the setting of no gastrostomy tube).

Baclofen pumps are used frequently for the treatment of CP-associated spasticity. Pumps are roughly 7 cm in diameter and 2.5 cm in depth. They are usually placed subcutaneously laterally on the lower abdominal wall. Direct intrathecal delivery utilizes much smaller doses than oral baclofen. We often encounter baclofen pumps in patients with CP during urologic reconstruction. Usually, they are surrounded by a pseudocapsule, which we do not penetrate. The catheter from the baclofen pump generally travels laterally from the pump, and therefore, this region should be avoided. One can still usually perform a Pfannenstiel or midline incision in the presence of a Baclofen pump. Laparoscopic or robotic ports may need to be placed higher than usual. We generally mature catheterizable channels (CC) at the umbilicus (away from the pump). If a urostomy is being created, it generally can still be placed on the side of the Baclofen pump if needed, though sometimes the site is slightly higher than usual.

Conclusion

Although cerebral palsy is due to a fixed cortical injury at birth, the bladder and bowel problems can progress throughout the life of the patient. As such, patients who had minor urinary complaints as children can progress to chronic urinary retention or bothersome incontinence as adults. Optimal management can include permissive chronic urinary retention with close observation for complications (e.g., hydronephrosis and bladder stones). When intervention is required, intermittent urethral catheterization or indwelling catheters should be avoided. Rather, excellent outcomes can be achieved with chemodenervation of the external urethral sphincter or CC creation with bladder augmentation. Surgeons should be aware that even if urodynamics demonstrate a large capacity, low pressure bladder, a CP bladder is still an upper motor neuron bladder, and that the low pressures may only be a result of chronic retention. When initiating intermittent catheterization through the urethra or through a newly created CC, *de novo* urge incontinence and loss of bladder compliance can develop after decompression of the chronic retention.

Acknowledgments None

Conflicts of Interest None

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Chapter 12
The Urologic Management of Huntington Chorea

David Ginsberg and Claudia Sevilla

Description of Disease

Disease Pathophysiology

Huntington disease (HD), also known as Huntington chorea, is an autosomal dominant disorder caused by a mutation in the huntingtin (HTT) gene on chromosome 4p16.3 due to cytosine-adenine-guanine (CAG) trinucleotide repeats [1]. The exact function of the huntingtin protein is unknown; however, it is necessary for normal development before birth primarily in the brain. Proposed roles include binding of proteins, protection from apoptosis, chemical signaling and transporting materials [2]. The disease exhibits variable penetrance depending on the number of CAG repeats, with full penetrance occurring with 40 or more repeats [3]. The exact pathophysiology is unknown, but it is believed to cause its main effects in the central nervous system due to aggregation of mutant huntingtin protein. CAG expansion has been shown to have a "gain of function" effect such that the mutant form of huntingtin protein gains a deleterious function leading to neuron loss [4].

Organs Affected

The central nervous system is primarily affected in HD. Neuron loss is thought be due to the toxic effect of huntingtin with CAG expansion which causes neuronal atrophy focused primarily in the corpus striatum of the basal ganglia, including

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the putamen and caudate [5]. Neurological symptoms include motor, cognitive, and psychiatric components [6]. *Chorea is the earliest and most classic finding in HD and involves involuntary movements of the trunk and limbs*. However, other motor deficits include dystonia, gait abnormalities, and hyperreflexia. Psychiatric symptoms are broad and include depression, aggression, delusions, and apathy. Cognitive deficits include memory loss, poor judgment, poor insight, and decreased concentration.

Key Testing for Diagnosis

The diagnosis of HD is a clinical diagnosis and is made by family history, characteristic features of the disease, as well as genetic confirmation of the CAG expansion. *Diagnostic genetic testing should be done in all symptomatic patients with clinical features of HD, with or without a family history of HD* [7]. Although HD consists of a multitude of signs and symptoms, diagnosis is made based on motor disturbance. This can be assessed using the motor assessment section of the Unified Huntington Disease Rating Scale (UHDRS) [8]. The second part of this motor assessment section involves a confidence diagnostic level in which a score of 0 is normal and a score of 4 equates to unequivocal motor abnormalities suggestive of HD ($\geq$99% confidence that the individual has HD) [9]. Given the advances with molecular testing, neuroimaging is no longer used to diagnose HD. However, if done, magnetic resonance imagining (MRI) of the brain will demonstrate caudate atrophy and correlates with cognitive decline [10].

Timeline of Progression

HD onset is subtle and progresses over several years. Disease progression is based on symptom severity. Patients typically live 10–20 years after initial diagnosis though some patients have been reported to live 30–40 years after being diagnosed [5].

Staging for HD is typically broken up into three different phases. In early stages of HD, cognitive deficits are focal including loss of short-term memory and executive system functioning [11]. Individuals also start to experience minor involuntary movements or subtle loss of coordination [5]. The progression of behavioral abnormalities is heterogeneous. In a large survey of 1238 HD patients, sadness, depression, and irritability started as early as the first year after onset [12]. In most cases, affected individuals remain globally functional in the earliest stage of HD.

In the middle stage of HD, chorea and motor deficits become more prominent, making it more difficult for individuals to tend to their daily activities. In addition, psychiatric symptoms worsen, and patients may start experiencing delusions or

hallucinations and may have changes in their sleep patterns [12]. Cognitive decline worsens leading to intellectual decline and memory loss, resulting in difficulties related to problem solving [5].

Once HD progresses into the late stage, patients experience global subcortical dementia [11]. Speech difficulty, weight loss and bowel/bladder incontinence occur [12]. Chorea is replaced with rigidity, bradykinesia and dystonia [5]. Essentially, patients need assistance with all activities of daily living and, in end stages, can become nonverbal and bedridden. However, despite the lack of communication in end stages, individuals may still maintain some sense of comprehension.

One other commonly used form of staging for HD is the Total Functioning Capacity (TFC) scale. This rating scale assesses an individual's functional abilities in five different domains including occupation, ability to manage finances, ability to perform domestic chores, ability to perform personal activities of daily living, and setting for level of care. The TFC score is used to determine a patient's disease stage on the Shoulson and Fahn rating scale (Fig. 12.1) [5, 13].

Table 12.1 Demonstrates the progression of symptoms and disability in conjunction with TFC scores and stage as defined by the Shoulson and Fahn rating scale. Excerpted with permission from *A Physician's Guide to the Management of Huntington's Disease (Third Edition),* Huntington's Disease Society of America (HDSA) [5].

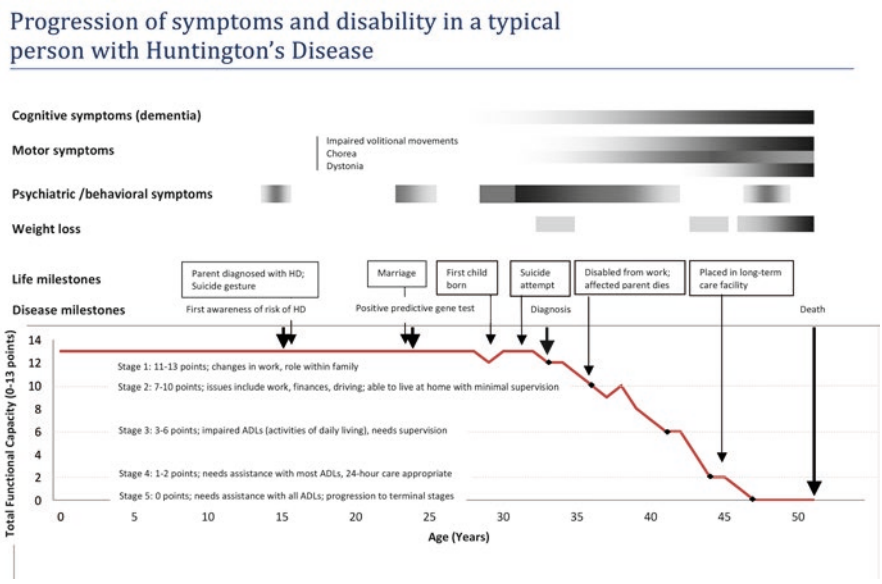

Fig. 12.1 Description of staging for HD

Table 12.1 Urodynamic findings in Huntington disease

	Potential UDS finding
Bladder	Normal
	Decreased capacity
	Detrusor overactivity
	Incomplete emptying
Urethral sphincter	Normal
	Detrusor-sphincter dyssynergia
Perineal musculature	Normal
	Choreiform movement during bladder filling

Operative Risk

There is a higher surgical risk for HD patients due to anesthetic issues, positioning and worsening of neurologic and cognitive symptoms. The anesthesiologist needs to use caution when administering anesthetic drugs as several of the psychotropic drugs used to treat HD can have potential interactions [14]. In addition, general anesthesia can aggravate baseline symptoms of chorea and psychosis [15]. Dysphagia is another common symptom in later stage HD patients and can be a risk factor for aspiration during intubation or extubation [16]. In later stages of HD, rigidity and dystonia can be seen which may make intraoperative positioning difficult [5]. Proper care should be taken to position patient carefully and minimize risks of peripheral nerve or musculoskeletal injury. A greater risk of perioperative bleeding has not been documented in HD patients; however, as affected individuals progress and mobility decreases, anticoagulation may be needed because these patients are at higher risk for venous thromboembolism [5].

Urologic Symptoms/Treatments

Expected Urologic Symptoms

Bladder dysfunction in HD patients has been minimally studied; however, there is evidence that these patients do have significant urinary symptoms. *The most common symptoms reported include lower urinary tract symptoms (LUTS) such as urgency, urinary incontinence, and incomplete bladder emptying* [17, 18]. Kolenc, et al. reported more frequent and severe urinary incontinence and overactive bladder symptoms in men with HD compared to controls. In addition, urinary function questionnaire data suggests that urinary symptoms interfere with daily life (21% men, 37% women) and sexual life (21% men, 33% women); however, only women with HD had significant impairment in quality of life (QoL) due to their LUTS [18]. In this same study, urodynamics (UDS) were performed in 12 HD patients and one

asymptomatic HD gene carrier. Findings include detrusor-sphincter dyssynergia (42%), detrusor overactivity (17%), and reduced detrusor capacity (<300 mL) (17%). Six HD patients also had an elevated post void residual (PVR) >100 mL. Wheeler et al. also found detrusor overactivity with normal sphincter function in 4 of 6 HD patients studied. Abdominal perineal musculature was found to exhibit choreiform contractions during filling and was suppressed during detrusor contraction [19]. Table 12.1 summarizes the potential UDS findings in patients with HD.

One prior study assessed Onuf's nucleus degeneration in HD patients to try and explain the cause of lower urinary tract dysfunction. There was found to be no evidence of quantitative anal sphincter electromyogram (EMG) or sacral reflex abnormalities. However, 81% of these patients had decreased tonic anal sphincter activity and voluntary activation, as well as lower sacral sensory thresholds and shorter reflex latencies which are likely caused by degeneration of other parts of the central nervous system [20].

Key Goals of Urologic Management

The role of the urologist will be most significant in mid and later stages of the disease as the affected individual progresses and develops worsening of symptoms, including loss of bladder control. Nevertheless, patients in early stages of the disease can also present with lower urinary tract symptoms (LUTS) including urgency, frequency, and nocturia due to detrusor overactivity therefore requiring intervention early on [18]. The urologist should be present when a HD patient's symptoms become bothersome enough to require intervention, and it should be the responsibility of the urologist to determine the appropriate treatment depending on the patient's stage of disease and severity of symptoms. If diagnostic interventions such as urodynamics are needed in equivocal cases, then the urologist should perform these tests in those individuals as needed.

With disease progression, affected individuals will become completely dependent on caregivers and lose motor ability, therefore treatments to improve urinary symptoms need to be chosen with this in mind. A patient may be unable to perform clean intermittent catheterization (CIC) due to loss of manual dexterity and may not have a caregiver willing or able to do so either; therefore, this may not be a viable treatment option for all HD patients. Furthermore, indwelling urethral catheters should be avoided if possible due to risks of infection and urethral erosion [21]. However, due to limited mobility as HD progresses, indwelling catheter drainage may be the best alternative for lower urinary tract management. In patients that develop neurogenic bladder, the most important risk factor is increased storage pressures which can ultimately lead to renal damage [22]. The objective of treatment is to prevent damage of the upper tracts in these patients that progress to this stage. Thankfully, this does not appear to be a common issue in patients with LUTS due to HD.

The goal of urologic care should be to focus on choosing treatments that maximize QoL in HD patients. At baseline, these individuals exhibit decreased ability to independently perform daily activities, have decreased mobility and are manifest with psychiatric disorders such as depression and anxiety. It is important for the urologist to keep in mind that urinary symptoms may be more impactful for HD patients, despite being mild, due to limitations in mobility or manual dexterity. For example, affected individuals may become more exacerbated by symptoms of urgency due to limited mobility, which can result in leakage of urine from not reaching restroom in enough time. Ultimately, treatment decisions should be made as a team keeping both the patient and caregiver in mind.

Treatment Options

Treatment options will vary and will be individualized based on the individual's primary symptoms and stage of the disease. In early stages of HD, patients may present with overactive bladder (OAB) symptoms such as urgency, frequency, nocturia, or urge incontinence. Treatment options should start with conservative management and progress to oral medications or third tier OAB treatments (botulinum toxin, neuromodulation) as needed [23]. Conservative management options include behavioral modification such as decreasing caffeine and fluid intake, timed voiding, or maintaining a bladder diary to understand voiding patterns. Individuals who fail behavioral modification should be started on oral medication [23]. *In the HD population, anticholinergics should be administered with extreme caution due to potential interactions of antipsychotic drugs that many HD patients take*. Drugs such as haloperidol and olanzapine can also have anticholinergic properties making side effects, such as cognitive impairment, worse [19, 24]. Beta agonists, such as mirabegron, may be a better first line option for HD patients. In the Parkinson disease population, a similar population in that there is a worry regarding anticholinergic load due to concomitant medications, OAB symptoms have been shown to improve using mirabegron with minimal side effects at the 6-month mark [25].

If LUTS persist despite medical treatment, urodynamics should be performed prior to offering additional therapy. Currently, intravesical onabotulinumtoxinA (BoNT-A) injection is approved for use in urinary incontinence due to detrusor overactivity associated with a neurological condition. This treatment has been shown to be effective in phase III randomized controlled trials at a dose of 200 units with side effects including elevated post void residuals and urinary tract infections [26, 27]. If an HD patient is willing to accept the risk of urinary retention requiring CIC then treatment with 200 units is an option. Other options for HD patients that are still voiding spontaneously include injection of

100 units of BoNT-A, which has shown to decrease urinary incontinence by 50% over 6 months without the need to catheterize in Parkinson's disease (PD) patients [28]. Furthermore, Vurture et al. showed significant improvement in OAB symptoms 4 weeks after the first BoNT-A injection with 100 units in PD patients and demonstrated that high preoperative PVR was the strongest predictor of treatment failure and need for CIC [29]. This suggests that HD patients with low preprocedural PVR may benefit the most from intravesical BoNT-A injection. Another option would be neuromodulation, though this is less accepted for the patient with a neurogenic bladder.

HD patients that fail intravesical BoNT-A and have persistent bothersome symptoms may benefit from more invasive surgical treatment. The simplest and least invasive option would be placement of a suprapubic tube. If avoidance of an indwelling catheter is preferred, then an ileal conduit may be performed which allows for adequate urinary drainage and avoids use of an indwelling catheter or the need for catheterization in this patient population. Less ideal in the HD population is a bladder augmentation +/− continent cutaneous diversion. This treatment option would require manual dexterity to perform CIC which HD patients lose in later stages of the disease. If the patient has a caregiver that can perform CIC, then this could be a viable treatment option.

A certain subset of HD patients may develop detrusor-sphincter dyssynergia (DSD) and elevated bladder pressures requiring intervention [30]. There is limited data to suggest that medication, such as alpha blockers or intravesical BoNT-A injection can help improve DSD [31]. CIC can be used to help keep bladder volumes low or in patients that have developed overflow incontinence, but this is only an option in those patients who still have motor function of their hands or who have a caregiver who can perform CIC. A suprapubic tube can also be used and is a safer and preferred option than an indwelling catheter [32]. BoNT-A injection into the external sphincter via cystoscopy or ultrasound guided transperineal approach is another treatment; however, a 2014 Cochrane meta-analysis review noted lack of high quality trials and the need for frequent, repeat injections, making this a less desirable, long-term treatment option [33].

External urethral sphincterotomy remains an appropriate option in male HD patients and can be done with laser, electrocautery, or cold knife. Sphincterotomy may have to be repeated in regular intervals in certain individuals and will possibly result in incontinence requiring external devices such as condom catheters [31]. Vainrib et al. demonstrated long-term durability (109 months) and low perioperative complications with a success rate from 50% to 85.7% after up to three repeat bladder neck incision/external sphincterotomy procedures [34].

Individuals that progress to later stages may develop neurogenic bladders due to detrusor underactivity/areflexia with severe overflow incontinence. Treatment options include indwelling catheter drainage (suprapubic tube or urethral catheter) or ileal conduit [22]. In addition, patients with LUTS and HD may also

have worsening incontinence from immobility issues, depression, or medications such as neuroleptics, tricyclic antidepressants or anticholinergics causing urinary retention [5]. All of these factors need to be assessed when treating a patient with HD, particularly in later stages of the disease as symptoms progress and need for medications may increase. Figures 12.2 and 12.3 describe a recommended timeframe for urologic intervention depending on the stage of the disease and symptoms present.

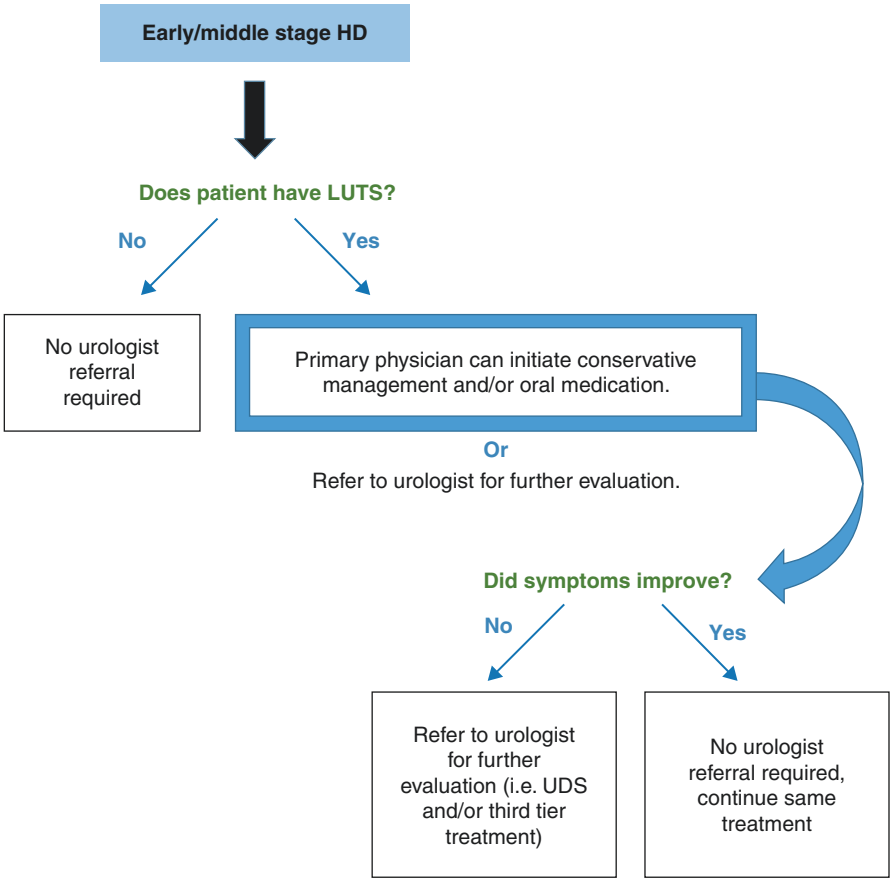

Fig. 12.2 Treatment map for early/middle stage HD

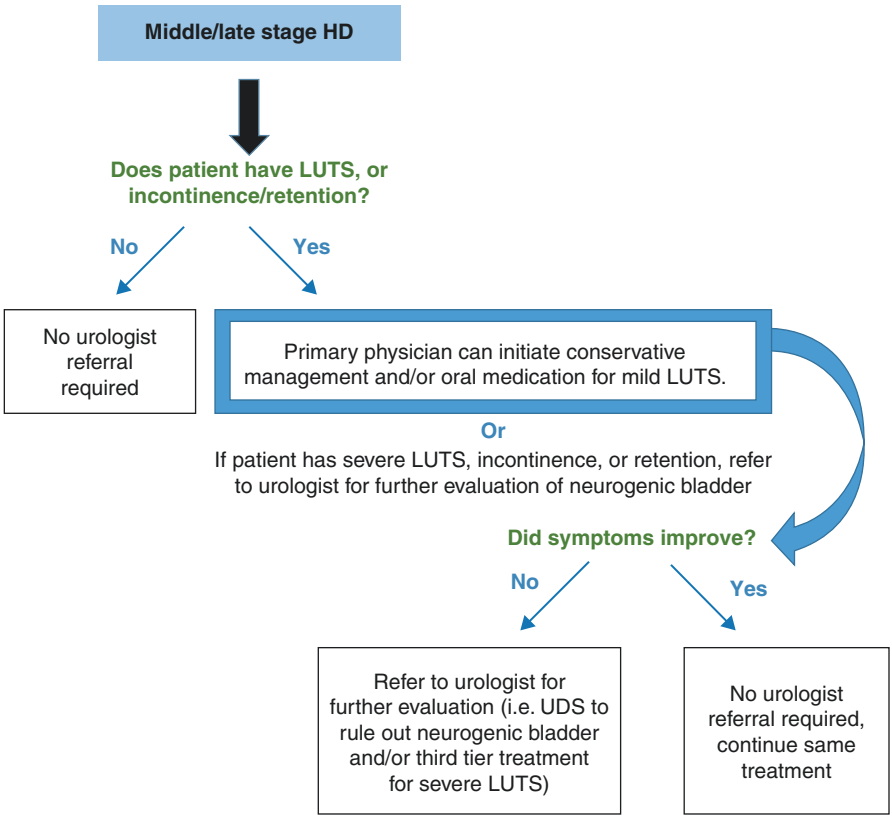

Fig. 12.3 Treatment map for middle/late stage HD

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Chapter 13
Neurourology in Multiple Sclerosis and Other Demyelinating Disorders

Natalia Hernandez and Rose Khavari

Introduction

Myelin covers most nerves in the central and peripheral nervous system and allows for better transmission of the signals of neural impulses. Demyelinating disorders affect myelin integrity and interrupt this transmission. Although demyelinating disorders can occur in various settings such as in hereditary disorders (such as Tay-Sachs disease and Krabbe disease), nutritional deficiencies (such as in Vitamin B12 deficiency), toxins (such as alcohol), or viral infections of central nervous system, primary demyelinating disorders are the most common. Primary demyelinating disorders include Multiple Sclerosis (MS), Monophasic disorders (optic neuritis, acute transverse myelitis) and Neuromyelitis Optica (NMO). NMO was previously considered a variant of MS; however, it mainly affects the optic nerve and spinal cord. In some cases, it may have urological symptoms similar to those in MS patients. Multiple sclerosis (MS) is the most common primary demyelinating disorder of the central nervous system and this chapter focuses mostly on MS. MS is a chronic inflammatory disease of the central nervous system with prevalence ranging between 50 and 300 per 100,000 people. About three quarters of patients with MS are female [1, 2].

Disease Pathophysiology

Multiple Sclerosis is a demyelinating disorder where the lesions can be found throughout the central nervous system, affecting progressively the white matter in the brain and spinal cord [3]. Neuropathological characteristics of MS include:

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axonal or neuronal loss, demyelination and astrocytic gliosis. Clinical disability is directly related to neurodegeneration, which is in result of progressive axonal or neuronal loss [1]. There are various triggers suggested for MS. Environmental risk factors may include geographical latitude, low vitamin D, smoking, obesity, and mononucleosis [1]. Additionally, genetic characteristics, such as carriers of the HLA DRB1∗15:01 allele have been associated with this disease [1].

Organs Affected

There are typical symptoms of MS at presentation, most frequent ones are monocular visual loss secondary to optic neuritis, limb weakness or sensory loss due to transverse myelitis, double vision due to brainstem dysfunction, or ataxia due to cerebellar involvement [2].

Throughout the course of the disease, MS impacts different organ systems causing spasticity, fatigue, impaired ambulation, ataxia, tremor, and neuropathic pain. Bowel dysfunction can cause constipation. Sexual dysfunction can occur, and cognitive impairment may result in depression and emotional lability. This emphasizes the need of a multidisciplinary and individualized approach to patients with MS with the goal of minimizing disease impact and optimizing quality of life [1].

Key Testing and Diagnosis

Diagnosis of MS requires clinical expertise, imaging and laboratory findings. Magnetic resonance Imaging (MRI) is currently the most important diagnostic and prognostic tool available, as it can interrogate the entire central nervous system in vivo [2]. Imaging changes related to inflammatory demyelination and alterations in the blood–brain barrier are characteristic of early MS. Changes in brain and spinal cord plaque size on MRI are related to neurodegeneration [2]. Additional evaluations, such as clonal expansion of immunoglobulin secreting B cells, also known as oligoclonal bands in the central nervous system are classic findings of MS. [2]

McDonald Criteria are the main diagnostic criteria, integrating MRI findings and number of attacks. Of note, cerebrospinal fluid (CSF) findings were recently integrated into the criteria after the 2017 revision of McDonald Criteria [1, 2].

Timeline of Progression

Early stages of MS are known by acute episodes of neurological deficits, known as relapses [1]. It is important to note that this neurological disorders affects primarily young females, with a mean age at onset of 30 years [3]. Symptoms are related to the CNS region affected on each relapse. Optic neuritis, which presents with visual impairment and pain with ocular movements, develops after acute inflammation of the optic nerve. Relapse-remitting course affects around 85% of MS patients, and about 50% of these patients will have disease progression over the next 11 years [3]. This form of the disease is described as episodes of neurological deficits followed by variable recovery and periods of stability, compared to progressive MS, which is characterized by a gradually increase in neurological disability. However, this terminology has evolved to now describe the presence or absence of MS activity by including relapses, progression new MRI lesions (inflammatory activity) and CNS atrophy (ongoing neurodegeneration) [4]. After MS diagnosis is confirmed, older age, male gender, worse disability at baseline and brain atrophy are predictors of faster progression to further disability and morbidity. On the other hand, women have a higher relapse rate and disability accumulation [1]. Additionally, the increase in lesion volume during the first 5 years after a clinically isolated syndrome is associated with greater disability after 20 years [1, 2].

Urologic Manifestations and Evaluations

Urinary Symptoms

Although urinary symptoms are rarely present on initial presentation, it has been described that one in 10 patients may have lower urinary tract symptoms at the time of diagnosis [5]. In general, urinary symptoms will be more prevalent after 6–8 years of diagnosis [6].

Patients with MS may have symptoms during storage, voiding or both phases of the micturition cycle. Storage symptoms such as urgency, frequency and urge incontinence are the most common lower urinary tract symptoms (LUTS) reported by MS patients [7]. Urinary frequency is one of the most common urinary symptoms, as it has been described that approximately 80–93% of MS patients report some degree of urinary frequency [3, 8]. This is of significant importance, as there has been a correlation described between storage symptoms with the expanded disability status scale (EDSS) and pyramidal tract involvement [6, 9]. Furthermore, voiding symptoms, such as hesitancy, incomplete emptying and urinary retention are present in 34–79% of this population [10, 11], .see Fig. 13.1.

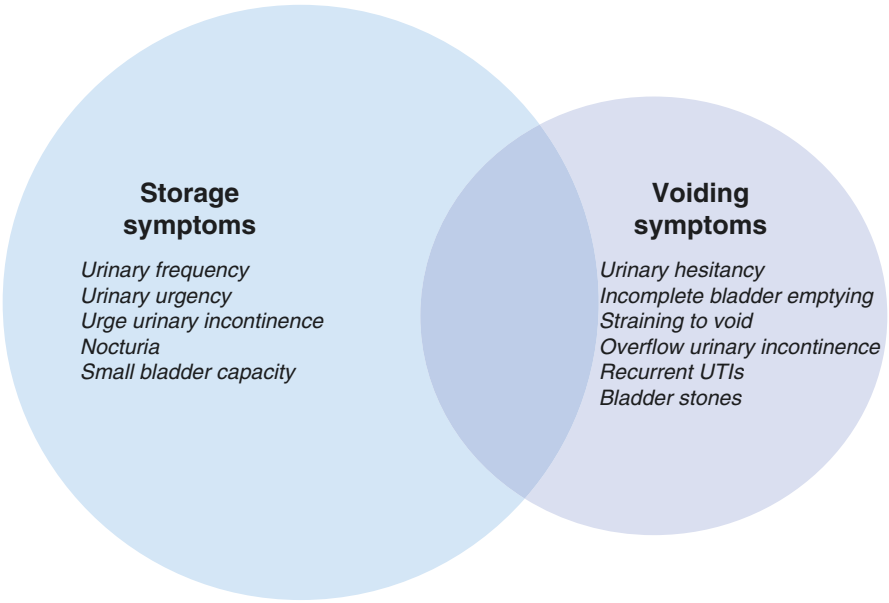

Fig. 13.1 Urologic manifestations of patients with MS

Table 13.1 Potential urologic signs/symptoms

Location	Symptom
Upper urinary tract	Hydronephrosis, pyelonephritis, kidney stones, vesicoureteral reflux, renal failure
Lower urinary tract	Storage symptoms: Urinary frequency, urgency, urge urinary incontinence, nocturia Voiding symptoms: Urinary frequency, hesitancy, incomplete emptying and urinary retention

Other urological complications include pyelonephritis, bladder stones, kidney stones, vesicoureteral reflux and renal failure have been described as probably the most common cause of hospitalization in MS patients [3] (Table 13.1).

Urologic Evaluation

Tailored evaluation for the MS patient is required, taking into account disease stage and length, neurologic and urologic symptoms, comorbidities and medications [6]. History taking with unique emphasis on LUTS and their impact on quality of life using quality-of-life (QoL) questionnaires are the starting point. Next, physical examination focusing on motor and sensory dysfunction, sacral and pelvic dermatomes is of pertinent importance [6]. Pontine signs such as dizziness, visual

disturbances may predict the future presence of neurogenic detrusor overactivity (NDO), while cerebellar signs may indicate detrusor sphincter dyssynergia (DSD) [6, 12]. Fowler and colleagues studied the relationship between urinary symptoms and neurological features of bladder dysfunction, and concluded that the severity of urinary symptoms was related to the degree of pyramidal impairment in the lower limbs, with both findings related to spinal involvement [13].

Aharony et al. recommend in addition to physical examination to obtain a complete history that includes quality of life assessment, urinalysis, urine culture and post void residual. It is important to note that unlike spinal cord injury patients, MS patients rarely suffer from upper tract deterioration, thus persistent and invasive evaluation of the upper tract is not required [6]. However, European Urology Guidelines for neurogenic bladder recommend ultrasound of the upper urinary tract every 6 months [14].

In 2013, Amarenco et al developed a decision-making algorithm for urological evaluation in MS patients. This tool is designated for neurologists and general practitioners, and allows proper identification of red flags that indicate referral to neurourology, such as recurrent urinary tract infections (UTIs), UTIs with fever, hydronephrosis, bladder diverticulum, reflux on ultrasound that indicate high intravesical pressure, compliance abnormalities and DSD [15].

Urodynamic Evaluation in MS

The use of Urodynamic Studies (UDS) on this patient population is under debate. Currently, the UK National Institute for Health and care Excellence (NICE) guidelines recommend not to offer UDS routinely for patients at low risk of upper tract complications. Additionally, The Neuro Urological Expert Study Group (GENULF) recommends UDS as part of the initial work up for MS [3]. Other studies have recommended UDS evaluation for MS patients with high post void residual (PVR) of urine (>150cc), failure of two attempts of medical therapy, obstructive symptoms (straining, hesitancy) and patients with hydronephrosis, increasing disability (EDSS >6.5) [7, 16]. In contrast to spinal cord injury patients, MS patients rarely have upper tract deterioration 28443147 [6].

Most common finding on UDS is neurogenic detrusor overactivity (NDO), found in 70% of this population. This could be explained by the loss of inhibitory cortical influence on brain stem activity [7]. Spinal cord plaques, present in 80% of patients, and intracranial lesions affecting cortical regions associated with the urinary system, such as the medial prefrontal cortex, insula, and pons, have been described as the etiology for NDO [6, 7]. When compared to patients with detrusor overactivity with no underlying neurological condition, patients with MS demonstrate a higher maximal detrusor contraction and a higher threshold volume for detrusor overactivity (DO) due to higher baseline PVR compared to normal population [17]. Table 13.2 summarizes UDS findings.

Table 13.2 Urodynamic findings in multiple sclerosis

UDS finding
Neurogenic detrusor overactivity (most common)
Higher maximal detrusor contraction compared to idiopathic detrusor overactivity
Higher threshold volume for DO. (Likely due to higher PVR)
Detrusor sphincter dyssynergia (DSD)
Detrusor underactivity
Decreased compliance (least common)

On the other hand, the prevalence of detrusor sphincter dyssynergia (DSD) increases with time after diagnosis from 13% at 4 years of diagnosis to 48% after 9 years of diagnosis [3]. It is important to note that some of these findings may coexist in this population, with 43% to 80% of patients presenting with DSD and either detrusor overactivity or underactivity [3]. Sacral involvement in MS is not as common as spinal and intracranial plaques (18–60% of patients), can lead to detrusor hypocontractility [6].

Management

Urologic care for MS patients starts with appropriate understanding of the correlation between neurological exam and urological manifestations of the disease. The progressive nature of MS is linked to worsening voiding dysfunction and imposes a challenge in management due to disability. Therefore, multidisciplinary approach including neurology, urology and rehabilitation medicine working together toward achieving continence, protecting the upper tract and improving quality of life [3]. Initial evaluation requires bladder diary, uroflowmetry with post void residual, and in some cases cystoscopy and urodynamic studies [3].

Non pharmacological lower urinary tract dysfunction management, such as ensuring adequate hydration, reduced caffeine intake are also applicable to this population. Pelvic floor physiotherapy has shown to improve functional bladder capacity, decrease urinary frequency and decrease the number of urinary incontinence episodes. Interestingly, when compared with neuromodulation and biofeedback, pelvic floor therapy can reduce the severity of lower urinary tract symptoms in this population [3, 18].

Antimuscarinics along with intermittent self-catheterization (ISC) can decrease storage symptoms, improving quality of life. It is important to consider the risk of cognitive impairment associated with antimuscarinics and their role in MS patients. The inability to cross the blood–brain barrier of Trospium provides a suitable option for patients with advanced stage of the disease [3]. Moreover, oral or intranasal Desmopressin has shown to decrease the episodes of nocturia in MS patients, thus improving sleep patterns and urinary symptoms. Studies have recommended the use

desmopressin not more than daily, due to the risk of hyponatremia, and should be given with caution in patients older than 65 [3, 19].

Intravesical therapy with onabotulinum toxin A (BoNT-A) was FDA-approved for refractory neurogenic detrusor overactivity secondary to Multiple Sclerosis and Spinal Cord Injury. Currently, there is level I evidence supporting BoNT-A in MS, with significant improvement in symptom severity, quality of life and UDS parameters [20–22]. Eighty-eight percent of MS patients required ISC after intravesical BoNT-A [23]. Therefore, it is suggested that patients agree and are taught ISC. Interestingly, the need of ISC did not impact quality of life outcomes [3, 21, 23]. Conversely, there is limited evidence for the use of BoNT-A for DSD management in this population. A meta-analysis showed improvements of this therapy 30 days after treatment are related to increased voided volume and lower detrusor pressures, however they highlight the need of reinjection and suggest sphincterotomy as an effective alternative to decreased bladder pressure [24].

Percutaneous posterior tibial nerve stimulation (PTNS) has shown to be well tolerated by MS patients, with an improvement in voiding dysfunction and urodynamic parameters, such as increase of more than 30% on cystometric capacity and reflux volume [25]. Patients should receive 30 min sessions every week for 10 to 12 weeks. In patients who respond to neuromodulation, they can undergo maintenance therapy of PTNS every 2 weeks [3, 26]. With a high patient satisfaction of 70% and improvement in quality of life, PTNS is a safe alternative for patients with MS who are disabled and can be more susceptible to side effects of medical therapy, such as anticholinergics [3].

For patients with refractory lower urinary tract symptoms, sacral nerve stimulation provides a minimally invasive option. In patients with neurologic voiding dysfunction, this therapy has shown to improve continence and urodynamic parameters, such as cystometric capacity after 6 months of implantation [3]. Due to the progressive neurological involvement of MS, long-term benefits of sacral neuromodulation have been difficult to achieve. Thus, some authors have recommended the use of this technique in patients with relapse–remitting MS who have been stable (no relapses) for at least 2 years [3, 27].

Surgical management in multiple sclerosis patients is recommended for refractory symptoms, inability to perform ISC through urethra due to disability, severe urinary incontinence and urological complications such as fistulae, sepsis, or renal failure [3]. Augmentation cystoplasty provides an appropriate option for patients who failed conservative management, have stable hand function, and are willing to perform intermittent self-catheterization (ISC). This procedure has shown to decrease maximum detrusor pressure, improve bladder capacity and quality of life [28]. A cutaneous continent urinary diversion can be offered to patients unable to perform ISC per urethra [3]. When progression of the disease leads to quadriplegia, worsening cognitive impairment and limited dexterity, a non-continent urinary diversion can be offered with an ileal conduit [29]. Additionally, bed ridden or wheelchair bound patients with severe and refractory symptoms can be offered this approach [3].

Operative Risks When it comes to urological procedures for patients with neurogenic bladder secondary to MS, few issues need to be addressed and discussed in the perioperative planning. As in case of most neurogenic bladder patients, hand dexterity, visual capability, mobility, and stability of the disease itself need to be assessed during the decision making. Although most urinary diversion procedures have acceptable outcomes in MS patients, complex reconstructive cases may not be an ideal option for MS patients with secondary progressive disease who have had multiple recent relapses and are declining at a rapid pace [29]. Authors would suggest a discussion with the patient's neurologist in regards to the individual patient's disease prognosis when stability of the disease is not determined. Additionally, choice and location of continent urinary diversions may be affected by patient's visual disturbances, hand dexterity limitation, or significant lower extremity spasticity and needs to be explored in detail with the patient and his/her care giver.

Another specific consideration in MS patients is the lower extremity spasticity that can affect lithotomy positioning. This can further challenge in office procedures such as intradetrusor onabotulinumtoxinA (BoNT-A) injection where spasticity is exacerbated by bladder injections.

Conclusion

MS is a progressive neurological disease that has significant urinary symptoms. Careful evaluation and individualized management is recommended for all MS patients with neurogenic lower urinary tract symptoms. Management of MS patients' urinary symptoms includes careful selection of appropriate oral overactive bladder medication, intradetrusor injection of onabotulinum toxin A, catheterization, and rarely augmentation cystoplasty or urinary diversion.

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Chapter 14
Amyotrophic Lateral Sclerosis and Motor Neuron Disorders

Giulia Lane and Paholo Barboglio Romo

Description of Disease

Amyotrophic lateral sclerosis (ALS) is a paralytic disease which affects both upper (motor cortex within the brain) and lower (brainstem and spinal cord) motor neurons [1, 2]. ALS is the most common diagnosis along a spectrum of motor neuron disorders which include primary lateral sclerosis (PLS, affecting upper motor neurons) and progressive muscular atrophy (PMA, impacting lower motor neurons) [3]. The prevalence of ALS is 3–5 per 100,000 people; it is more common among males and older individuals [1]. Epidemiological studies have found that those with history of military service, tobacco abuse, heavy metal, electromagnetic field exposure, and trauma are at risk for developing ALS [1].

Pathophysiology ALS is most often sporadic; however, there are a minority (10%) of cases that are familial [1]. At least 25 gene mutations have been associated with both familial and sporadic ALS. Notably, *Superoxide dismutase 1* (SOD1) was the first gene discovered and *chromosome 9 open reading frame 72* (C9ORF72) is the most commonly mutated gene in ALS. (1) Specific gene variations have been found to correlate with ALS phenotypes and can be predictive of disease progression [1]. Three common molecular pathways leading to neuronal death have been discovered: (1) disruption of protein homeostasis leading to intracellular protein aggregates, (2) abnormalities in RNA processing causing deposits and aggregates, and (3) cytoskeletal abnormalities impairing axonal structures [1].

Pathologically, motor neuron death within the motor cortex and spinal cord is the key finding in ALS [1]. Consistent with the molecular pathways, histologic evidence of protein aggregates, called Bunina bodies, can be found in the brainstem and spinal

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cord motor nuclei [3]. However, clinically, the diagnosis of ALS is made by experienced neurologists based on defined criteria and is augmented by laboratory and neurophysiologic testing [4]. The rationale behind the commonly performed laboratory analyses (complete metabolic panel, creatinine kinase, vitamin B12 level, copper level, serum protein electrophoresis) and radiologic studies (MRI) is to exclude other causes of the patient's symptoms [3].

The average age of onset is 43–52 years for familial ALS and 58–63 for sporadic ALS [4]. At presentation, the symptoms of the ALS are heterogeneous since they are dependent on the neurons affected [1, 2]. However, symptoms of upper motor neuron involvement include spasticity and hyperreflexia while lower motor neuron disease results in weakness, atrophy, and fasciculations [3]. Cognitive dysfunction secondary to frontotemporal dementia is common, occurring in up to 50% [4].

Notably the bladder, bowel, and sphincter function are spared in classic ALS, and should lead to consideration of alternative etiology of symptoms [1, 3, 4]. Specifically, if patients present with urinary urgency and limb spasticity, primary lateral sclerosis should be considered first in their differential diagnosis.

Guidelines for the diagnosis of ALS include the 1994 El Escorial criteria, the 2000 revised El Escorial criteria, and the 2008 Awaji criteria for application of electrophysiology in diagnosis of ALS [3–5] (Table 14.1). Despite the improved sensitivity in diagnosis, the average time between symptom onset and diagnosis of ALS is between 10 and 18 months [4].

Timeline of Progression *ALS is progressive and terminal, with average death due to respiratory paralysis occurring in the vast majority (90%) of patients 3–5 years after diagnosis* [1, 4]. However, much like presentation, the course of progression is heterogeneous [2]. There is no cure for ALS and therefore the mainstay of treatment has been supportive management of symptoms. The ALS Functional Rating Scale-Revised (ALSFRS-R) is a standardized method to assess patient's functional status [6]. Currently, there are two FDA-approved pharmacotherapies, riluzole and edaravone, which have been found to decrease progression of symptoms by 2–3 months [1].

Operative Risk *Patients with ALS are at increased risk of cardiopulmonary complications and therefore cardiac and pulmonary function should be evaluated preoperatively* [7]. Due to autonomic dysfunction, patients with ALS have increased risk of cardiovascular complications. Furthermore, bulbar (pharyngeal) and respiratory muscle weakness leads to increased bronchial secretions and sialorrhea and also places patients at increased risk for aspiration and infection perioperatively [4, 7]. Currently, guidelines recommend that procedures requiring sedation should be limited after vital capacity falls below 50% of predicted [4]. Furthermore, patients with ALS have an increased risk for deep venous thrombolysis (annual incidence of 2.7%) compared to the general population [4]. Some studies have raised the concern that surgery may accelerate the progression of ALS; however, the literature regarding this is scant [8]. Due to the high perioperative risk, it is important to discuss code status and end-of-life decisions, incorporating a palliative care team, prior to proceeding to the operating room [4].

Table 14.1 Revised El Escorial criteria

Presence of:
Signs of lower motor neuron degeneration by clinical, electrophysiologic, or neuropathologic evaluation
Signs of upper motor neuron degeneration by clinical examination
Progressive spread of symptoms of signs within a region to other regions, as determined by history or exam
Together with the absence of:
Electrophysiological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration
Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs
Principles of the Awaji Shima consensus:
1. Evidence of LMN loss (reduced inferential pattern on full contraction and increased firing rate)
2. Evidence of reinnervation (motor units of large amplitude and longer duration
3. Fibrillation and sharp waves or fasciculation potentials
Diagnostic categories
1. Clinically definite ALS is defined by clinical or electrophysiological evidence by the presence of LMN as well as UMN signs in the bulbar region and at least two spinal regions or the presence of LMN and UMN signs in three spinal regions
2. Clinically probable ALS is defined on clinical or electrophysiological evidence by LMN and UMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs
3. Clinically possible ALS is defined when clinical or electrophysiological signs of UMN and LMN dysfunction are found in only one region; or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs. Neuroimaging and clinical laboratory studies should have been performed and other diagnoses must have been excluded

Adapted from Brooks, 1994 and de Carvalho 2008

General Treatment Options While there is no cure for ALS, there are two FDA-approved medications available for its treatment. Riluzole has been approved since 1995 and while the exact mechanism of action is unknown, riluzole inhibits glutamate release and this, along with other mechanisms, has been found to inhibit excess neuronal firing [1, 9]. In two studies, riluzole was found to delay time to tracheostomy or death by 2–3 months; however, there was no difference in mortality between the control and treatment groups in both studies [9].

Edavarone is an intravenous therapy FDA approved (2017) for treatment of ALS based on one randomized study from Japan which found that decline from baseline ALS Functional Rating Scale-Revised (ALSFRS-R) score was less in the treatment group compared to the control group. However, the inclusion criteria in the study were restrictive and therefore the value of the medication among the general ALS population has been doubted [3, 10]. Edavarone's mechanism is unknown, but it is thought to act by decreasing oxidative stress [1].

Urologic Symptoms/Treatments

Expected Urologic Symptoms Traditionally, ALS has been known to spare the bladder and sphincter muscles from characteristic weakness [1]. Recent literature has cited the prevalence of lower urinary tract symptoms (LUTS) to be between 33 and 44% with 14–33% of patients reporting urgency urinary incontinence [11–13]. However, it is important to note that these studies include patients along the entire motor neuron disorder spectrum (including primary lateral sclerosis and progressive muscular atrophy) [11–14].

In 2011, a study of 54 patients with ALS found that there was a high correlation between post-void residual (PVR) and ALSFRS score ($R^2 = 0.95$, $p = 0.025$) and the Modified Ashworth Scale, a measure of spasticity on lower limbs ($R^2 = 0.165$, $p = 0.002$) [13].

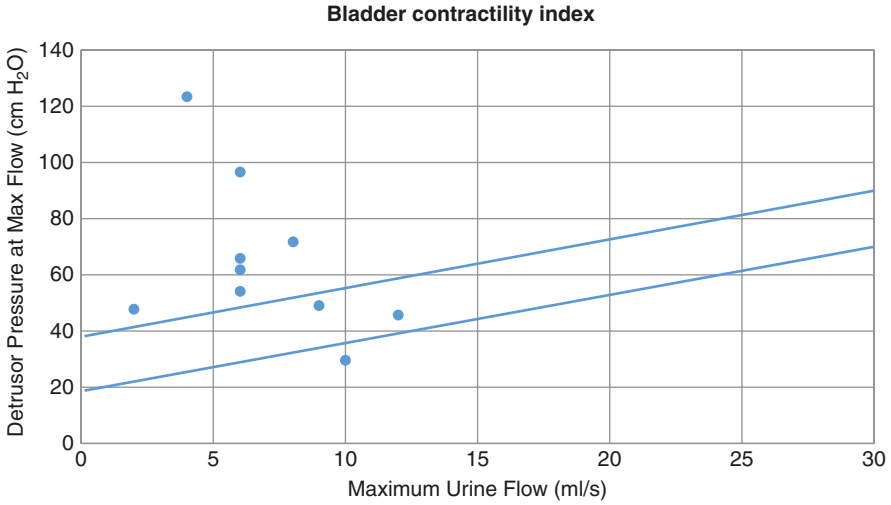
In 2017, Arlandis reported incidence of both subjective and objective data on LUTS and urodynamic findings among patients with ALS [11]. This survey found that although LUTS and UI were prevalent, the impact of urinary symptoms on quality of life (as measured with the QOL-IPSS) was mild to moderate (mean score 2.1 ±1.5) [11]. On urodynamic studies, 70% of patients had neurogenic detrusor overactivity and all but one (90%) had evidence of detrusor sphincter dyssynergia [11] (Table 14.2). Seven out of ten patients had bladder outlet obstruction as defined by the bladder contractility index, however only three of these patients had PVR greater than 50 mL [11] (Graph 14.1). The authors excluded benign prostatic hyperplasia (BPH) as cause of the bladder outlet obstruction by performing transrectal prostate ultrasound which showed a mean prostate size of 25 mL and PSA evaluation [11, 14].

Using the same data set, Vazquez-Costa found no relationship between bladder symptom scores (ICIQ-SF, OAB-V8, IPSS) and measures of clinical progression of ALS (phenotype, ALSFRS-R score, time since onset) on multivariable analysis [14]. He also found no relationship between impaired executive function/behavioral impairment and scores in ICIQ-SF, OAB-V8, and IPSS or rates of clinically significant LUTS [14]. Finally, the author evaluated the relationship between urinary symptoms and disease survival and found that survival was similar between patients

Table 14.2 Urodynamic findings

Study	*N*	Mean Age	Mean ALSFRS-R	Detrusor	Sphincter	MCC (avg)	*p*Det at Qmax (avg)	Qmax (avg)	PVR (avg)
Arlandis 2017	10	62	33	Overactive (50%)	Non-relaxing (90%)	355 mL	65 cm H_2O	7 ml/s	111 mL

pDet detrusor pressure, *MCC* maximum cystometric capacity, *Qmax* maximum flow, *PVR* post-void residual



Graph 14.1 Bladder Contractility Index created from data from Arlandis et al. (2017)

with and without clinically significant LUTS (70.6 vs 62.9 months, $p = 0.69$) and similar between patients with and without urodynamic findings of neurogenic bladder (70.6 months vs 28.2 months $p = 0.19$) [11].

Key Goals of Urologic Management There is no literature regarding the urologic management of patients with motor neuron disorders; however, the principles follow established guidelines in Neurourology [15, 16]. Diagnostic evaluation including a history and physical exam with attention to urine storage and emptying and bowel function can be augmented by a bladder diary and quality of life questionnaires [16]. Urinalysis, blood chemistry, renal and bladder ultrasound, uroflow, and PVR are recommended part of routine assessment of neurourology patients [15, 16]. Ultimately, the aims for urologist consist of protection of the upper urinary tract, maintaining lower urinary tract function and continence and improving patient quality of life [16]. *Patients with motor neuron disorders (ALS, PLS, PMA) have not been found to be at risk for upper tract deterioration, as is seen with other etiologies of neurogenic bladder*. However, there has been an association between elevated PVR and bothersome lower urinary tract symptoms [13]. Urodynamic studies have not been well described in this population and its clinical utility is unknown. However, one study evaluated 10 symptomatic patients with urodynamics and found neurogenic detrusor over activity and detrusor–sphincter–dyssynergia in the majority of patients (7/10 patients with ALS, PMA, and PLS) [17].

Urologic Treatment Options The standard of care for patients with ALS and motor neuron disorders consists of a multidisciplinary management of symptoms [3]. It is important for the Urologist to consider how their recommendation will impact the comprehensive treatment of patients with ALS.

Treatment of Storage Symptoms Pure storage symptoms are reported among 6–26% of patients with ALS with up to 33% of patients reporting urgency incontinence [11–13]. Behavioral therapy such as avoidance of bladder irritants and timed voiding are an important consideration of symptom management, especially if the patient has significant cognitive or motor weakness. Pharmacotherapy for storage symptoms (urgency, frequency) can be considered with caution and awareness of the patient's overall pharmacotherapeutic burden. Patients with ALS may already be receiving anticholinergics and tricyclic antidepressants for the treatment of sialorrhea (excess drooling) [3]. Similarly, minimally invasive therapies such as neuromodulation and chemodenervation may be considered, but may require coordination with the patient's treatment team as patients may be receiving botulinum toxin therapy for other symptoms of their disease or may have contraindications to sacral neuromodulation (such as need for future MRIs) [3].

Treatment of Voiding Symptoms Evaluation of PVR is recommended in symptomatic patients with ALS. In a study of 54 patients with ALS, elevated PVR was correlated with symptomatic LUTS (32 mL vs 129 mL in asymptomatic versus symptomatic group) [13]. ALS may be associated with spasticity of the pelvic floor muscle, leading to incomplete emptying and urinary retention [13]. However, these symptoms could also be explained by the high prevalence of DSD in patients with ALS [17].

First-line treatment of patients with voiding symptoms may include pelvic floor physical therapy as it theoretically may help pelvic floor spasticity and possible DSD. A review of the patient's medication list is warranted in those presenting with voiding symptoms (retention, hesitancy, weak stream) or elevated PVR, which may be an unintended consequence of anticholinergic therapy for sialorrhea or dextromethorphan/quinidine therapy for pseudobulbar affects. If urinary symptoms are felt to be secondary to adverse effects of medications, discussion with primary neurologist may be necessary to evaluate risk and benefits or propose alternatives.

If voiding symptoms are secondary to benign prostatic hyperplasia (BPH), the addition of alpha-blocker medication may be useful in patients with voiding symptoms. *However, due to high perioperative risk and prevalence of DSD, urodynamic studies should be strongly considered prior to surgical interventions for BPH*. When indicated, bladder outlet procedures (transurethral resection of prostate) are best approached with a multidisciplinary effort to ensure the patient is surgically optimized. Patients who are not surgical candidates may benefit from minimally invasive, office-based, options to treat benign prostatic hyperplasia (Rezum, UroLift) although these have not been studied within this population.

Catheterization may be necessary in patients with significant urinary retention, especially nearing end of life. It is important to recognize that patients with ALS may have significant barriers to intermittent catheterization including cognitive impairments, motor weakness, and communication difficulty. In these patients, indwelling urethral or suprapubic catheters may be considered after a discussion of their increased risk of infection and urolithiasis [18].

Conclusion

Traditionally, ALS is thought to spare the bladder and sphincters and therefore urologic findings in these patients should lead to evaluation of an alternative neurologic diagnosis. However, recent studies show that lower urinary tract symptoms are common and are correlated to incomplete emptying or urinary retention [11, 13, 17]. Urodynamic studies have shown that neurogenic detrusor overactivity and DSD are common in this population [17]. Urologic evaluation and management of patients with ALS should be individually tailored and may benefit from a multidisciplinary approach. Specific attention is recommended prior to prescribing anticholinergic medication and administering botulinum toxin therapy (since patients may already be taking these for other symptoms of ALS). Furthermore, a multi-disciplinary preoperative evaluation is recommended prior to indicated surgical interventions due to high perioperative morbidity.

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Chapter 15
Urologic Complications of Friedreich's Ataxia

Elizabeth V. Dray

Introduction

Friedrich's ataxia (FRDA) is the most common hereditary ataxia, affecting between 1/20,000 and 1/250,000 individuals of European descent [1]. First described by Nicholaus Friedreich in 1863, FRDA is generally diagnosed in adolescence with a constellation of gait disturbance, dysarthria, pathognomic musculoskeletal findings, and cardiac abnormalities [2]. While urologic manifestations of FRDA are not well described, the existing literature indicates that they are common and bothersome to patients with this disease.

Pathophysiology

FRDA is an autosomal recessive disorder typically caused by a homozygous GAA triplet repeat-expansion in the intron of the FXN gene on chromosome 9 [3, 4]. In a minority of cases (~2%), a heterozygous expansion and point mutation are present [5]. This intron expansion is thought to silence the FXN gene via epigenetic aberrations [6]. FXN encodes frataxin, a protein which is widely expressed in the human body, with high levels found in the heart, spinal cord, liver, pancreas, and skeletal muscles. It is involved in the activity of iron–sulfur cluster-containing components in the mitochondrial respiratory chain. Decreased frataxin levels lead to increased mitochondrial iron deposits, oxidative stress, lipid peroxidation, and cell death [7].

The widespread expression of this gene is likely responsible for the diverse constellation of symptoms found in individuals affected by FRDA. Neurologic symptoms stem from a combination of peripheral sensory neuropathy, spinocerebellar

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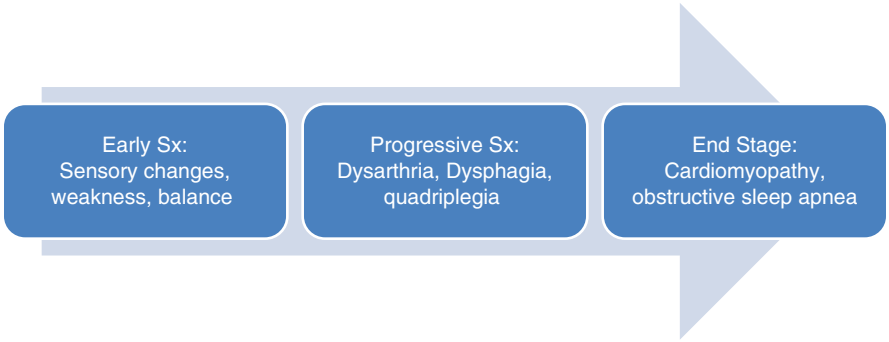

Fig. 15.1 Disease course

tract degeneration, cerebellar and supratentorial changes. Gait ataxia is an early symptom, which typically develops between 10 and 16 years of age and progresses to wheelchair reliance by the third decade. Dysarthria and dysphagia typically advance with disease duration. Optic neuropathy, nystagmus, and, in some cases, blindness may also occur, as well as sensorineural hearing loss. Musculoskeletal abnormalities include scoliosis, which often requires surgical correction, and foot deformities (pes cavus, talipes equinovarus). Pancreatic involvement leads to increased prevalence of diabetes mellitus compared to age-matched controls [8].

Cardiomyopathy is another hallmark of FRDA, and is responsible for >50% of disease-related deaths. Repolarization abnormalities (T wave inversion, ST depression or elevation) are frequently seen on electrocardiogram (ECG) even in early stages of the disease process. Echocardiogram may show concentric cardiac wall-thickening. Approximately 20% of individuals will have a reduced ejection fraction [9]. As the disease progresses, atrial fibrillation and heart failure may develop, ultimately leading to patient death.

Classically, FRDA presents between 10 and 16 years of age, with 36.5 being the average age of death [10]. Mortality is typically secondary to congestive heart failure and arrhythmias. Late onset and very late onset FRDA present at >25 years of age and > 40 years of age, respectively [11]. These atypical presentations are usually associated with a milder phenotype, less pronounced non-neurologic symptoms, and variable progression. Earlier onset and rapidity of neurologic decline is correlated with increased size of the GAA triplet expansion [4, 12]. Figure 15.1 summarizes the disease course.

Imaging

While there are no imaging criteria for the diagnosis of FRDA, MRI studies have shown cerebellar atrophy, as well as gray matter loss in the precentral gyri, corpus callosum, and pyramidal tracts. Diameter of the spinal cord is also reduced, especially at the cervical and thoracic level [13].

Diagnosis

Prior to the discovery of the genetic basis for FRDA in 1996, diagnosis of this disease was imprecise. Diagnosis is now based on identification of the characteristic homozygous GAA expansion on polymerase chain reaction. Clinical suspicion of the disorder is raised in children and adolescents with progressive ataxia and dysarthria. Exam findings include loss of lower limb deep tendon reflexes, distal vibratory sensation, and proprioception as evidenced by nose-finger ataxia and impaired heel-shin slide [11]. Babinski's sign is typically positive. Non-neurologic findings such as scoliosis, foot abnormalities, and ECG changes may also aid in diagnosis.

Treatment

Progression of FRDA is inevitable, and disease-modifying therapies have not yet been developed. Treatment is multidisciplinary and largely supportive, and should begin with referral to an ataxia specialist and genetic counseling. Recently published clinical management guidelines have supported the following baseline evaluations: neurological exam, ECG and echocardiogram, communication and swallow evaluation by speech therapy, physical therapy assessment for muscle strength and stability, auditory evaluation, vision screening, blood glucose testing, and Epworth sleepiness scale for identification of obstructive sleep apnea (OSA) [14]. Blood glucose testing, OSA evaluation, and auditory testing should be repeated annually. Patients should be referred to cardiology for palpitations or abnormal cardiac testing results. If blood glucose and glucose tolerance tests are abnormal, first-line intervention is diet and exercise. Initiation of an insulin regimen is necessary if behavioral modifications are not effective. Intensive inpatient rehabilitation programs may prolong mobility and aerobic exercise regimens may improve fatigue. Orthopedic surgery is indicated for scoliosis with >40% curvature. Prior to any surgical intervention, intensive cardiac clearance should be undertaken. Finally, it is advisable to work closely with palliative care as the disease progresses. Figure 15.2 summarizes the overall disease treatment goals.

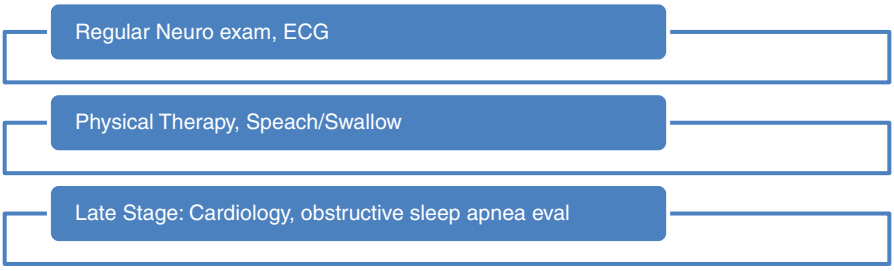

Fig. 15.2 Treatment goals

Urologic Manifestations of Friedreich's Ataxia

Urologic literature on FRDA is limited; however, urologic symptoms appear to be common and bothersome. An early study by Vezina et al. in a small cohort of FRDA patients showed that 53% of individuals reported urinary urgency and urge urinary incontinence [15]. On UDS, 41% of these patients had detrusor overactivity (DO) and 37.5% showed detrusor sphincter dyssynergia (DSD). In a study of mixed hereditary ataxias, Diez Rodríguez found that 85.5% of patients suffered from urinary urgency [16]. In this cohort, common UDS findings were detrusor overactivity (61.7%), DSD (37.5%), and impaired contractility (23.5%), with a high correlation between UDS findings and clinically reported symptoms. Normal UDS results were documented in 15% of patients. The impact of these early reports is somewhat lessened by the inaccuracy of FRDA diagnoses prior to genetic testing.

More recently, Musegante administered a series of validated questionnaires evaluating urinary symptoms to 258 patients with genetically confirmed FRDA [17]. Eighty-two percent of patients who responded to the questionnaires reported lower urinary tract symptoms (LUTS) and 22% of patients reported that these symptoms impacted their quality of life. The most common complaint was urinary frequency (63%), followed by nocturia in 46% of patients and urinary incontinence in 36%. Eighteen percent of respondents reported difficulty voiding. Subsequently, 22 of these patients agreed to undergo UDS (average age 32 years). Urinary urgency (75%) and urge incontinence (61%) were disproportionately present in this group when compared to the total cohort. Four patients had normal UDS results, 8 (28.5%) had DSD, 5 (17.9%) were found to have DO, and 9 patients (32.6%) had decreased detrusor contractility. Post-void residual (PVR) > 100 cc was common (39%). No patients were found to have impaired compliance. Interestingly, no association was found between reported urinary urgency and DO on UDS. While 4 of these patients had mild-to-moderate hydronephrosis on renal ultrasound, all serum creatinine values were normal.

Pelvic symptoms are not limited to urinary complaints. A questionnaire-based study by Lad et al. of genetically confirmed FRDA patients showed that urinary, bowel, and sexual symptoms frequently coexist in the population [18]. Of the 59 patients in this study (average age 35 years), 80% reported LUTs, 64% reported bowel complaints, and 83% ascribed to sexual symptoms. Frequency (75%) and urgency (59%) were the most common urinary complaints. Constipation was reported in 86% of individuals with bowel complaints. Seventy-three percent of patients with urinary complaints also had bowel dysfunction, and all patients with sexual dysfunction also had LUTs. Increased severity of LUTS was noted in patients with late-onset FRDA and those with longer duration of disease. Of note, despite the prevalence of urinary symptoms in this study, only 24% of patients had prior treatment for urinary complaints. Table 15.1 summarizes common urinary symptoms and urodynamic findings.

Table 15.1 Urologic symptoms/findings

Common symptoms
Urinary urgency/frequency
Nocturia
Urinary incontinence
Constipation
Urodynamics:
PVR > 100
DO
DSD
Bladder compliance normal

In summary, most FRDA patients experience LUTS, with urinary urgency and frequency being the most common complaints, and these symptoms appear to be undertreated. UDS abnormalities are varied, and may include DO, DSD, and decreased detrusor contractility. Bowel and sexual symptoms are common in the setting of urinary complaints and bothersome considering the young age of the patient population.

Urologic Treatment in Friedreich's Ataxia

Consensus guidelines for care of patients with FRDA recommend PVR assessment and urinalysis in all patients with urologic symptoms [14]. Initiation of clean intermittent catheterization (CIC) is recommended with PVR > 100 cc; however, extrapolating from data for neurologic and non-neurologic incomplete bladder emptying, this may be overly conservative [19, 20]. Based on the high prevalence of DSD on UDS and poor correlation between urologic symptoms and UDS findings in the existing literature, a low threshold for performing UDS in this patient population is advisable [15–17]. It is reasonable to consider a renal ultrasound in the setting of decreased compliance or DSD; however, there is no data regarding upper tract deterioration in this disease. As with other neurogenic bladder conditions, repeat UDS should be performed in the setting of changing symptoms or worrisome baseline UDS findings.

No trials regarding treatment of urologic symptoms in FRDA exist, and therefore no evidence-based recommendations on pharmacotherapy can be made. Extrapolating from the neurogenic bladder population, a urinary antispasmodic is the appropriate first-line therapy for storage symptoms, followed by Intravesical Botox® if refractory. In patients with incomplete bladder emptying who cannot perform CIC due to functional limitations, suprapubic tube placement should be considered. Patients with bowel symptoms should be encouraged to make dietary modifications and referred to gastroenterology as constipation may impact urinary complaints. Patients should also be evaluated for sexual dysfunction. While

Table 15.2 Key urologic interventions

CIC for urinary retention
Anticholinergics for OAB
Onabotulinum for OAB
Surgical Risk: High due to respiratory weakness, potential cardiac pathology

phosphodiesterase inhibitors may be considered for erectile dysfunction, cardiology should be consulted prior to initiating therapy to avoid cardiac complications. Finally, prior to any urologic surgery, thorough cardiac clearance is obligatory. Table 15.2 summarizes the urologic treatment goals.

Conclusion

FRDA is an early onset, progressive neurologic condition with potentially significant bothersome urinary symptoms. Urologic care is mostly supportive and focused on reducing the quality of life impact from urinary incontinence and/or retention. Since FRDA patients carry significant surgical risk due to underlying respiratory weakness and cardiac pathology, any operative procedure needs considerable preoperative evaluation and clear treatment goals need to be discussed.

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Chapter 16
The Urologic Impact of Guillain–Barré Syndrome

Elizabeth V. Dray

Introduction

Guillain–Barré Syndrome (GBS), first described in 1916, is an acute flaccid paralysis [1]. It is the most common acute paralytic syndrome in the world, with an incidence of 1.1 cases/100,00 person-years and an estimated lifetime risk of around 1/1000 [2]. The incidence of GBS increases approximately 20% per decade of life over the age of ten. Men comprise a disproportionate number of those affected (OR 1.78, CI 1.26–2.33) [3]. For many years, the urologic impact of this disease was thought to be negligible. In fact, bladder and bowel involvement was believed to argue against this diagnosis. A growing body of evidence now supports the presence of significant urologic dysfunction in individuals with GBS.

Pathophysiology

GBS is a polyneuropathy affecting peripheral nerves and their spinal nerve roots that typically occurs within 4 weeks of an inciting illness. Two-thirds of individuals report prior respiratory or gastrointestinal symptoms [4]. *Campylobacter jejuni* is the most commonly identified preceding infection, and is identified in 25–50% of adults with the disease. Other commonly diagnosed pathogens include cytomegalovirus, Epstein-Barr virus, varicella zoster, Influenza A, *Mycoplasma pneumoniae*, and *Haemophilus influenzae*. Emerging data has also established an association with arboviruses, including the Zika virus [5]. The association between GBS and vaccinations is overstated, and appears to have been largely confined to the H1N1 vaccination administered in 1976 [6]. It is believed that molecular mimicry between

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carbohydrate antigens of the pathogenic organism and neuronal self-antigens is responsible for the development of the disorder [7]. The vast majority of patients exposed to these microbes will not develop GBS; however, host factors determining a predisposition to autoimmunity have not been fully characterized [8].

GBS has been classified into multiple subcategories, of which Acute Inflammatory Demyelinating Polyneuropathy (AIDP) and Acute Motor Axonal Neuropathy (AMAN) are the most common. Geographic variations between these subcategories exist, with AIDP being the dominant form of GBS in Europe and AMAN in Asia. AMAN is driven by direct axonal injury, and is thought to be secondary to humoral-mediated attacks on the nerve axolemma. Supporting this model, elevations in complement fixing IgG1 and IgG3 antibodies directed against axonal gangliosides (anti-GM1 and anti-GD1a ab) have been found in patients with AMAN [9]. The etiology of the AIDP is less well characterized. Inflammatory infiltrates of T cells and macrophages involving the peripheral nerves and spinal roots have been identified and are thought to incite demyelination. Early complement activation appears to also be involved in attacks on Schwann cells [10]. Demyelination may recover or, if severe, can lead to axonal death and irreversible nerve injury.

GBS is typically heralded by parasthesia, pain in the back or limbs, and progressive bilateral weakness of the extremities, which is often ascending [3]. Presence of sensory disturbances increases the likelihood of this diagnosis. Paralysis is rapidly progressing and neurologic decline continues for 12 hours to 4 weeks after symptom onset [11]. Ultimately, 20–30% of patients will require mechanical ventilation and the majority will be unable to walk unaided at symptom nadir [7]. Other symptoms include autonomic dysfunction, which may provoke life-threatening arrhythmias, ocular nerve involvement, and ataxia (Miller Fischer Syndrome) [12]. Mortality in the acute setting is 3–7%, and is typically secondary to pulmonary and autonomic complications [13]. After symptoms plateau, patients slowly improve, with the majority of neurologic gains made by 1 year. Significant residual defects remain in up to 20% of affected individuals. Typically, the disease course is monophasic; however, recurrence has been reported in 7% of patients [14]. Figure 16.1. summarizes disease progression.

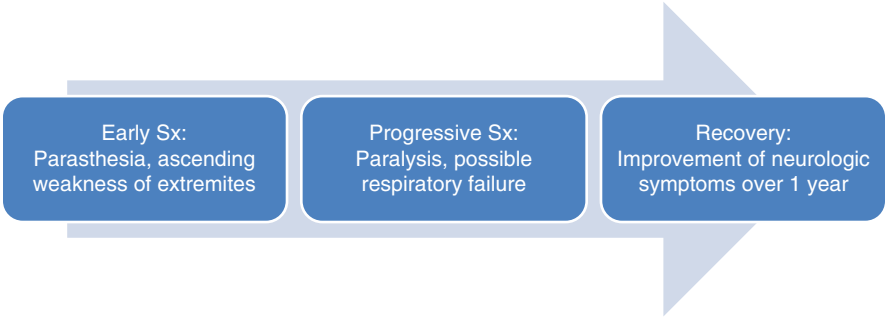

Fig. 16.1 Disease progression

Imaging

Imaging is not a standard diagnostic modality for GBS. However, brain and spinal cord imaging may rule out other neurologic disorders which may be confused with GBS, such as brainstem stroke or spinal cord compression.

Diagnosis

Diagnosis of GBS is predominantly based on clinical exam findings and patient history. Exam reveals the pathognomic symmetric flaccid paralysis. Deep tendon reflexes are diminished or absent, in keeping with a peripheral neuropathy. Babinski's sign is negative, decreasing the likelihood of a CNS lesion. Analysis of cerebrospinal fluid (CSF) should be performed to rule out infectious diseases or malignancy which may mimic GBS symptoms. In patients with GBS, CSF typically shows a diagnostic albuminocytologic dissociation, meaning that CSF protein levels are elevated in the setting of a normal cell count. It should be noted that this dissociation is not present in 50% of patients early in the disease course and 15% of patients with GBS have a mild increase in CSF cell count [15, 16]. Various criteria have been proposed using clinical and CSF findings to aid in the diagnosis of GBS, most recently being the Brighton criteria, which has been validated in both the adult and pediatric populations [15, 17].

Nerve conduction studies (NCS) can be helpful in the diagnosis of GBS but are not obligatory [7]. They are, however, necessary for classification of GBS into axonal or demyelinating variants although distinction between these entities is not always possible. They should be performed at 2 weeks post-onset for maximum diagnostic yield.

Treatment

After the diagnosis of GBS has been established, all patients should be hospitalized until neurologic progression has stabilized [18]. During progression, pulmonary and cardiac status should be evaluated every 2–4 hours; therefore, admission to the intensive care unit is ideal. Prompt supportive care is imperative. If respiratory distress, hypercarbia, hypoxemia, or decreased vital capacity is present, mechanical ventilation may be indicated. Bradycardia and hypotension are common: in severe cases, a temporary cardiac pacemaker is necessary. A swallowing assessment to evaluate risk of aspiration followed by nasogastric tube placement if indicated should be performed. If a patient is not ambulatory, deep venous thrombosis prophylaxis should be initiated. Pain is present in two-thirds of patients during the acute stage of the disease and should be addressed [19]. During the plateau and recovery stage, physical and occupational therapy can assist in rehabilitation and treatment of fatigue.

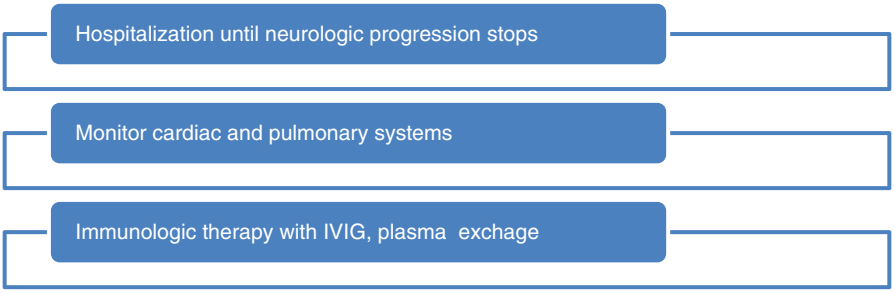

Fig. 16.2 Treatment goals

Immunologic therapy is the mainstay of modern GBS treatment. Both intravenous immunoglobulin (IVIG) and plasma exchange have been proven to be superior to supportive care alone in reduction of nerve damage and time to clinical improvement [20, 21]. Treatment should be initiated as soon as possible after onset of symptoms. Little data is available regarding retreatment of individuals with refractory or prolonged disease courses and no benefit has been shown with addition of steroids to immunologic therapy [3, 7]. Figure 16.2. summarizes treatment goals.

Urologic Manifestations of Guillain–Barré Syndrome

While urologic dysfunction has traditionally been thought to be uncommon in GBS, or even argue against the diagnosis of GBS, that is not the case. In fact, in the first description of GBS by Georges Gauillon, urologic dysfunction was noted in 25% of patients [1]. While many case reports and small series have been published, only four studies with medium-sized cohorts evaluating urologic symptoms exist in the contemporary literature. Sakakibara et al. published a retrospective study of 28 patients with acute GBS (average age 37, 68% male) [22]. Seven of these patients reported voiding complaints (25%), most commonly difficulty voiding (6). Urinary retention was noted in three, urinary urgency in two, and urge incontinence in two. In all patients, urinary symptoms occurred after onset of muscle weakness. Urologic symptoms were associated with more severe muscle weakness. All patients had resolution of urologic symptoms and urinary retention over the course of their recovery. Urodynamic studies (UDS) were performed in only four symptomatic patients, and showed detrusor areflexia in one patient and detrusor overactivity (DO) in two. Sakakibara published a second, prospective, study with a non-overlapping cohort of patients in 2009 ($N = 65$, average age 42 years, 63% male) [23]. Voiding symptoms were noted in 27.7% of these patients. The majority of

patients (24.6%) reported difficulty voiding, 9.2% had frank urinary retention, and 7.7% reported urinary urgency. No patients reported urinary incontinence in this cohort. Again, urologic symptoms were associated with increased muscle weakness. A significant association was also noted between urinary symptoms and constipation. All but one patient with urinary retention resolved in the acute stage of the disease, with one patient requiring clean intermittent catheterization (CIC) for approximately 10 months. UDS were performed on nine symptomatic patients in this cohort. Eight of these patients (89%) were found to have DO, seven patients had underactive or acontractile detrusor (78%), and one patient showed tonic activation of the external sphincter. No follow-up UDS were performed to evaluate resolution of abnormalities.

While these studies suggest urologic symptoms consistently occur in approximately one-quarter of patients with GBS, their selective use of UDS prevents conclusions regarding the urodynamic characteristics of this disease. A prospective trial by Naphade et al. of 38 patients showed a disparity between urologic symptoms and UDS abnormalities in GBS patients [24]. In this cohort (average age 28 years, 76% male), UDS abnormalities were identified in 60.53% of patients in the acute setting, while subjective urinary symptoms were only reported in 26.3%. All patients who complained of urinary symptoms identified difficulty voiding, five had urinary retention requiring catheterization, and two had urgency. Again, no patients had incontinence. Patients with the axonal form of GBS were more likely to report urinary symptoms, as were those with constipation. In this study, no relationship was found between reported urologic symptoms and maximum degree of disability. Again, all symptoms resolved during recovery (2 months post-onset). UDS were performed on all 38 patients. Twenty-three patients had abnormal studies. An acontractile or underactive detrusor was found in 20 patients (although incomplete bladder emptying was only noted in six), six patients were reported to have detrusor-sphincter dyssynergia, and three had DO. In contrast to reported urologic symptoms, UDS abnormalities were associated with worsening muscle weakness.

While these data suggest that urologic symptoms resolve in most or all patients with GBS, a substantial number of individuals have residual urologic complaints in longitudinal studies. In one questionnaire-based study, 17.1% of patients reported urinary problems at a median of 6 years post-onset (range 1–13.8 years) [25]. Another study primarily evaluating long-term bladder outcomes in the GBS population reported a higher prevalence of urinary symptoms [26]. In their cohort of 66 patients (average age 55.6 years, median time from onset 6.1 years, 63.6% male), 59.1% of patients reported nocturia, 39.4% urinary urgency, and 33.4% frequency. These symptoms had a significant impact on patient quality of life: 15% percent of patients stated that bladder problems interfered substantially with their lives and 32.7% had mixed or dissatisfied urinary quality of life on the American Urological Association symptom index. Table 16.1 summarizes common urologic symptoms.

Table 16.1 Common urologic symptoms

Affects 25% patients acutely
Associated with more muscle weakness
Short term: difficulty voiding, retention
Long term: nocturia, urgency

Table 16.2 Key urologic interventions

Indwelling catheter during acute phase if respiratory failure
Intermittent catheterization for retention if preserved hand function
Voiding trial after neurologic recovery
Anticholinergics for persistent OAB after recovery

In summary, urologic symptoms occur in approximately one-quarter of patients with GBS. As expected from a peripheral nerve lesion, the majority of these patients develop decreased or acontractile detrusor activity with urinary difficulty or urinary retention; however, detrusor overactivity, urgency, and frequency can also occur. Beyond the acute and recovery phases of this disease, a significant percentage of patients will have ongoing, bothersome urinary complaints, although further studies regarding the characteristics of these persistent symptoms are needed.

Urologic Treatment in Guillain–Barré Syndrome

In the acute setting, urologic care should be determined by degree of neurologic disability. If a patient requires mechanical ventilation, an indwelling urethral catheter should be placed. If a patient has intact upper extremity function in the setting of urinary retention, they should be started on a CIC regimen. The majority of patients with acute urinary retention will resume volitional voiding as their disease resolves and appropriate bladder management should continue until this occurs. No guidelines exist regarding UDS in this population, but if urinary retention or bothersome urinary symptoms persist after the patient's neurologic recovery has plateaued, UDS may help define residual urologic abnormalities. As persistent urologic symptoms are relatively uncommon, other etiologies of urologic complaints (e.g., benign prostate hyperplasia in men) should be ruled out. Once these have been addressed, treatment should be symptom-based, such as initiating antispasmodics for OAB symptoms or continuing CIC for symptomatic incomplete bladder emptying. Patients with persistent urinary retention may benefit from InterStim™ placement, although this has only been shown in a single case report [27]. As most patients recover urologic function, more aggressive surgical intervention is usually not warranted to address urologic symptoms. Table 16.2 summarizes key urologic interventions.

Conclusion

Guillain–Barré Syndrome is an acquired, acutely progressing neurologic condition that results in flaccid paralysis. The condition can be associated with significant respiratory and cardiovascular morbidity during the progressive phase. Acute urologic symptoms are present in approximately 25% of patients and usually are associated with urinary retention. Most patients recover both neurologic and urologic function but some patients continue to have persistent lower urinary tract symptoms that require treatment.

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Chapter 17
Spinal Muscular Atrophy/Lambert Eaton Myasthenic Syndrome

Gregory Vurture, Benoit Peyronnet, and Benjamin M. Brucker

Introduction

Spinal muscular atrophy and Lambert Eaton Myasthenic Syndrome are progressive neurologic conditions that cause proximal neurologic weakness. Urologic symptoms can be present in both and may impact quality of life. In this chapter, we review the disease pathophysiology, urologic manifestations, and the urologic care team's role in caring for these patients.

Disease Pathophysiology

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder which is characterized by progressive muscle weakness and atrophy [1]. SMA occurs due to a genetic mutation in the survival motor neuron 1 (SMN1) gene. SMN1 is normally needed for mRNA synthesis in motor neurons [2]. Specifically, the SMN protein is part of a complex of proteins that are responsible for the survival of anterior horn cells of the spinal cord and motor nuclei of the lower brainstem [3]. Thus, a mutation in SMN1 results in impaired survival of these neurons. The mutation most commonly noted of SMN1 is a biallelic deletion of exon 7 [4]. Those with a heterozygous deletion of SMN1 are asymptomatic and of a carrier state. The variation in severity of the disease is due to the presence of copies of survival motor neuron 2 (SMN2) gene. SMN2 is nearly identical to SMN1 and encodes the same protein. Mutations in SMN2 alone do

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not result in SMA, but mutations in both SMN1 and SMN2 result in embryonic death [5]. Those with more severe clinical manifestations of SMA are noted to have less copies of SMN2 [6].

Lambert Eaton Myasthenic Syndrome (LEMS), unlike SMA, is an acquired autoimmune disease characterized by antibodies directed against presynaptic voltage-gated calcium channels [7]. The antibodies in LEMS impede calcium flux that is needed for acetylcholine release. Ultimately, this results in a reduction of acetylcholine released from presynaptic neurons despite normal postsynaptic acetylcholine receptors, normal acetylcholine presynaptic concentration, and a normal quantity of acetylcholine vesicles [8]. As a result, these patients manifest with a distinct presentation of muscular weakness. The etiology of LEMS seems to be associated with small cell lung cancer and thus manifests as a paraneoplastic syndrome. The mechanism by which this occurs is believed to be due to the presence of voltage-gated calcium channels on the surface of small cell lung cancer cells and the development of autoimmunity to those voltage-gated calcium channels [9]. The cause of development of LEMS in those without small cell lung cancer is largely unknown, although there is literature to suggest an association of LEMS with other autoimmune disease [10, 11].

Organs Affected

SMA typically presents in infanthood and is the most common cause of monogenic infant mortality [12]. *Neurologic symptoms vary by disease stage but all will have diffuse symmetric proximal muscle weakness with more weakness in the lower extremities than the upper extremities* [13]. In addition, SMA patients will be areflexic in the extremities. Children will characteristically assume a frog-leg position characterized by abducted hips and flexed knees when sitting [14]. Otherwise typically, SMA patients will also present with fasciculations of the tongue, loss of respiratory strength (weak cry, weak cough, respiratory distress), and difficulty swallowing/feeding [15]. Juvenile or late-onset SMA is more commonly seen in adults and associated with milder neurologic symptom severity. Adults with SMA will more likely present with trouble climbing stairs or a history of falls as a result of proximal weakness of the lower more so than upper extremities [16]. As a result, an adult with SMA can be wheelchair-dependent.

LEMS patients also present with proximal muscle weakness of the lower extremities and areflexia, but are also characterized by autonomic dysfunction. Autonomic dysfunction in these patients manifests as dry mouth due to reduced salivation, erectile dysfunction in men, slow pupillary light response time, blurred vision, and constipation [17, 18]. In addition, these patients characteristically have improvement of their muscular weakness and return of deep tendon reflexes with exercise [19, 20].

Key Testing for Diagnosis

The diagnosis of SMA or LEMS should be suspected in any individual with unexplained proximal muscle weakness, hypotonia, areflexia, and tongue fasciculations. SMA is more common in the pediatric population but late-onset SMA can be present in adolescents and adults. LEMS is more associated with adults, commonly seen as a paraneoplastic syndrome of small cell lung cancer, and has autonomic dysfunction.

SMA can be confirmed with molecular genetic testing for the detection of homozygous exon 7 deletion in the SMN1 gene [13]. Presence of an SMN1 mutation suggests the presence of SMA. Muscle biopsy and electromyography are not needed due to the availability of genetic sequencing.

LEMS can be confirmed with repetitive nerve stimulation (RNS) and anti-P/Q--type voltage-gated calcium channel (VGCC) antibody testing. An RNS study will demonstrate an increase in compound muscle action potential (CMAP) after exercise that is reproducible [21]. The CMAP will be at least one hundred percent compared to the before exercise value. Anti-P/Q-type VGCC antibodies are present in approximately 90% of LEMS patients [22]. A high titer of P/Q-type VGCC antibodies highly suggests a diagnosis of LEMS [23].

Timeline of Progression

SMA can be categorized into 5 types (types 0–4) which correlate with the presence of SMN2 copies. The number of SMN2 copies seems to correlate directly with age of onset and inversely with prognosis [13, 24–28]. Figure 17.1 summarizes SMA subtypes.

Treatment

There is one treatment approved for SMA, nusinersen. This intra-thecal injection modulates the SMN2 gene. It is effective in approximately 40% of patients.

Type	Age of Onset	Life expectancy	Number of SMN2 Copies
0	Prenatal	< 6 months	1
1	< 6 months	< 2 years	2
2	6 to 18 months	10 to 40 years	3
3	> 18 months	Late adulthood	3–4
4	> 5 years	Normal lifespan	> 4

Fig. 17.1 SMA subtypes

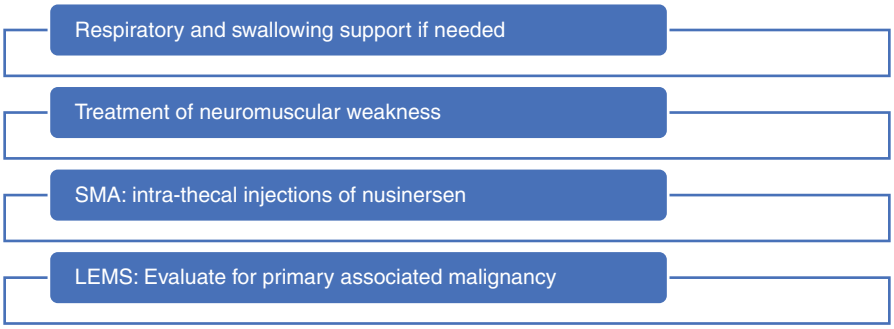


Fig. 17.2 Treatment goals

There is no cure for LEMS at this time. Treatment focuses on treating neuromuscular weakness associated with LEMS. This included potassium channel blockers, cholinesterase inhibitors, and possibly intravenous immunoglobulin therapy.

Figure 17.2. summarizes general treatment goals.

Operative Risk

SMA patients require a multidisciplinary approach for their surgical care. *These patients are most at risk for restrictive lung disease as a result of operation due to increased sensitivity to neuromuscular blocking drugs*. As a result, a pulmonologist should be part of the patient's treating team to provide a preoperative pulmonary assessment. All patients should also have aggressive chest physiotherapy postoperatively [29]. Studies have not shown any particular anesthetic technique that is contraindicated in this population [30, 31]. *LEMS patients similarly have increased sensitivity to neuromuscular blocking agents* and are at risk for prolonged proximal muscle weakness and respiratory failure [32]. Thus, risks and benefits of any surgical intervention should be weighed on an individual basis for SMA and LEMS patients.

Urologic Symptoms/Treatments

To date, only one study has examined enuresis and urinary incontinence in SMA [33]. Gontard A et al. focused on children and adolescents, the primary patient population of SMA, and gauged the prevalence of urinary symptoms in these patients. They found that approximately 30% of SMA patients had urinary symptoms relating to enuresis and urinary incontinence [33]. The authors discuss that urinary incontinence in these patients is underreported, overlooked, and not treated adequately. Patients with SMA can be expected to have detrusor overactivity and detrusor sphincter dyssynergia contributing to severe lower urinary tract symptoms [34].

Table 17.1 SMA/LEMS urologic symptoms

• Urinary urgency/frequency
• Nocturia
• Urinary retention (LEMS)
Urodynamics:
• DO
• DSD

As LEMS is characterized by autonomic dysfunction, there have been reports of urinary retention in this population [35, 36]. Autonomic dysfunction leads to detrusor underactivity which contributes to urinary retention in these patients. Table 17.1 summarizes urologic and urodynamic symptoms in SMA/LEMS

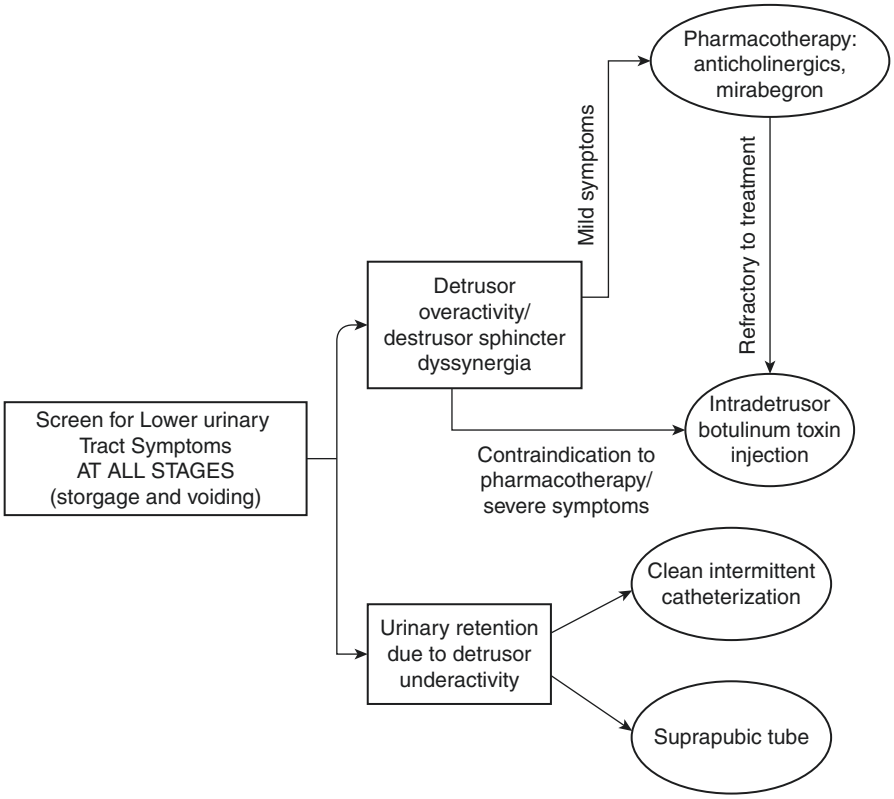
Key Goals of Urologic Management

Management of SMA and LEMS requires a multidisciplinary approach. Urinary incontinence should be screened for in this population. Parents of SMA patients can potentially believe that their child's enuresis is normal for age and not a sequela of the disease. In both neuromuscular disorders, urinary symptoms can occur at any stage of disease progression and thus should be screened for throughout the disease process.

Treatment Options

Urinary incontinence in SMA should be managed according to the severity of symptoms and with consideration for the quality of life of the patient. *Evidence suggests that neuromuscular blocking agents should be avoided in SMA and LEMS* [30–32]. Detrusor overactivity and detrusor dyssynergia that contribute to neurogenic bladder symptoms have traditionally been managed with anticholinergics such as oxybutynin; however, more recent data suggest a safer side-effect profile in patients with neurological disorders with the use of beta-3 adrenergic receptor agonists such as mirabegron [37–40]. In cases that are refractory to medication or in patients whose symptoms are severe, it may be possible to manage symptoms with intradetrusor botulinum toxin injection, although the effect in SMA or LEMS patients has not been fully studied on urologic symptoms. The use of botulinum toxin in patients with similar neurological disorders has proven to be quite effective for detrusor overactivity due to neurogenic causes [41–44], but data on SMA and LEMS is lacking. In both SMA and LEMS, patients with chronic urinary retention can be managed with clean intermittent catheterization or a suprapubic tube, using similar strategies as those used for managing non-neurogenic patients with chronic urinary retention [45]. However, evidence has shown efficacy of 3,4-diaminopyridine in the treatment of urinary retention in LEMS as a potential consideration before utilizing catheterization methods [36].

Treatment Map



Note: Efficacy of intradetrusor botulinum injections have not been established in LEMS or SMA. Case reports have been published documenting successful botulinum toxin treatments in SMA patients for dysphagia [46].

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Chapter 18
Urological Care for Patients with Diabetes-Induced Lower Urinary Tract Dysfunction

Kelly Bree and Yahir Santiago-Lastra

Introduction

As of 2015, an estimated 9.4% of the US population was affected by diabetes [1]. It is currently the seventh leading cause of death in the USA and primary cause of kidney failure, lower limb amputations, and adult-onset blindness. Type 2 diabetes (DM2) accounts for the majority of cases (90–95%), with type 1 diabetes (DM1) representing the remaining 5–10%.

Both DM1 and 2 are polygenic diseases, where many common variants contribute to overall disease risk. The hereditability, defined as sibling-relative risk, is higher for type 1 diabetes (RR 15) compared to type 2 diabetes (RR 3). Despite the genetic component of this disease, global rates of diabetes are outpacing genetic variation, suggesting environmental influences also are critical in development of both types of diabetes [2].

The underlying characteristic defining diabetes is hyperglycemia secondary to either β-cell immune-mediated destruction (DM1) or insulin secretory defects (DM2). Hyperglycemia leads to tissue damage in particular subsets of cells (e.g., capillary endothelial cells of the retina, the mesangial cells of the renal glomerulus, and neurons of the peripheral nerves), which are unable to adequately downregulate their intracellular glucose transport in the setting of hyperglycemia [3].

Hyperglycemia, as well ischemic factors and inflammation, contributes to the progressive loss of nerve fibers affecting both the autonomic and somatic divisions of the nervous system [4]. Urologic sequelae include lower urinary tract (LUT) dysfunction and sexual dysfunction including erectile dysfunction and retrograde

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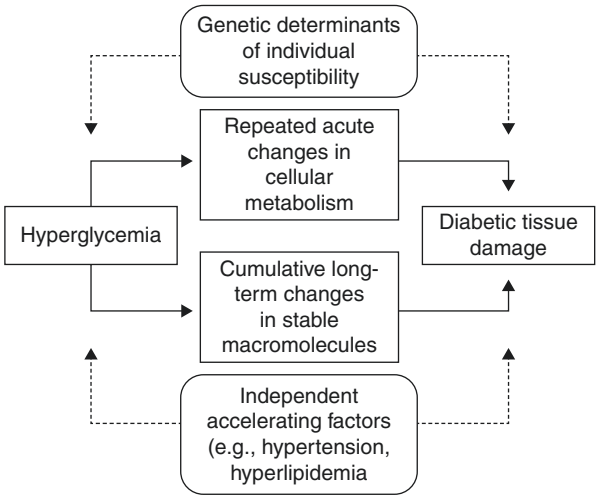

Fig. 18.1 General features of hyperglycemia-induced tissue damage (Image: Brownlee [3])

ejaculation, all of which have a marked effect on quality of life. Figure 18.1 summarizes a model of hyperglycemia-induced tissue damage.

Incidence and Presentation

LUT dysfunction is extremely common among diabetic patients with over 43–87% of type 1 diabetics and 25% of type 2 diabetics reporting symptoms [5]. The classic triad of diabetic bladder dysfunction described by Frimodt Moller in 1976 consisted of decreased bladder sensation, increased bladder capacity, and poor bladder emptying. However, it is now evident that diabetic LUT dysfunction encompasses a much wider array of symptoms including overactive bladder (OAB), voiding dysfunction, and urinary retention [6]. A recent study of nearly 1400 diabetic patients demonstrated that 22.5% had OAB, and 48% of those with OAB experienced urinary incontinence [7].

Diabetic bladder dysfunction is a slowly progressive insidious process that begins with the loss of viscerosensation of the bladder secondary to loss of autonomic afferent innervation [4]. Patients subsequently experience an impaired bladder sensation and increased duration of time between voids, resulting in delayed micturition reflexes, detrusor remodeling, asymptomatic increase in bladder capacity, and urinary retention [8]. Numerous studies also implicate the bladder urothelium as another potential important target of diabetic oxidative damage resulting in increased urothelial mass and alterations in neurotransmitter expression with potential resultant decreased sensory ability [9].

The initial presentation of diabetic bladder dysfunction is widely variable. Due to the insidious nature of the disease, as well as concomitant pathologic conditions

Table 18.1 Symptoms/findings

Urinary urgency/frequency
Decreased bladder sensation
Increased bladder capacity
Urinary retention
Urinary tract infection
Urodynamics:
DO
Decreased bladder contractility
Normal bladder compliance

such as benign prostatic obstruction and stress urinary incontinence, it can be difficult to isolate voiding dysfunction solely attributable to diabetes. Current research in animal models, as well as human patients, suggests that the diabetic bladder undergoes evolution over the course of disease progression from an initial compensated stage to a future decompensated atonic bladder demonstrable on urodynamics [8, 10]. As such, it is not uncommon for the slow insidious onset of diabetic bladder dysfunction to go unnoticed for some time with some patients presenting initially with urinary tract infection due to incomplete emptying, while others may present with any number of both storage and voiding lower urinary tract symptoms [9]. Table 18.1 summarizes common voiding symptoms and urodynamic findings among diabetic patients.

Diagnosis

A thorough history and physical examination of diabetic patients with symptoms of diabetic bladder dysfunction should be performed. Anal sphincter tone, saddle anesthesia, and bulbocavernosus reflex should be assessed on exam and a complete pelvic exam should be performed on all female patients to rule out concomitant pelvic organ prolapse. Recommended laboratory tests include urinalysis with culture, given the high rate of bacterial cystitis in this population, as well as tests assessing for diabetic control and end-organ damage (e.g., glycosylated hemoglobin (HbA1c), serum glucose, urea, and creatinine) [11]. Neurologic disorders that can mimic those found in diabetes should be excluded including cerebrovascular accidents and lumbar disk disorders.

Urodynamics (UDS) is the cornerstone to understanding urinary symptoms and developing treatment plans. The American Urologic Association advocates postvoid residual (PVR) measurements to assess for incomplete emptying and urodynamic testing to understand bladder physiology for diabetic patients [12]. There are currently no guidelines on when to perform UDS or how frequently. Urodynamic findings during the early compensated stage often demonstrate involuntary detrusor contractions, while the later decompensated stage findings are notable for impaired detrusor contractility and areflexia [6].

Table 18.2 Proposed natural history of progression of diabetic bladder dysfunction

	Early Phase →	Late Phase
	Compensated Function	Decompensated Function
	Time Course/Risk factors ??	
Clinical:	**Storage problems**	**Voiding Problems**
Urodynamics:	**Overactive Bladder**	**Atonic Bladder**
In-vitro:	**Hypercontractile Detrusor**	**Hypocontractile Detrusor**

Pathophysiology and Timeline of Progression

Diabetes is a progressive insidious disease, as is its effect on the bladder. Development of diabetic bladder dysfunction has been associated with aging, duration of diabetes (>8 years in women, >9 years in men), and worse metabolic control demonstrated by elevated glycosylated hemoglobin levels [8].

The pathogenesis of diabetic bladder dysfunction is multifactorial, resulting in alterations in detrusor muscle physiology, neuronal impairment, as well as urothelial dysfunction [11]. During the early phase, hyperglycemia-induced osmotic polyuria results in compensatory bladder hypertrophy with resultant myogenic and neurogenic alterations [13]. Urodynamic findings at this time may demonstrate detrusor overactivity secondary to the autonomic neuropathy and detrusor myopathy, but these patients have not yet developed sensory impairment characteristic of late phase disease [14]. In the late phase, damaged tissues induce irreversible bladder dysfunction. Accumulation of oxidative stress products due to prolonged hyperglycemia results in continued myogenic changes and increasingly weak detrusor contractility [10].

Suburothelial C fiber and intramural Aδ fiber nerves are important in the initiation of micturition and both of these pathways can be affected by diabetes. A recent study in female type 2 diabetics demonstrated decreased responses of Aδ and C fibers within the bladder mucosa of those with detrusor underactivity [14].

Table 18.2 summarizes urologic symptom progression.

Treatment

The management of diabetic bladder dysfunction varies considerably depending on each patient's complaints, symptom severity, and impact on quality of life. Treatments can be generally categorized into behavioral, pharmacological, and surgical and are directed at improving symptoms and addressing urodynamic abnormalities. Table 18.3 summarizes various treatment options.

Table 18.3 Urologic interventions

Behavioral therapy
OAB
Anticholinergics/B3 agonists
Onabotulinum
Neuromodulation
Urinary retention
Alpha adrenergic antagonist
Bladder outlet procedure (men)
Intermittent catheterization

As the first stage, non-invasive treatment options should be considered. Evidence suggests that development of diabetic bladder dysfunction is a function of both disease duration and degree of hyperglycemia, and, therefore, improvement in glycemic control should be encouraged. Lifestyle modifications including weight loss and alteration to diet and fluid intake have been shown to improve LUTS among diabetic patients [15, 16].

Weight loss can lead to significant improvement in patient's symptoms with improvement in glycemic control, potential reversal of insulin dependence in type II diabetics, and substantial improvement in urinary symptoms, especially urinary incontinence. Among obese women, a 5–10% weight loss has been shown to result in a greater than 50% reduction in incontinence episodes [17].

Bladder training is recommended with voiding every 2–4 hours with double voiding, which will help prevent urinary incontinence and result in more complete bladder emptying. Among patients with a hypotonic or atonic bladder, self-catheterization should be the primary treatment modality with catheterizations performed to maintain residuals less than 400 cc and avoid incontinence [11].

Pharmacologic Modalities

For those diabetic patients with overactive symptoms refractory to lifestyle modifications, anticholinergic and beta-3 agonists represent the cornerstone of treatment. Anticholinergics with longer active formulations have been found to be more effective with a better side effect profile. Patients with PVR > 200 cc are at high risk for urinary retention, a known side effect of this medication class, and many studies do not recommend utilization of anticholinergics in this population. Myrbetriq (Mirabegron) is a beta-3 selective receptor agonist that results in detrusor relaxation that is currently FDA-approved for treatment of OAB symptoms with a more favorable side effect profile than the anticholinergics; however, caution must be exercised in prescription of this medication in those with uncontrolled hypertension [18].

The tricyclic antidepressant, imipramine, also represents another treatment option for those with detrusor overactivity. While it has proven useful in the

management of diabetic autonomic dysfunction, including incontinence, given its risk of serious cardiac events, it is infrequently utilized [11].

Pharmacologic treatment options for the late phase of diabetic bladder dysfunction characterized by detrusor hypocontractility are limited. Past therapy has included alpha-adrenergic antagonists and muscarinic receptor agonists (e.g., bethanechol) to stimulate detrusor muscarinic receptors or cholinesterase inhibitors (e.g., distigmine) to diminish degradation of acetylcholine. While use of alpha-adrenergic antagonists has shown some benefits, especially among patients with concomitant BOO, studies have documented few beneficial effects of muscarinic receptor agonists and cholinesterase inhibitors, as well as unfavorable side effects, making their application very limited, and evidence to support their use sparse [19].

Surgical Modalities

Those patients with symptoms refractory to conservative and pharmacologic therapy may be candidates for surgical interventions.

Surgical treatments for OAB include intradetrusor injection of onabotulinumtoxin A, percutaneous tibial nerve stimulation (PTNS), and sacral neuromodulation (SNM). Both onabotulinumtoxin A injection and SNM have proven as effective treatment options in the diabetic population; however, while PTNS has had documented efficacy in the non-diabetic population, formal studies in the diabetic population are lacking [9].

Female patients with refractory stress urinary incontinence may be candidates for midurethral or autologous fascial sling. Surgery is associated with impressive cure rates; however, patients may be at higher risk for treatment dissatisfaction and complications, including urgency incontinence and incomplete bladder emptying [20, 21].

Patients with detrusor hypocontractility may be offered procedures to lower outlet resistance such as bladder neck incisions or transurethral resection of the prostate. In men with detrusor hypocontractility who underwent TURP, there is literature suggesting long-term symptomatic improvement for up to 7 years postoperatively [22]. Further studies need to be performed to evaluate the efficacy of bladder outlet reduction surgery in those with diabetes-associated detrusor hypocontractility. In addition to the treatment of OAB and urge incontinence, SNM is also an effective treatment option for non-obstructive urinary retention. Studies document a mean response rate in this patient population of approximately 54% [23]. Long-term success rates among diabetic patients undergoing SNM treatment for urinary retention are similar to non-diabetic patients; however, diabetic patients do have a higher risk of infection [24].

Operative Risk in the Diabetic Patient

Glycemic control in the perioperative setting is critical to safe and successful surgical outcomes in the diabetic population. Pre-operative glycemic control can be accessed via HbA1c measurement. There are currently no guidelines for HbA1c cutoff for surgical eligibility; however, HbA1c < 7% has been associated with decreased infectious complications and lower rates of cardiac ischemic events among diabetic patients undergoing noncardiac surgeries [25, 26].

The effects of surgical stress and anesthesia can result in hyperglycemia due to alterations in normal glucose hemostasis, increasing the risk of postoperative sepsis, endothelial dysfunction, cerebral ischemia, and impaired wound healing [27].

Conclusion

An increasing number of patients are being diagnosed with diabetes each year. Diabetic bladder dysfunction is a common and costly complication of diabetes. Due to the insidious onset of disease, many patients will delay seeking urologic evaluation. Unfortunately, loss of bladder sensation once it develops is irreversible and long-term follow-up is necessary. Surveillance of diabetic patients and assessment of their voiding symptoms should be performed, including measurement of post-void residual and urodynamic assessment, to help identify patients at risk and prevent long-term complications.

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Part III
Urological Care of Patients with Advanced Neurological Conditions

Chapter 19
Home Health Care Needs and Nursing Considerations

Lisa Irene Mathias

Chapter Content: Key Nursing Considerations for Urologic Management of the Spinal Cord Injured Patient with Neurogenic Bladder in the Home Care Setting.

The modern nurse practices in a complex, ever-changing, and specialized environment that focuses on evidence-based care and treatment with a multidisciplinary approach to overall patient wellness. The goals of nursing care, regardless of the complexities, remain the same – promotion of health, prevention of illness, and care of the mentally ill, physically ill, disabled, and dying people of all ages and in all care and community settings [1]. As part of an interdisciplinary team, the home care nurse is in a unique position to assist in the planning, implementation, and evaluation of the urological care for individuals with advanced neurological conditions. Communication across the spectrum of care as well as across institutions is not uncommon. With an extraordinary view into the patient's day-to-day challenges and successes, the home care nurse's role extends beyond basic assessment and care to that of spiritual confidant and advisor, advocate for physical and mental wellness, and liaison between care access points. Nursing considerations on the assessment and management of the urologic needs of the neurogenic bladder patient (NGB) patient will be explored.

A bladder management program must be developed to allow the patient to empty their bladder completely on a regular basis and should support the patient's adaptive abilities and level of independence. The bladder management plan should help establish and maintain bladder and kidney health and prevent UTI, stone formation, strictures, autonomic dysreflexia, and moisture-associated skin damage (MASD.) The term moisture-associated skin damage (MASD) is an umbrella term that includes a spectrum of dermal injuries characterized by inflammation and erosion/denudation of the epidermis from prolonged exposure to moisture or

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various irritants. There is evidence in the literature that associates MASD with other skin issues and injuries such as incontinence-associated dermatitis, intertriginous dermatitis, periwound skin MASD, peristomal moisture skin damage, cutaneous fungal/bacterial infections, and pressure injuries [2, 3].

It is estimated that there are more than 250,000 people living in America with a spinal cord injury and more than 80% of these individuals exhibit some degree of bladder dysfunction [4]. The crucial importance of the home care nurse in understanding and supporting the urological wellbeing of the NGB patient is integral in obtaining positive patient outcomes and improved quality of life. The home care nurse will see NGB patients on all aspects of the continuum from the newly injured patient to those who have been managing for many years. In addition, depending on the level and severity of the neurologic condition, your patient may be sensate or insensate and will have a wide range of physical abilities and challenges. For example, in a cross-sectional study of patient with SCI, only about 21% reported normal voiding; therefore, the home care nurse can expect to see a variety of urinary management modalities [4]. It is estimated that 30% of SCI patients are hospitalized one or more times during any given year following injury with an average length of stay of 22 days. Acute and chronic genitourinary diseases are one of the leading causes of these hospitalizations. Following discharge, approximately 89% of patients return to a private home or residence [5].

Challenges for the patient with neurogenic bladder range from psychological and spiritual considerations to physical and medical concerns. For example, many patients suffer from body image disturbance as well as self-presentational concerns about appearance, social stigma, and a desire to "normalize" their postinjury body through strategies of covering up visible disabilities [6]. NGB patients may discuss the need to hide urinary drainage bags or ostomy appliances, camouflage bladder accidents by layering clothes/incontinence pads, or use strong deodorants or perfumes to hide the odor of urine for fear of appearing "unclean" in public. The patient may purposefully maintain a chronically dehydrated state to avoid the need to catheterize while away from home or reduce the risk of a humiliating incontinent episode in public. Conversations with your patient related to self-care deficits such as hygiene may be difficult, but are necessary, and should be done thoughtfully and gently with the goal of providing support and education to the patient and family. The home care nurse should identify nursing diagnoses related to the psychosocial and spiritual domains such as spiritual distress, risk for impaired mood regulation/depression/anxiety, disturbed body image, ineffective coping, risk for loneliness, or risk for social isolation [7]. Once identified, the home care nurse may begin to provide compassionate emotional and psychological support for the patient and may reach out or alert the patient's primary care physician, social worker, or psychiatrist/therapist to request referrals or further assistance for the patient.

Transportation limitations and financial constraints are frequently noted by patients as primary social stressors and contributing factors that lead to difficulty in adhering to treatment recommendations and overall decreased quality of life. Many patients utilize family, friends, church organizations, and other social supports to

assist them in managing day-to-day concerns. While these supports are crucial, they can be limiting to the patient and foster a feeling of dependence. Understanding and utilizing national support services or services unique to your area can assist the patient in overcoming these challenges and provide patients with autonomy and independence. Becoming familiar with your local services that support patients, families, and caregivers is essential. Partnering with case management or helping to facilitate a social work referral may be required. Many communities provide "dollar rides" and other transportation services. The Veterans Affairs Office also offers many transportation and social support services for veterans and their families. Additional resources are listed at the end of this chapter.

Nursing Considerations on Conservative Urinary Management

Patients who utilize behavioral techniques, incontinence pads or briefs, condom catheters, or incontinence clamps should be assessed for their ability to safely utilize these modalities effectively. Understanding your patient's baseline urologic function is vital in identifying concerning changes in urologic status and managing their urologic safety over time.

Behavioral techniques such as timed voiding, Kegel exercises, and fluid management may help the patient improve urinary symptoms by training the bladder to empty on a predictable schedule. Encourage your patient to drink the same volume of fluid at the same time every day. Patient's should avoid drinking more than 64 ounces of fluids daily and should avoid drinking caffeinated beverages and alcohol. Patients may try bladder training exercises that increase the time the patient holds their bladder by 15 minutes each week with a goal of holding the bladder for 2–3 hours. Kegel exercise, if possible for the patient to perform, should include contracting the muscles for 10 seconds with a rest of 5 seconds in between each Kegel with a goal of two sets of 15 reps daily. Valsalva and Credé maneuvers are generally not recommended as primary methods of bladder emptying. If your patient is utilizing these techniques, then consistent nursing assessment is key in identifying potential complications such as hernia, hemorrhoids, and abdominal bruising [8]. Once identified, the patient's urologist should be contacted for treatment direction and further management.

Penile clamps may also be used to effectively manage male urinary incontinence. The patient's ability to manually attach and detach the device must be assessed. In addition, the patient's ability to adhere to a timed voiding regimen is essential as these devices must be released every 2–4 hours to allow for urination and cannot be used during sleep. Benefits of this tool include patient independence and a normalized urination schedule. Nursing assessment for these devices includes checking for correct placement and appropriate size of the device, adequate circulation when in use, skin assessment, and checking the device for erosion or signs of wear.

Condom Catheters are convenient and widely used by many men to manage urinary leaking. A properly fitted condom catheter is essential in managing incontinence and protecting perineal tissue. Benefits of the condom catheter include ease of use as they are applied once in a 24-hour period and can be utilized 24 hours/day. Condom catheters also allow for assessment of intake and output and easy management of urine through drainage collection bags. A poorly fitted condom catheter, however, can be frustrating for the patient and caregiver and allow for dissatisfaction due to leakage, MASD, and concern for odor. Nursing assessment should include ease and ability of the patient/caregiver to apply the device, comfort of the patient, as well as episodes of leaking while wearing the device. Proper grooming and removal of pubic hair (especially at the base of the penis) is essential for maximum adherence. A daily skin assessment is essential to avoid issues such as dermatitis, skin erosions, balanitis, fungal infections, and intertrigo. A polymer-cyanoacrylate protective barrier film may be considered as part of the daily skin management regimen when utilizing this device. Patients and caregivers should be taught how to properly clean their urinary drainage bags utilizing a dilute bleach and water solution (1:10) or vinegar and water solution (1:3) every other day to reduce the bacterial content and odor within the collection bags [9].

Incontinence pads and briefs may be utilized as a primary means of managing urinary incontinence or as an adjunct therapy to manage leaks between intermittent catheterizations or with indwelling catheters. Use of these products, while convenient, can place the patient's skin at risk for MASD. Caution must be used to protect the skin from contact with saturated pads/briefs. *Identifying risk factors and utilizing prevention strategies to reduce the risk of skin maceration, erythema, edema, blistering, excoriation, and erosion is the cornerstone of care.* The pH of healthy skin ranges from 5.0 to 5.5 while the pH of urine ranges from 4.8 to 8.0. Choosing a skin cleanser that is more acidic and supports the skin's acid mantle while avoiding alkaline products that can alter the pH of the skin will support tissue health and reduce opportunistic bacterial or fungal growth. In addition, dilute urine has a more neutral pH and is less irritating to the skin so encouraging good hydration is essential. Prevention of skin maceration through the use of barrier products to reduce the exposure of skin to irritants is advised. Treatments can include cyanoacrylate formulations, petrolatum-based ointments, silicone-based barrier creams, zinc oxide-based products, and polymer film applications. Skin protectants such as solvent-based polymer film barriers and zinc oxide-thickened mechanical ointments show the highest level of supporting evidence for prevention and management of MASD [10].

Customized or specialized equipment or surfaces can help reduce your patient's risk for developing worrisome skin damage or pressure ulcers. Utilize your physical medicine and rehabilitation (PM&R) physician as well as community supports such as wheelchair seating assessment and calibration centers to provide assistance with chair fitting, obtaining specialized cushions such as a ROHO cushion, and obtaining a specialty bed or surface for home use. The home care nurse should routinely inspect the patient's skin and use an established skin risk assessment tool, such as the Braden scale, to address identified risk factors and develop a plan of care

Table 19.1 Skin break down risk-reduction interventions include

Minimizing moisture on the skin and use of protective skin barrier products
Turning schedule – turning the patient every 2 hours or more (depending on risk assessment findings)
Avoid positioning the patient on bony prominences such as the trochanters and sacrum
Using specialized support surfaces
Frequently inspecting the skin under devices, braces, and splints
Using a custom-fit wheelchair with pressure-relieving cushions
Establishing a pressure-release regimen for wheelchair sitting
Providing nutritional counseling, patient education, and patient support

[11]. Of note, many patients live in their chairs or spend considerable amounts of time in their chairs. If the patient has had urinary or fecal leakage or has spilled food/drinks in their chair, this can be a source of odor and possibly place the patient at risk for bacterial or fungal infections. Check with your PM&R physician or wheelchair seating specialist for directions on cleaning chair surfaces. If skin breakdown occurs, consult specialized wound care services for wound assessment and treatment [11]. Treatment options may include both surgical and nonsurgical interventions, depending on wound stage, location, and depth [11]. Table 19.1 summarizes methods for reducing skin breakdown in neurogenic bladder patients.

Nursing Considerations on Urinary Management with Catheters

Clean intermittent catheterization (CIC) is a preferred method for bladder management for many NGB patients. CIC via urethra or through a continent cutaneous reservoir fosters patient independence, shows improved bladder compliance and maintenance over time, and reduces barriers to sexual intercourse more effectively than in patients with indwelling catheters. Nursing assessment should focus on the patient's ability to provide CIC as recommended by the physician and interventions provided to reduce patient risk. Assessing the patient's skin for evidence of superficial or opportunistic skin infections is essential. Complications of CIC include bleeding, urethral false passage, urethral strictures, and bladder or urethral perforation. Any complaint by the patient of pain, bleeding, or sensation of blockage while catheterizing should be further assessed and reviewed with the patient's urologist [12, 13].

UTI is the most frequent complication of CIC [8]. Helping your patient understand their symptoms of UTI can prevent delay in obtaining care, worsening kidney function, hydronephrosis epididymitis, prostatitis, and sepsis. Typical symptoms of UTI in the NGB patient population include a strong persistent urge to urinate even after catheterization or with indwelling catheters, hematuria, cloudy/malodorous urine, fever, chills, malaise, increased spasticity, suprapubic discomfort, and

autonomic dysreflexia. According to recent literature, approximately 30% of CIC patients get bacteriuria and 7–10% of the patients using CIC will get UTI and need to be treated with antibiotics [14]. Assisting your patient in obtaining a sterile urine sample for culture may be needed to avoid results that include multiple organisms requiring re-testing (skin or vaginal flora) or a patient's attempt to provide a urine sample from a urine collection device. Patients with chronic dysuria or colonized bladders, those with multiple antibiotic allergies, or patients with a sequela from frequent antibiotic use such as clostridium difficile may benefit from daily bladder irrigations with tap water/distilled water, normal saline, or saline instillations infused with antibiotics such as Gentamicin. A recent study indicated that Gentamicin bladder instillations decreased symptomatic UTI episodes and reduced need for oral antibiotics in patients with neurogenic bladder on CIC. In addition, the proportion of multidrug-resistant organisms in urine cultures decreased from 58.3% to 47.1% ($p = 0.04$), and the rate of gentamicin resistance did not increase [15].

Nursing management of indwelling catheters includes assessment of the device for adequate drainage, daily skin assessment, and assisting the patient in providing catheter changes approximately every 4 weeks or as needed. Patient education on keeping the collection bags to dependent drainage is essential. Leaking via urethra or around the insertion site of a suprapubic catheter may indicate improper placement of the device, an issue with the drainage of the device, or evidence that the catheter is occluded with mucus or debris. Providing education to the patient and caregiver on flushing the catheter is required. With concern for UTI, urine samples should be obtained from a freshly placed catheter or directly from the patient's bladder. If MASD or pressure wounds are noted around a catheter site, steps should be taken to educate the patient on protective barrier product, the use of drain sponges, and pressure reduction strategies.

Nursing Considerations on Surgical Interventions for Urinary Management

Ideally, care of the NGB patient undergoing urostomy or urologic diversion surgery should begin pre-operatively with education of the patient and family about the changes in body image and function that will occur. Utilizing the services of a certified Wound, Ostomy, and Continence Nurse (WOCN) for stoma cite marking, providing comprehensive patient education support and materials, as well as identifying resources for postsurgical concerns may help the patient adapt to postsurgical changes. Ostomy education, skill kits, and videos sponsored by the American College of Surgeons can be found at https://www.facs.org/educatin/patient-education/skills-programs/ostomy-program/adult-ostomy [16]. In the initial postoperative phase, wound assessment, and care take precedence. Surgical incisions typically proceed through the normal healing process of hemostasis, inflammation, proliferation, and early remodeling within the first 14 days from surgery. Wounds

that deviate from this process can become chronic. The most common time for wound dehiscence to occur is within the first 5–8 days after wound closure [15]. Signs of wound infection such as fever, a change in the exudate (increased, purulent), increased pain, increased redness/swelling, or spreading warmth from the incision site are concerning. Contact the patient's surgeon with any concerns regarding wound healing or with suspicion for infection.

Following the initial postoperative phase, nursing care should focus on educating your patient on management of their urostomy and should include some of the following points:

- Empty the pouch when it is 1/3–1/2 full – this reduces the weight of the appliance and allows for better adhesion.
- Change the appliance one to two times weekly and as needed for leakage.
- Remove the appliance gently and observe the stoma and mucocutaneous junction. The stoma should be moist and pinkish-red and the mucocutaneous junction intact.
- Skin should be free of denuded areas or rashes. Wash the skin with warm water and pat dry.
- Measure the stoma and cut the wafer to fit.
- Use the "hold and mold" process following application of the appliance. Hold the appliance in place for 1–2 minutes as the wafers are heat and pressure sensitive.
- Connect to a leg bag during the day or a night drainage bag.

If you suspect that your patient has a urinary tract infection, ideally, the urine sample should be obtained via catheterization of the stoma; however, obtaining the specimen from a newly applied urostomy pouch is also acceptable.

After a urological ostomy procedure is completed, there are several complications that can occur. These are summarized in Table 19.2:

Use of stoma powder and antifungal powder, no-sting liquid skin sealants, steroid sprays, and antibiotic powders may be used to treat these skin irritations. The use of creams and ointments is not recommended, as they will cause issues with pouch adherence. The Wound Ostomy and Continence Nursing Society has developed a peristomal skin assessment guide that can be utilized to assist the home care nurse in troubleshooting peristomal complications. See http://www.psag-consumer.wocn.org.

Table 19.2 Ostomy complications

Skin irritations: Contact dermatitis, superficial fungal infections, mechanical site trauma from appliance removal, and folliculitis.
Mucocutaneous junction separation – a gap develops around the stoma and the peristomal skin.
Leakage – if the appliance is not fitted properly, leakage can occur.
Retraction – the stoma can move inward if weight gain occurs or scar tissue grows.
Stenosis – The stoma opening begins to close.
Peristomal hernia/prolapse – this occurs when the intestine presses outward.
Necrosis – this is tissue death of the stoma.

Caring for your patient with an orthotopic neobladder involves assisting the patient in a progressive and timed-toileting routine. This progressive routine will allow the neobladder to gradually increase its urine storage capacity and promotes continence. A written voiding schedule and voiding diary should be kept for the first few weeks following surgery. Patients should be taught CIC in the event that they cannot empty their neobladder or if the physician requests measurement of the postvoid residual. The most common reason for difficulty in emptying the neobladder is the amount of mucus produced by the intestinal lining of the neobladder. If your patient reports difficulty in emptying the neobladder, the patient should be taught to irrigate their neobladder with a push/pull technique using 60 ml of tap water/distilled water or normal saline. Repeat irrigations until there are only a few shreds of mucus in the syringe.

In conclusion, home management of the NGB patient's urinary health is of utmost importance for improving and maintaining the patient's sense of spiritual, physical, mental, and social wellbeing as well as preventing complications such as urinary tract infections and moisture-associated skin damage. A successful urologic treatment plan should utilize all aspects of available support and provide the patient with a comprehensive resource checklist. Patient education and empowerment are critical. Items to include on the patient's checklist prior to discharge of the patient from home care services include: all written patient education and instruction handouts and pamphlets, postsurgical instructions, a schedule of follow-up provider visits, transportation/personal support contacts, prescriptions for medications and durable medical equipment, a provider contact list with the names and numbers of the patient's multidisciplinary team, troubleshooting tips and tricks, and individualized personal assessment plans that assist the patient in determining when they should contact their providers. Table 19.3 lists additional online resources for caregivers and patients.

Table 19.3 Online neurogenic bladder resources

Ostomy:
https://www.hollister.com
https://www.coloplast.com
https://www.convatec.com
https://www.ostomy.org
Wound:
https://www.wocn.org
Home health care/nursing
https://www.aaa1b.org
https://www.suna.org
General urologic care
https://www.va.gov
https://medicare.gov
https://www.urologyhealth.org

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Chapter 20
Prevention of Urologic Morbidity in Progressive Neurologic Patients

Christopher S. Elliott and Kazuko Shem

Introduction

Changes in bladder function are a common occurrence in individuals afflicted with progressive neurologic disease. The alterations in urinary function, either alone or in conjunction with nongenitourinary systems, can lead not only to a decrease in quality of life but also significant morbidity [1–4]. The role of the urologist can be quite important in minimizing quality of life effects and in preventing adverse secondary health outcomes. For this to occur, however, a working knowledge of the patients' disease state, its effect on bladder storage/emptying, and the resultant sequelae of inappropriate management need to be understood. In addition, the effect of the disease on related body systems must also be appreciated. Unfortunately, while the basic genitourinary dysfunction expected to occur with various progressive neurologic diseases is available in textbooks, the optimal bladder management strategy and appropriate follow-up for those afflicted with these diseases is often difficult to ascertain. In many instances, prior experience and personal intuition may be all that one has. The following chapter will attempt to bridge this gap by focusing not on specific neurologic diseases or how they might affect the genitourinary system, but rather on common accompanying issues that may warrant close attention, specifically loss of independence, altered nutritional states, bowel dysfunction, and genitourinary infection.

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Understanding Disease Progression

To begin any patient evaluation, a thorough understanding of the individual's bladder storage and emptying is necessary. For those unable to store or empty well, behavioral, pharmacologic, and surgical interventions, which are highlighted in other portions of this book, may be considered. *The storage and emptying characteristics of an individual's bladder are often further complicated by the progressive neurologic disorder's effect on motor function which may severely exacerbate an otherwise minor bladder disturbance.* For example, low degree detrusor overactivity issues coupled with an inability to quickly ambulate or transfer to a toilet can result in profound incontinence that is not easily managed. In many cases, we find that common therapeutic approaches are ineffective as they are overshadowed by the accompanying degree of motor impairment. Decreases in motor function can also provide challenges in the patient with emptying difficulty as intermittent bladder catheterization may prove to be physically impossible secondary to decreases in upper extremity dexterity or increases in lower extremity spasticity [5]. Bladder management decisions can be further compounded by caregiver availability (or lack thereof).

In most instances, it is also beneficial to understand an individual's expected rate of neurologic decline when making bladder management decisions. This is especially helpful in those expected to experience a rapid decline in overall function, specifically where the treating urologist might consider preemptive catheterization (either condom, urethral or suprapubic) to manage incontinence, poor emptying, or a combination of both. Continued neurologic assessments on routine follow-up visits are also essential to continually gauge the current and future viability of an individual's bladder management strategy. We often find that a progression of bladder management modalities is needed during the course of progressive neurologic decline and observe that patient acceptance of these changes is enhanced when a roadmap has been provided in prior discussions. In addition to frequent neurologic assessment, we find that periodic postvoid residuals (when applicable), renal-bladder ultrasound tests, and symptom checks are useful in maintaining an optimal bladder management strategy. The timing of these assessments is often individualized based on the neurologic disease, and is further augmented through good communication between the multiple physicians that are part of the treatment team (neurologists, gastroenterologists, infectious disease, physical medicine and rehabilitation, primary care, etc.) which can sound the alert when significant changes occur.

Urinary Calculi

When considering progressive neurologic decline, the urologist is also at times required to consider nutritional and metabolic disturbances that can influence overall genitourinary health and in particular, stone formation. For the most part, these nutritional changes in and of themselves have little effect on overall

renal function; however, the resultant increase in urinary stone risk can lead to complications. The genesis of stones in those with progressive neurologic disease is usually multifactorial. For many, decreases in weight-bearing status can lead to bone resorption with resultant hypercalciuria and an increased risk of kidney stone formation [6]. While the bone resorption is not easily addressed, hypercalciuria can often be offset with increased fluid intake [7]. Unfortunately, many patients have difficulty adhering to recommendations that call for increases in fluid intake, specifically those affected by bladder storage/emptying issues where an increase in urine output directly increases the chances of urinary incontinence [8]. To the contrary, we find that a large majority of individuals with neurologic decline intentionally restrict their fluid consumption in order to improve their continence status. When combined, hypercalciuria and fluid restrictions work to increase the risk of kidney stones and the possibility of resultant ureteral obstruction, renal colic, and in rare cases obstructive pyelonephritis. We attempt to monitor this with questions about urinary frequency, urinary volumes, and annual renal-bladder ultrasound testing. Our typical recommendations include 24 hour urine volumes of at least 1500 mL (2000 mL per day in those with a history of genitourinary stones) and our inquiries are often aided with patient void/catheter diaries of urine output over a 24 hour period in the day or two leading up to office visit. We have found that the patients most at risk for kidney stone complications are those summarized in Table 20.1.

In addition to kidney stones, the formation of bladder stones can also be problematic in those with progressive neurologic dysfunction. Bladder stones may result from poor emptying of the bladder, however, more often are secondary to indwelling catheters used for bladder management. For those employing indwelling catheters, bladder stones generally develop as encrustations on the catheter, which subsequently fall off into the bladder during tube changes. These remaining encrustations reside in the bladder to grow over time (as the passive nature of bladder drainage with a catheter does not propel them out of the bladder) [10, 11]. Bladder stones can usually be identified on screening renal-bladder ultrasound and may be removed in either an office or operating room setting depending on the size and number. In those with indwelling catheters and a history of bladder stones, we often consider the use of Renacidin (citric acid/glucono-delta-lactone/magnesium carbonate) instillations (25 cc for 20 minutes daily) in addition to increasing fluid consumption (which in this population should not be problematic from an incontinence standpoint) to decrease the rates of formation. Individuals with recurrent bladder stones secondary to indwelling catheters should also be screened and treated for urease splitting bacterial organisms (specifically Proteus mirablis) that are associated with rapid stone development and catheter obstruction [12].

Table 20.1 Risk factors for renal stone formation in neurogenic bladder patients.

Bedbound/quadriplegia
Ileostomies (with resultant dehydration due to high outputs)
Feeding tubes secondary to dysphagia, reduced free water supplement
Prior history of stone formation [9]

Gastrointestinal Concerns

The urologist charged with the care of individuals with progressive neurologic decline must also consider the gastrointestinal (GI) tract in their overall patient management. In most cases of neurologic deterioration, dysfunction of the GI tract is associated with constipation. Constipation, particularly in its more severe forms, can lead to an increased risk of urinary incontinence, decreased bladder capacity, and in rare cases ureteral obstruction [13]. The presence of constipation is typically assessed with direct patient questioning, and when there is a significant suspicion, a plain film abdominal X-Ray and/or rectal examination should be performed. In those with progressive neurologic deterioration, constipation issues can be further exacerbated with pharmacotherapy, notably anticholinergic medications used for treating urinary incontinence [14]. In instances where constipation is a problematic issue, therapeutic alternatives for detrusor overactivity including beta-3 agonists, botulinum toxin, and neuromodulation can be considered [15]. A routine bowel program to avoid constipation using stool softener, mild laxatives, and/or suppositories should also be considered [16]. Further contemplation of a colostomy should also be taken in those with severe GI dysfunction. In these individuals, concomitant suprapubic catheter placement, ileovesicostomy or ileal conduit creation may also be warranted, as individuals with severe GI dysfunction typically have significant coexisting genitourinary problems. Table 20.2 summarizes GI concerns.

Urinary Tract Infections

Perhaps the most common problem in the neurogenic bladder population are urinary tract infections (UTI). *In those with progressive neurologic disease, urinary infections are sometimes obvious, but in many cases it may be difficult to discern if a clinically significant UTI is present owing to the fact that many patients have chronic bacteriuria and nonspecific symptoms* [17]. We typically try to first dichotomize our progressively neurologic patients by bladder management method type when considering the diagnosis and management of UTIs. In those spontaneously voiding, urinating into diapers or voiding into condom catheters (where the bladder is not being instrumented), we believe that bacteria in the urine (unless due to contaminant) is abnormal and should be treated when accompanied by bothersome symptoms. In unusual cases where recurrent UTIs occur and bacterial persistence develop (the same bacteria found repeatedly and found soon after appropriate treatment), we commonly will check a postvoid residual and obtain genitourinary imaging (ultrasound or

Table 20.2 Basic GI treatment recommendations for progressive neurogenic bladder population

Identify and manage constipation
Optimize bladder medications to reduce GI motility impact
Maintain routine bowel program
Consider recommending colostomy for refractory GI symptoms

computed tomography) to rule out an infectious nidus (typically a stone). In cases of significantly elevated postvoid residual, we commonly place a temporary (3–5 day) indwelling catheter to facilitate bladder emptying during antibiotic treatment to augment the bactericidal effects of antibiotics with effective bladder flushing. In the rare cases where a nidus is present, we typically remove it.

It is in those managed with chronic indwelling catheterization (urethral or suprapubic) or intermittent catheterization, however, that UTI diagnosis and management is generally more challenging. In this instrumented population that always has some degree of bacteriuria, it is often not clear if the organism or organisms found in the urine are responsible for the patients' complaint, as no reliable test exists to differentiate pathologic from nonpathologic bacteriuria [17]. To this end, it is *often found that constipation, bladder stones, neurologic disease flares, or other alternative explanations are present on closer inspection and are the true causative agent of UTI-like symptoms [*18]. When another obvious cause is not present, we typically will treat an individual with an appropriate course of antibiotics (after obtaining a bacterial culture with antibiotic sensitivity testing) to see if the offending symptoms improve. If the symptoms do not resolve dramatically, we generally will repeat our search for an alternative explanation.

The main difficulty we commonly encounter in the population with progressive neurologic disease is that many of the physicians of varying subspecialties who are part of the treatment team do not understand that chronic bacteriuria is expected secondary to one's bladder management instrumentation (and is even present when they have no problem/complaint). Hence, overtreatment of asymptomatic bacteriuria can be commonplace and may further complicate bacterial antibiotic resistance patterns, bowel habits (with increased loose stool and soiling), and the possibility of C. dificile colitis [19]. We find that patient and caregiver education is paramount when attempting to promote antibiotic stewardship in the neurogenic bladder population. *This education includes training that cloudy urine, malodorous urine, and the presence of bacteria in the urine alone are not reasons to seek antibiotic treatment.* Rather, febrile illness without other cause and new onset incontinence are considered far more reliable symptoms of a true UTI. At the very least, we ask that our patients seek us out when two or more UTIs are found in 6 months or three or more UTIs are found in a year's time, as this is considered abnormal and warrants a urologic investigation (voiding/catheterization diary x 24 hours, renal-bladder ultrasound, symptom assessment of what is driving UTI treatment, and postvoid residual/urodynamics (if applicable)). Table 20.3 summarizes recommendations for identifying and treating UTIs in progressive neurogenic bladder population.

Table 20.3 Identifying and treating UTIs in progressive neurogenic bladder population

Consider treating symptomatic voiding patients with bacteria in urine
Avoid treating asymptomatic patients with catheters and bacteria in urine
Color/clarity of urine is not always diagnostic of UTI in patients with catheters
Patients with 2 UTI/6 months or > 3 UTI/year need urologic evaluation

Cognitive Changes

Other nonurologic considerations that may need to be made in patients with progressive neurological disease is declining cognitive function that may influence a provider's bladder management recommendations. We have encountered this phenomena in multiple situations where intermittent catheterization is an ideal bladder management strategy from a functional perspective only to discover that a patient cannot be compliant secondary to not being able to either: (a) cognitively understand why they are being asked to catheterize; (b) remember to catheterize on a time schedule; or (c) recall the necessary physical steps involved in the act of self-catheterization. In these instances, without consistent caregiver support, a seemingly appropriate management strategy will ultimately fail.

Conclusions

Given the complex nature of progressive neurological disorders and the interplay between urologic dysfunction, physical impairment, and potential cognitive disability, a multidisciplinary approach is recommended, which may include: a physiatrist to coordinate care and maximize function given neurological limitations, a neurologist to diagnose and medically treat the neurologic condition, the urologist to optimize genitourinary care, and the physiatrist or a gastroenterologist to manage concurrent bowel issues when necessary. In addition, and more importantly, good communication between providers is essential to minimize therapeutic overlap, avoid improper treatment, and provide updates to the group when significant events occur that might alter the therapeutic treatment plan. While this chapter alone is insufficient in and of itself to fully educate a urologist in the care of those with progressive neurologic decline, we hope that the framework encourages the reader to participate in the care of this special population where one can significantly improve the quality of life in an oft-underserved group.

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Index

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